Technoleg Iechyd Cymru
Health Technology Wales

# Evidence Appraisal Report

# Antimicrobial barrier caps for use with haemodialysis catheter hubs

## Appraisal summary

The aim of this review was to address the following question: What is the clinical and cost effectivness of antimicrobial barrier caps for use with haemodialysis catheter hubs in reducing catheter-related bloodstream infections?

We identified two prospective, cluster-randomised trials evaluating the use of antimicrobial caps (specifically, ClearGuard HD) for haemodialysis catheters. One study compared ClearGuard against standard caps, whereas the second study compared ClearGuard to a needle-free connector (Tego) plus disinfectant cap (Curos). Both studies were undertaken in the US, which may limit the generalisability to Welsh care.

All outcomes were reported per 1,000 central venous catheter days. Compared to standard caps, ClearGuard had improved rates of overall blood stream infections (based on positive blood culture) and hospital admissions over the 12-month follow-up period. No difference was observed for duration of hospitalisation or intravenous (IV) antibiotic starts. Analysing the last six months of the study period only, ClearGuard had significantly lower rates of overall blood stream infections (BSI), hospital admissions and hospitalisation-days.

Compared to Tego plus Curos, ClearGuard had improved rates for overall blood stream infections (based on positive blood culture), catheter-related blood stream infection, central line associated blood stream infection and IV antibiotic starts.

An additional retrospective study was also identified and demonstrated improved rates of central line-associated blood stream infections with ClearGuard compared to a standard needle-free connector (Tego). However, it is uncertain whether the findings of this study are generalisable due to its design and limitations.

Study-defined catheter-related blood stream infection and central-line-associated blood stream infection can be inconsistent across different studies; only one study specifically reported on these outcomes.

We did not identify any relevant economic evidence on antimicrobial caps for haemodialysis central venous catheters. A cost consequence developed by HTW suggested that the additional upfront costs with ClearGuard caps may be outweighed by savings accrued through a reduction in BSI events. However, there is uncertainty around the baseline BSI event rate in Wales and the costs associated with managing these events. Sensitivity analysis revealed that the analysis is sensitive to changes in key input parameters.

We did not identify relevant evidence pertaining to organisational or patient issues (including patient preference/experience studies).

## 1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: What is the clinical and cost effectiveness of antimicrobial barrier caps for use with haemodialysis catheter hubs in reducing catheter-related bloodstream infections?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

## 2. Health problem

Chronic kidney disease affects between 6 to 8% of the Welsh population (WRCN 2016). It is often undiagnosed and mild in severity, although it can develop into more a more severe condition and coexisting conditions are associated with increased severity (NICE 2014). In some cases, chronic kidney disease can develop into end-stage kidney disease. Worldwide prevalence of end-stage renal disease is increasing each year (Wu et al. 2020) and risk of developing chronic kidney disease increases with age (NICE 2014).

Haemodialysis is the most common treatment option for people who develop end-stage kidney disease. Haemodialysis involves flowing blood from the body through a dialysis machine, which filters waste from the blood before it is returned to the patient's body. According to the UK Renal Registry, 24,366 adult patients were receiving in-centre haemodialysis and 1,323 adult patients were receiving home haemodialysis in 2018 (UK Renal Registry 2020). Incidence and prevalence of haemodialysis is higher in Wales than in other parts of the UK (WRCN 2016).

A central venous catheter (CVC) is a type of access used for haemodialysis. Despite various infection prevention initiatives, CVC-use for haemodialysis can commonly lead to blood stream infections (BSIs), hospitalisation, mortality, and increased health care costs (Hymes et al. 2017, Fisher et al. 2020).

## 3. Health technology

Antimicrobial barrier caps are screwed on to the end of a catheter hub after haemodialysis has finished, and are designed to have antimicrobial or antiseptic activity to prevent catheter-related blood stream infections (CRBSIs). CVCs remain capped until the next haemodialysis session.

One such device is ClearGuard HD. The inside of the ClearGuard cap contains a rod coated in chlorhexidine; when the cap is screwed on to the catheter, the rod sits within the liquid-filled catheter hub and releases the chlorhexidine into the surrounding lock solution. ClearGuard replaces a standard cap or connector, and should be replaced at every haemodialysis session. The maximum time use for each cap is three days (NICE 2020).

Experts at consultation were not aware of antimicrobial caps being used with haemodialysis CVCs in Wales; most experts did report use of antimicrobial lock solutions.

# 4. Clinical effectiveness

For full details on the methods for this evidence review, see Section 11.

We identified two cluster-randomised trials (CRTs) on the use of antimicrobial barrier caps (Brunelli et al. 2018, Hymes et al. 2017). CRTs differ from randomised controlled trials in that they randomise clusters rather than randomising individual participants; in this case clusters were defined as a pair of pre-matched dialysis centres. Both studies were carried out in the US and used ClearGuard HD antimicrobial barrier caps as the intervention. Hymes et al. (2017) compared ClearGuard caps to standard caps, whereas Brunelli et al. (2018) compared ClearGuard caps to Tego (a needle catheter connecter) used with Curos (a disinfecting cap to be used with Tego). See Table 1 for further detail and study characteristics.

We also identified one retrospective study comparing use of ClearGuard caps and Tego needlefree connectors (no Curos) as part of a quality improvement study (Weiss & Qureshi 2021). This analysis was also in the US healthcare setting (see Table 1 for further detail and comments on reliability).

The evidence we identified evaluated ClearGuard antimicrobial caps as the intervention; we did not identify any evidence evaluating other antimicrobial caps.

## 4.1 Antimicrobial barrier cap versus standard cap

One CRT compared antimicrobial barrier caps (ClearGuard) to standard catheter caps (Hymes et al. 2017). This study included a one-month pre-intervention period and 12-month follow-up period; Hymes et al. (2017) reported no significant difference between ClearGuard and standard caps during the initial one-month baseline period for any defined outcome.

Outcomes for the 12 month period (n = 2,470) are detailed in Table 2. Hymes et al. (2017) did not report rates of central line-associated blood stream infections (CLABSI) or CRBSI specifically, but did report overall rate of BSIs, based on positive blood culture episodes per CVC-days; patients were censored for the first 21 days of the study to avoid including pre-existing BSIs, and double counting was avoiding by only including additional infections in the same patient if they occurred at least 21 days after the last reported infection. Positive blood culture rate for the 12 month follow-up was significantly lower with ClearGuard than with standard caps (0.26 versus 0.59/1,000 CVC-days; incidence rate ratio [IRR] 0.44, 95% confidence interval [CI] 0.23 to 0.83, p = 0.01).

Hospital admissions for BSI was also significantly lower in the ClearGuard group that the standard cap group (0.28 versus 0.47/1,000 CVC-days; IRR 0.6, 95% CI 0.37 to 0.97, p = 0.04). No significant difference was observed for hospitalisation-days or IV antibiotic starts.

Hymes et al. (2017) performed several subgroup analyses, although it is not clear whether the study was adequately powered for these analyses. Subgroup analysis of patients who entered the study with a new CVC (n = 678) showed significantly lower positive blood culture rate in the ClearGuard Group than the standard cap group (0.16 versus 0.50/1,000 CVC-days; p = 0.02).

Hymes et al. (2017) reported increasing rates of positive blood culture episodes each quarter of the study period (Winter, Spring, Summer, Autumn) for the standard caps group, resulting in greater difference between ClearGuard and standard caps in the later six months of the 12-month follow-up. The authors suggest this is due to routine seasonality with infections more likely during warmer summer months. Additional sub-analysis showed that rates for positive blood culture episodes, hospital admissions and hospitalisation-days for the last six months of the follow-up were significantly lower in the ClearGuard group versus the standard cap group (see Table 2 for data). It is not clear if this analysis was part of prospective study design, or whether

the study was powered for this analysis (number of participants included in the six-month subgroup was not clearly reported).

## 4.2 Antimicrobial barrier cap versus needlefree connector plus antimicrobial connector cap

One CRT compared antimicrobial barrier caps (ClearGuard) to needlefree connectors (Tego) used with a disinfecting cap (Curos) (Brunelli et al. 2018). The Tego needlefree connector is designed to act as a 'closed system', and Curos is designed to kill the organisms on the outside of Tego with 70% isopropanol alcohol (Brunelli et al. 2018). The study included a three-month run-in period and a 13-month intervention period. During the run-in phase patients were treated according to the standard practice of the facility they attended (including the use of Tego) to establish whether BSI rates were equivalent between study arms at baseline. Brunelli et al. (2018) reported no significant difference in positive blood culture rate between the two study groups during the run-in period (other outcomes not reported).

Outcomes for the intervention period population (n = 1,671) are listed in Table 2. Overall positive blood culture episodes were significantly lower in the ClearGuard group compared to the Tego+Curos group (0.28 versus 0.75/1,000 CVC-days; IRR 0.37, 95% CI 0.20 to 0.68, p = 0.001).

Other outcomes were reported as 'exploratory analyses' using electronic records, which included data such as microbiology and National Healthcare Safety Network (NHSN) surveillance. CRBSI rates were significantly lower in the ClearGuard group compared to Tego+Curos (0.12 versus 0.33/1,000 CVC-days; IRR 0.37, 95% CI 0.19 to 0.72, p = 0.003), as was CLABSI rates (0.20 versus 0.59/1,000 CVC-days; IRR 0.35 95% CI 0.17 to 0.70, p = 0.003). IV antibiotic starts following a positive blood culture was also significantly lower in the ClearGuard group than the Tego+Curos group (0.20 versus 0.56/1,000 CVC-days; IRR 0.37, 95% CI 0.21 to 0.62, p <0.001).

To account for the potential confounding of latent infections from catheters colonised before the study, Brunelli et al. (2018) also performed a subgroup analysis for patients who entered the study with a new CVC (n = 1,239). The rate was significantly lower in the ClearGuard group than the Tego+Curos group (0.22 versus 0.77/1,000 CVC-days; IRR 0.28, 95% CI 0.13 to 0.59, p<0.001).

## 4.3 Antimicrobial barrier cap versus needlefree connector

One retrospective study analysed CLABSI rates from a quality improvement initiative that used ClearGuard antimicrobial caps and Tego needlefree connector (Weiss & Qureshi 2021); CLABSI rates was the only outcome of interest reported (see Table 2).

There were two phases to the study. In the first 5-month study period both ClearGuard caps (n = 967) and Tego (n = 1,044) were used as part of an initial assessment. CLABSI rates were significantly improved in the ClearGuard group compared to the Tego group (0.03 versus 0.70; p<0.0001). Due to the reduction in CLABSI rates, all patients were switched to using ClearGuard during the second study period. At final analysis (first study period + second study period), CLABSI rates in the ClearGuard group (n = 4,614) were still significantly lower than the Tego group (n = 1,320; p<0.0001).

## 4.4 Adverse events

Both Hymes et al. (2017) and Brunelli et al. (2018) reported no device-related adverse events during their respective studies.

## Table 1. Included studies: design and characteristics

<table>
<tr><th>Study reference</th><th>Methods, setting</th><th>Participants</th><th>Intervention(s)</th><th>Outcomes</th><th>Comments</th></tr>
<tr>
<td>Brunelli et al. (2018)</td>
<td>Cluster-randomised trial (CRT).<br><br>US, multicentre (n = 40).<br><br>Facilities were pre-matched based on: (1) pre-study BSI rate, as reported to the CDC NHSN from February to July of 2015; (2) the number of patients with a CVC; and (3) geographic location. One of each matched pair was then randomly allocated either ClearGuard or Tego+Curos.<br><br>Run-in phase Aug 2015 to Oct 2015.<br><br>Intervention phase Nov 2015 to Nov 2016.</td>
<td>Inclusion criteria: All patients with CVCs for dialysis at participating centres.<br><br>Exclusion criteria: History of heparin (n = 9 patients) or chlorhexidine allergy (n = 0); patients with <21 days CVC were excluded from primary analysis (but included in sensitivity analysis).<br><br>Key patient demographics for the intervention period are detailed in the table below.<br><br>
<table>
<tr><th></th><th>ClearGuard</th><th>Tego+Curos</th></tr>
<tr><td>No. centres</td><td>20</td><td>20</td></tr>
<tr><td>No. patients</td><td>826</td><td>845</td></tr>
<tr><td>Age, yr</td><td>63.7±14.4</td><td>62.0±15.3</td></tr>
<tr><td>Sex (%), male</td><td>421 (51)</td><td>435 (51)</td></tr>
</table>
<br>Authors report that participant characteristics are reasonably balanced between the 2 arms, with the exception of age (p = 0.02) and race (32% in the ClearGuard arm versus 42% in the Tego arm were Black, omnibus p<0.001).</td>
<td>Intervention: ClearGuard HD antimicrobial barrier cap<br><br>Comparator: Tego needlefree haemodialysis connector (ICU Medical) plus Curos disinfecting cap for Tego (3M Healthcare).<br><br>During the 3-month run-in phase, both study arms were treated based on standard policy at that facility (including use of Tego).<br><br>When entering the intervention phase, facilities allocated to the Tego+Curos group began using Curos (and continued using Tego). Facilities allocated to ClearGuard converted from Tego to ClearGuard.</td>
<td>• Positive blood culture rate<br>• Rate of CRBSI<br>• Rate of CLABSI<br>• Positive blood culture rate for new CVCs<br>• IV antibiotic starts<br>• Device-related adverse events</td>
<td>All centres had previously used Tego before inclusion of the study.<br><br>To avoid double-counting the same BSI, patients were censored and a PBC counted only if it occurred 21 days or more after a previously reported PBC in the same patient. To account for biologic latency between catheter seeding and clinical manifestation of BSI, at-risk time began on day 21 after first receipt of study intervention and continued until end of study, death, CVC removal, or loss to follow-up.<br><br>The study included additional exploratory analyses in areas that were not sufficiently powered by the study design, and have therefore not been included in this report. These areas are: CVC exchange rate, CVC removal rate, thrombolytic use rate, hospitalisations for BSI, mortality rate.<br><br>Lock solution was not required to be reported. 33% of all procedures provided this information, of which >95% used saline solution.</td>
</tr>
</table>

<table>
<tr><th>Study reference</th><th>Methods, setting</th><th>Participants</th><th>Intervention(s)</th><th>Outcomes</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Protocol was changed once to change the intervention period from 12 to 13 months.<br><br>Standard infection prevention procedures/policies were not reported.</td></tr>
<tr><td>Hymes et al. (2017)</td><td>Cluster-randomised trial (CRT).<br><br>US, multicentre (n = 40).<br>Centres were pair-matched based on (1) positive blood culture rate and (2) number of patients with CVCs. One of each matched pair was then randomly allocated either ClearGuard or standard caps.<br><br>1-month pre-intervention period November 2014<br><br>12 month follow-up 1 December 2014 to 30 November 2015.</td><td>Inclusion criteria: All haemodialysis patients with a tunnelled CVC.<br><br>Exclusion criteria: known allergy to chlorhexidine (none reported).<br><br>Key patient demographics for the follow-up period are detailed in the table below.<br><br><table><tr><th></th><th>ClearGuard</th><th>Control</th></tr><tr><td>No. centres</td><td>20</td><td>20</td></tr><tr><td>No. patients</td><td>1,245</td><td>1,225</td></tr><tr><td>Age, yr</td><td>61.5±15.1</td><td>60.6±15.1</td></tr><tr><td>Sex (%), male</td><td>654 (53)</td><td>666 (54)</td></tr></table><br>Authors reported that outcomes within the subgroup of white and non-white participants were analysed and found to be comparable.</td><td>Intervention: ClearGuard HD antimicrobial barrier cap<br><br>Comparator: Standard CVC caps (MPC-125 end caps, Molded Products Inc.).</td><td>• Positive blood culture episodes<br>• Rate of hospital admissions<br>• Rate of hospitalisation days<br>• IV antibiotic starts<br>• Device-related adverse events</td><td>In order to avoid counting pre-existing BSIs, patients were censored for the first 21 days after entering the study. To avoid double-counting the same BSI, patients were censored and a positive blood culture counted only if it occurred 21 days or more after a previously reported positive blood culture in the same patient, Patients were censored at CVC removal, death, withdrawal from intervention, or loss to follow-up.<br><br>Analysis group included those who transitioned to fistula or graft, and those who left the facility (e.g. death, lost-to follow-up).<br><br>Standard infection prevention policies were followed, including clean gloves, face shield, dressing and cleansing of site, etc.</td></tr>
</table>

| Study reference | Methods, setting | Participants | Intervention(s) | Outcomes | Comments |
|---|---|---|---|---|---|
| Weiss & Qureshi (2021) | Retrospective observational study<br><br>US, multicentre (n = 13)<br><br>5 month study period May-September 2018, followed by an additional 9 month period (October 2018-June 2019). | **Inclusion criteria:** Patients undergoing haemodialysis.<br><br>**Exclusions:** 1 patient was excluded based on physical incompatibility of CVC with chlorhexidine coated caps. No patients were excluded based on known allergy to chlorhexidine.<br><br>n = 5,934 (across both study periods)<br><br>Mean age 61.3 years<br>47.1% female | **Intervention:** ClearGuard HD antimicrobial barrier cap (ICU Medical)<br><br>**Comparator:** Tego needlefree connector (ICU Medical)<br><br>In the first study period patients data was analysed from a group using ClearGuard and a group using Tego.<br><br>In the second study period, patients were transitioned to just using ClearGuard. | • Rate of CLABSI | This is a retrospective analysis of a quality improvement initiative, and therefore includes several limitations.<br><br>Full patient data/demographics was not available; therefore there is a risk of confounding characteristics within the study groups and limiting the generalisability of the study.<br><br>The allocation method, or reason why a patient may receive ClearGuard versus Tego in the initial study period, was not reported.<br><br>Standard infection procedure/policies were not reported. |

BSI: blood stream infection; CLABSI: central line-associated bloodstream infection; CRBSI: catheter-related bloodstream infection; CVC: central venous catheters; IRR: incidence rate ratio; PBC: positive blood culture.

## Table 2. Antimicrobial barrier compared to comparator/control: outcomes

| Outcome | Evidence source(s) | Number of centres/participants | Population | Absolute effect | Relative effect [95% CI] (interpretation) | Comments on reliability |
|---|---|---|---|---|---|---|
| **Antimicrobial barrier caps versus standard caps** | | | | | | |
| Positive blood culture episodes, episodes/1,000 CVC-days | Hymes et al. (2017) | 40 centres, 2,470 participants | Haemodialysis patients, tunnelled CVC | -0.33/1,000 CVC-days<br><br>(0.26 versus 0.59) | IRR 0.44 [0.23 to 0.83], p = 0.01 (favours antimicrobial barrier caps) | NA |
| Hospital admissions for BSI, episodes/1,000 CVC-days | Hymes et al. (2017) | 40 centres, 2,470 participants | Haemodialysis patients, tunnelled CVC | -0.19/1,000 CVC-days<br><br>(0.28 versus 0.47) | IRR 0.60 [0.37 to 0.97], p = 0.04 (favours antimicrobial barrier caps) | NA |
| Hospitalisation-days for BSI, episodes/1,000 CVC-days | Hymes et al. (2017) | 40 centres, 2,470 participants | Haemodialysis patients, tunnelled CVC | -1.44/1,000 CVC-days<br><br>(3.24 versus 4.68) | IRR 0.69 [0.41 to 1.16], p = 0.2 (favours neither) | NA |
| IV antibiotic starts, episodes/1,000 CVC-days | Hymes et al. (2017) | 40 centres, 2,470 participants | Haemodialysis patients, tunnelled CVC | -0.10/1,000 CVC-days<br><br>(1.68 versus 1.78) | IRR 0.94 [0.74 to 1.19], p = 0.6 (favours neither) | NA |
| Positive blood culture episodes, episodes/1,000 CVC-days (last 6 months only | Hymes et al. (2017) | 40 centres, participants NR | Haemodialysis patients, tunnelled CVC | -0.50/1,000 CVC-days<br><br>(0.22 versus 0.72) | IRR 0.31 [0.12 to 0.79], p = 0.01 (favours antimicrobial caps) | Sub-analysis of quarterly results (Winter, Spring, Summer, Autumn), showed increasing PBC episodes in the control arm each quarter, resulting in a greater difference between ClearGuard and standard caps in the later 6 months (Summer and Autumn significant differences were also reported for hospitalisation and hospitalisation-days). Authors suggested this may be due to the seasonal trending of |

| Outcome | Evidence source(s) | Number of centres/participants | Population | Absolute effect | Relative effect [95% CI] (interpretation) | Comments on reliability |
|---|---|---|---|---|---|---|
| | | | | | | bacteraemia ('summer bloom'); this trend was not observed in the ClearGuard arm. |
| Hospital admissions for BSI, episodes/1,000 CVC-days (last 6 months of study) | Hymes et al. (2017) | 40 centres, participants NR | Haemodialysis patients, tunnelled CVC | -0.20/1,000 CVC-days<br><br>(0.28 versus 0.48) | IRR 0.57 [0.33 0.98], p = 0.04 (favours antimicrobial caps) | NA |
| Hospitalisation-days for BSI, episodes/1,000 CVC-days (last 6 months of study) | Hymes et al. (2017) | 40 centres, participants NR | Haemodialysis patients with tunnelled CVC | -2.52/1,000 CVC-days<br><br>(2.42 versus 4.94) | IRR 0.49 [0.25 to 0.96], p = 0.04 (favours antimicrobial caps) | NA |
| **Antimicrobial barrier caps versus needlefree connector plus disinfecting connector cap (Tego+Curos)** | | | | | | |
| Positive blood culture episodes, episodes/1,000 CVC-days | Brunelli et al. (2018) | 40 centres, 1,671 participants | Haemodialysis patients with CVC | -0.47/1,000 CVC-days<br><br>(0.28 versus 0.75) | IRR 0.37 [0.20 to 0.68], p = 0.001 (favours antimicrobial caps) | NA |
| CRBSI, episodes/1,000 CVC-days | Brunelli et al. (2018) | 40 centres, 1,671 participants | Haemodialysis patients with CVC | -0.21/1,000 CVC-days<br><br>(0.12 versus 0.33) | IRR 0.37 [0.19 to 0.72], p = 0.003 (favours antimicrobial caps) | This study defined CRBSI as: (1) analysis is performed on a per-patient basis (maximum of one PBC per patient) to ensure no duplicate counting of the same infection; (2) to better ensure that PBCs were related to the CVC, only PBCs designated as access-related on the National Healthcare Safety Network (NHSN) forms of patients with CVCs were included; (3) to help rule out skin contamination, only PBCs with recognized pathogens (no common commensals) were |

| Outcome | Evidence source(s) | Number of centres/participants | Population | Absolute effect | Relative effect [95% CI] (interpretation) | Comments on reliability |
|---|---|---|---|---|---|---|
| | | | | | | included; and (4) PBCs with polymicrobial growth were excluded because this may be an indication of contamination. |
| CLABSI, episodes/1,000 CVC-days | Brunelli et al. (2018) | 40 centres, 1,671 participants | Haemodialysis patients with CVC | -0.39/1,000 CVC-days<br><br>(0.20 versus 0.59) | IRR 0.35 [ 0.17 to 0.70], p = 0.003 (favours antimicrobial caps) | PBC was considered CLABSI if it was (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. |
| IV antibiotic starts (within 3 days of a PBC), episodes/1,000 CVC-days | Brunelli et al. (2018) | 40 centres, 1,671 participants | Haemodialysis patients with CVC | -0.36/1,000 CVC-days<br><br>(0.20 versus 0.56) | IRR 0.37 [0.21 to 0.62], p <0.001 (favours antimicrobial caps) | NA |
| **Antimicrobial barrier caps versus needlefree connector (Tego)** | | | | | | |
| CLABSI episodes/1,000 CVC-days | Weiss & Qureshi (2021) | 13 centres, 2,011 participants | Haemodialysis patients with CVC | -0.67/1,000 CVC-days<br><br>(0.03 versus 0.70) p<0.0001 | NR | HTW has only included the outcome for the first 5-month study period, where people were given either ClearGuard or Tego. At final analysis (first study period + second study period), ClearGuard had a significantly lower rate CLABSI compared to Tego (p<0.0001). |

BSI: blood stream infection; CI: confidence interval; CRBSI: catheter-related blood stream infection; CLABSI: catheter-line-associated blood stream infection; CVC: central venous catheter; IRR: incidence rate ratio; IV intravenous; NR: not reported.

## 4.5 Ongoing trials

We did not identify any ongoing trials evaluating antimicrobial caps for central venous catheters used in haemodialysis.

# 5. Economic evaluation

## 5.1 Economic literature review

The literature searches for this review were also screened for economic evidence. No relevant economic evidence was identified.

## 5.2 *De novo* economic analyses

A cost-consequence analysis was conducted to estimate the cost of using antimicrobial caps in comparison to standard caps. This evidence review identified clinical evidence for ClearGuard HD caps only, therefore the cost-consequence analysis was based upon the use of the ClearGuard HD caps. The analysis includes the upfront costs associated with each cap type and the cost associated with managing BSI events.

### 5.2.1 Data sources and methodology

The analysis is based on a hypothetical cohort of 1,000 haemodialysis patients with a tunnelled CVC. Based on a manufacturer estimate reported in NICE MIB234, it was assumed that haemodialysis patients would need a CVC for an average of 132 days (NICE 2020). Thus, a total of 132,000 CVC days were considered in the analysis. Based on Hymes et al. (2017), it was assumed that the rate of hospital admissions for BSIs would be 0.47 per 1,000 CVC-days with standard caps and 0.28 per 1,000 CVC-days with ClearGuard.

The cost associated with each cap type was based on values reported in NICE MIB234 (NICE 2020). Standard caps costs were reported to cost £0.30-£0.40 per cap. A midpoint cost of £0.35 per cap was used in this analysis. The cost of ClearGuard caps was reported to be £4.00 for a pair of caps. It was assumed that standard caps would need to be disinfected with an alcohol wipe (including those containing 2% chlorhexidine gluconate) at a cost of £0.02 per wipe.

It was assumed that haemodialysis would be needed three times per week. It was further assumed that two CVC caps would be required for each haemodialysis session and that the caps would need to be replaced at each session. Applying these assumptions to the unit costs above, results in a cost of £12.00 per week when using ClearGuard caps and £2.16 per week when using standard caps.

The cost associated with BSIs was estimated using a value for the management of CRBSIs reported in NICE medical technologies guidance on Tegaderm CHG IV securement dressings (NICE MTG25). Note that this makes the assumption that all of the BSIs were CRBSIs and so could result in an overestimation of the BSI cost. NICE MTG25 reported an estimated cost of £9,990 for the management of a CRBSI event. This value was inflated to 2020 prices using IMF price indices, giving a cost of £11,268 for each CRBSI event.

### 5.2.2 Sensitivity analysis

Sensitivity analysis was conducted to explore key areas of uncertainty. One such area was the expected cost savings that might be accrued through a reduction in the number of BSI events. Hymes et al. (2017) reported a statistically significant reduction in the number of hospital admissions for BSI per 1,000 CVC-days in the ClearGuard group compared to standard caps.

However, this reduction did not translate into a statistically significant reduction in the number of hospitalisation days for BSI per 1,000 CVC-days.

In the base case, total BSI costs were estimated using BSI event rates and assuming a fixed cost for each BSI event. An alternative approach was adopted in sensitivity analysis whereby a cost per day was estimated for BSI events by dividing the overall cost of £11,268 by an assumed length of stay of 10 days. This cost per day was then applied to the average number of hospitalisation days from Hymes et al. (2017), which reported 4.68 hospitalisation days per 1,000 CVC days for standard caps and 3.24 hospitalisation days per 1,000 CVC days for ClearGuard.

The uncertainty around the magnitude of the potential costs savings that may be accrued through a reduction in BSIs was further explored in sensitivity analyses based on those conducted in NICE MTG25. The external assessment centre (EAC) for NICE MTG25 estimated an alternative cost of £8,868 for CRBSIs by using a bottom-up costing approach based on resource usage advised by experts. This value was inflated to 2020 prices using IMF price indices, giving a cost of £10,002 for each CRBSI event. In addition, the EAC varied the value by ±50% in sensitivity analysis. These alternative values were explored in scenarios considered in the HTW analysis.

There was also uncertainty around the proportion of BSIs reported in Hymes et al. (2017) that are likely to be CRBSIs. In the base case, the cost of managing CRBSIs was applied for all BSIs requiring hospital admission. However, clinical experts advised that is likely to lead to an overestimation and estimated that only 70-80% of the BSIs are likely to be CRBSIs. Therefore, a sensitivity analysis was conducted in which the cost of CRBSI was only applied to 70-80% of the BSIs.

There was also uncertainty around the costs associated with standard caps. Experts advised that standard caps are typically supplied as part of standard catheter kits. Therefore, the impact of assuming no cost for standard catheter caps was explored in sensitivity analysis.

Alternative baseline rates of BSI were also considered in sensitivity analysis based on values presented in NICE MTG25. The value used in the base case analysis in NICE MTG25 was sourced from Bion et al. 2013 a study which reported on an initiative known as 'Matching Michigan', which aimed to reduce CRBSIs in ICU and establish standardised reporting. The value applied in the analysis was from the final quarter of the initiative's timeframe by which time the CRBSI rate had fallen from 3.7 to 1.48 per 1,000 CVC days. NICE MTG25 considered alternative scenarios based on lower estimates reported in the Wales and Scotland. An alternative value of 0.19 CRBSIs per 1,000 CVC days was presented based on a report from Welsh Health Boards of CRBSIs in critical care in 2013 while a value of 0.30 per 1,000 CVC days was presented based on the CRBSI rate in ICUs in Scotland.

### 5.2.3 Results

The results of the analysis are presented in Table 3. It shows that the initial costs are higher due to the increased cost associated with the ClearGuard caps. However, this cost increase was outweighed by downstream cost savings associated with a reduction in the number of BSIs (25 fewer BSIs with antimicrobial caps compared to standard caps with associated cost savings of £279,618). Thus, overall, the use of antimicrobial caps was estimated to result in net savings of £94,064 in this hypothetical cohort of 1,000 patients.

**Table 3. Cost-consequence analysis results (per 1,000 patients)**

| Cost type | Standard Caps | Antimicrobial caps | Difference |
|---|---|---|---|
| Cap costs | £39,600 | £226,286 | £186,686 |
| Alcohol wipe costs | £1,131 | £0.00 | -£1,131 |

| Cost type | Standard Caps | Antimicrobial caps | Difference |
|---|---|---|---|
| CRBSI-related costs | £699,046 | £419,428 | -£279,618 |
| **Total** | **£739,777** | **£645,713** | **-£94,064** |

### 5.2.4 Sensitivity analysis results

The results of the sensitivity analysis are presented in Table 4, which shows the estimated total costs associated with standard caps and antimicrobial caps in a range of different scenarios. It can be seen that the analysis was found to be sensitive to many of the changes considered. Most notably, there were four scenarios where the conclusion of the analysis changed, with antimicrobial caps found to be more costly than standard caps. This included a scenario based on hospitalisation days reported in Hymes et al. (2017), a scenario where the CRBSI cost was reduced by 50% and two scenarios where the baseline CRBSI event rate was lowered to values observed in critical care in Welsh health boards and ICUs in Scotland.

**Table 4. Sensitivity analysis results (per 1,000 patients)**

| Modelled scenario | Total costs | | |
|---|---|---|---|
| | Standard Caps | Antimicrobial caps | Difference |
| Base case | £739,777 | £645,713 | -£94,064 |
| Costs estimated using average number of hospitalisation days from Hymes et al. (2017) | £697,203 | £708,181 | £10,978 |
| CRBSI cost of £10,002 as estimated by the EAC in NICE MTG25 | £676,960 | £608,023 | -£68,937 |
| CRBSI cost + 50% | £1,019,396 | £813,484 | -£205,911 |
| CRBSI cost - 50% | £460,159 | £477,942 | £17,783 |
| CRBSI cost only applied to 70% of BSI events | £530,064 | £519,885 | -£10,179 |
| CRBSI cost only applied to 80% of BSI events | £599,968 | £561,828 | -£38,140 |
| No cost for standard caps | £700,177 | £645,713 | -£54,464 |
| Baseline CRBSI event rate from 'Matching Michigan' study in 2010 (1.48 per 1,000 CVC days) | £2,241,983 | £1,547,036 | -£694,946 |
| Baseline CRBSI event rate from critical care in Welsh health boards in 2013 (0.19 per 1,000 CVC days) | £323,324 | £395,842 | £72,517 |
| Baseline CRBSI event rate from ICUs in Scotland in 2013 (0.30 per 1,000 CVC days) | £486,931 | £494,005 | £7,074 |

## 6. Organisational Issues

At consultation, HTW asked experts for clarification on standard care for the prevention of CRBSIs. Most experts reported use of antimicrobial lock solution and noted that there is standardised care at the local level, but they were not aware of a national standard of care for haemodialysis catheters in Wales. One expert noted that the broad principles of epic3 guidelines on preventing healthcare-associated infections are followed (Loveday et al. 2014).

Two experts noted that the most important change in practice to reduce the number of CRBSIs would be to reduce the number of CVCs in use, namely through early arteriovenous fistula or graft creation.

Users of ClearGuard caps are trained using videos via the company website; further training can be requested at no additional cost (NICE 2020). Health care professionals may also need awareness training regarding chlorhexidine allergy. No cases of chlorhexidine allergy were reported in the studies identified in this review.

## 7. Patient issues

Our literature search did not identify any evidence on patient issues (including patient experience or preference) relating to antimicrobial barrier caps for central venous catheters used in haemodialysis.

## 8. Conclusions

The aim of this review was to address the following question: What is the clinical and cost effectiveness of antimicrobial barrier caps for use with haemodialysis catheter hubs in reducing catheter-related bloodstream infections?

We identified two cluster-randomised trials for ClearGuard HD antimicrobial barrier caps; all outcomes were calculated according to episodes per 1,000 CVC-days. Both studies were undertaken in the US, which may limit the applicability of the outcomes to the Welsh healthcare setting. Furthermore, one expert noted that use of Tego in Wales appears to be low, which may limit the usefulness of Tego as a comparator.

In both studies, ClearGuard demonstrated improved overall rates of BSIs compared to both standard caps, and a needle-free connector plus antiseptic cap (Tego+Curos), respectively. The study that compared ClearGuard with Tego+Curos reported both CRBSI and CLABSI rates; both were significantly lower in the ClearGuard group than the Tego+Curos group.

Compared to standard caps, ClearGuard had significantly lower rates of hospital admission, but did not demonstrate significant differences in hospitalisation-days during the 12-month period. Sub-analyses of the last six months of the study period, where PBC rates in the standard caps group had increased, did subsequently show significantly lower rates of hospital admissions and hospitalisation-days in the ClearGuard group by comparison. However, it is uncertain what factors led to the continual increase in PBC rates in the control arm throughout the study period. The authors suggest seasonal trending; expert input noted that the cause is likely multifactorial, and most experts had not observed this trend in their own experience. It is also unclear whether the study was designed and powered for such analyses. Hospitalisation outcomes were not reported in the study that compared ClearGuard with Tego+Curos.

Rate of IV antibiotic starts also did not differ between ClearGuard and standard caps. However, IV antibiotic starts were significantly lower in the ClearGuard group when compared to Tego+Curos in the other study.

Both studies reported no device-related adverse events.

An additional retrospective analysis was identified which demonstrated significantly fewer CLABSIs in a ClearGuard Group compared to Tego alone. However, study design had several limitations, which limits the generalisability of the findings.

Experts at consultation noted that antimicrobial lock solution is used in Welsh centres. Antimicrobial lock solution as a comparator was included in the evidence selection criteria, but we did not find any evidence comparing antimicrobial caps to antimicrobial lock solution.

No relevant economic evidence was identified in the literature. An economic analysis developed by HTW suggested that the additional upfront costs associated with ClearGuard caps may be outweighed by savings accrued through a reduction in BSI events. However, there is uncertainty around the baseline BSI event rate in Wales and the costs associated with managing BSI events. Sensitivity analysis revealed that the analysis is sensitive to changes in key input parameters, with ClearGuard caps found to be more costly overall in some of the alternative scenarios modelled.

## 9. Contributors

The HTW staff and contract researchers involved in writing this report were:

- J Washington, Information Specialist – literature searches
- L Elston, Health Services Researcher – clinical author
- M Prettyjohns, Principal Researcher – health economics author
- A Evans, PPI Officer – PPI lead
- K McDermott, Project Manager – project management

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

Experts who contributed to this appraisal:

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- Doug Killion, Vi Vice President, ClearGuard Commercial Operations, ICU Medical
- Kieron Donavan, Consultant Nephrologist and Senior Lecturer
- Peter Phillips, Director, SMTL.

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## 11. Evidence review methods

We searched for evidence that could be used to answer the review question: What is the clinical and cost effectiveness of antimicrobial barrier caps for use with haemodialysis catheter hubs in reducing catheter-related bloodstream infections?

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts. Appendix 2 gives details of the search strategy used for Medline. Search strategies for other databases are available on request.

Appendix 3 summarises the selection of articles for inclusion in the review.

## Appendix 1. Inclusion and exclusion criteria for evidence included in the review

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | People who receive central venous catheters for haemodialysis | |
| **Intervention** | Antimicrobial barrier caps for use with haemodialysis catheter hubs, including ClearGuard HD cap | |
| **Comparison/ Comparators** | Other antimicrobial interventions such as:<br>• 'scrubbing' of the hub with % chlorhexidine gluconate in 70% alcohol<br>• Antimicrobial lock solutions<br>Standard central venous catheter caps. | |
| **Outcome measures** | • Reduction in catheter-related bloodstream infections (CRBSIs)<br>• Reduction in central line-associated bloodstream infections (CLABSIs)<br>• Infection-related morbidity or mortality<br>• Adverse events<br>• Cost | |
| **Study design** | We will prioritise the following study types, in the order listed:<br>• Systematic reviews.<br>• Randomised comparative trials.<br>• Non-randomised comparative trials.<br>• Single-arm trials that report any relevant outcome.<br>We will only include evidence for " lower priority" evidence where outcomes for each condition/symptom of interest are not reported by a " higher priority" source.<br>We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison. | |
| **Search limits** | Studies in English | |
| **Other factors** | None | |

# Appendix 2. Medline search strategy

| Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 19, 2021> | | |
|---|---|---|
| **Product Name** | | |
| 1 | (clearguard or curos or swabcap or tego connector).tw. | 10 |
| **Haemodialysis** | | |
| 2 | exp Renal Dialysis/ | 115620 |
| 3 | (hemod?al?s* or haemod?al?s*).tw. | 79048 |
| 4 | (renal adj2 dialys*).tw. | 2911 |
| 5 | or/2-4 | 138107 |
| **Central Venous Catheters** | | |
| 6 | Central Venous Catheters/ | 2530 |
| 7 | Catheterization, Central Venous/ | 15437 |
| 8 | Catheters, Indwelling/ | 18809 |
| 9 | (central venous catheter* or CVC or CVCs).tw. | 14285 |
| 10 | (catheter* adj2 (hub*2 or cap*2)).tw. | 385 |
| 11 | (central adj2 line*).tw. | 5406 |
| 12 | or/6-11 | 41920 |
| **Anti-infective agents** | | |
| 13 | anti-infective agents, local/ | 17166 |
| 14 | ((antimicrobial or anti-microbial or antiseptic or anti-septic or antiinfective or anti-infective) adj2 (hub*2 or cap*2)).tw. | 151 |
| 15 | ((antimicrobial or anti-microbial or antiseptic or anti-septic or antiinfective or anti-infective) adj2 (agent* or lock*)).tw. | 28205 |
| 16 | Chlorhexidine/ | 8535 |
| 17 | (chlorhexidine or chlorohexidine or chlorohexadine or chlorhexadine).tw. | 11120 |
| 18 | or/13-17 | 52993 |
| **Set Combination** | | |
| 19 | (5 or 12) and 18 | 1340 |
| 20 | 19 or 1 | 1348 |
| 21 | limit 20 to english language | 1252 |

## Appendix 3. Flow diagram outlining selection of relevant evidence sources