NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

ClearGuard HD antimicrobial barrier caps for preventing haemodialysis catheter-related bloodstream infections

How medical technology guidance supports innovation

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 ClearGuard HD antimicrobial barrier caps are recommended for preventing catheter-related bloodstream infections in people with central venous catheters having haemodialysis.

1.2 Do not use ClearGuard HD caps in people allergic to chlorhexidine.

1.3 Cost modelling shows that over 1 year ClearGuard HD caps are likely to be cost saving compared with standard treatments. ClearGuard HD caps are estimated to save, per person:

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- £351 compared with standard caps and wipes
- £1,096 compared with antimicrobial line lock solution, standard caps and wipes
- £568 compared with Tego needleless connector and Curos disinfecting caps.

  Savings were from the lower incidence rate and associated cost of treating catheter-related bloodstream infection with ClearGuard HD caps.

Why the committee made these recommendations

ClearGuard HD caps are used with central venous catheters in haemodialysis. They are different from standard caps because they contain a rod that is coated in the antimicrobial chlorhexidine acetate to prevent infection. Other options for preventing infection are the Curos disinfecting cap, used with Tego needleless connectors, and antimicrobial line lock solutions.

Clinical evidence shows that using ClearGuard HD caps instead of standard caps, Tego plus Curos, or line lock solutions reduces the risk of catheter-related bloodstream infections.

Cost analysis shows that they lead to cost savings because of reduced infections.

Therefore, ClearGuard HD caps are recommended.

2 The technology

2.1 ClearGuard HD antimicrobial barrier caps (ICU Medical) are for use with central venous catheters (CVC) in haemodialysis. The cap has a rod that extends into the CVC hub. The rod and cap threads are coated in chlorhexidine acetate, a broad-spectrum antimicrobial that aims to reduce pathogenic organisms in the CVC lock and therefore reduce the risk of catheter-related bloodstream infections (CRBSI).

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Care pathway

2.2 ClearGuard HD caps are for use on CVC lines between haemodialysis sessions to reduce the risk of infections. They replace standard caps and wipes. Other options include the Curos disinfecting cap (recommended for further research by NICE) used with Tego needleless connectors, and antimicrobial line lock solutions. ClearGuard HD caps cannot be reused once removed and need to be replaced during every dialysis session. The recommended maximum use time for the cap is 3 days. The caps are not currently used in the NHS. The external assessment centre and experts do not believe that using ClearGuard HD caps would alter the current pathway and say that minimal training is needed.

Innovative aspects

2.3 ClearGuard HD caps have a coating of chlorhexidine acetate, a broad-spectrum antimicrobial agent, on the rod and cap threads. They release chlorhexidine acetate into the catheter lock solution, which remains inside the catheter hub in between treatments.

Intended use

2.4 ClearGuard HD antimicrobial caps are an alternative to standard caps, or caps and connectors, on central venous catheters, to reduce the risk of CRBSI during haemodialysis for end-stage kidney disease.

2.5 ClearGuard HD antimicrobial caps are for use by healthcare professionals trained in haemodialysis. The company and experts agree that minimal training would be needed. The caps can also be used by patients and carers doing haemodialysis at home, after they have had training in safe home haemodialysis.

Costs

2.6 ClearGuard HD caps cost £4 per pair. Haemodialysis would normally be needed 3 times a week and the caps are replaced at each dialysis session, leading to a cost of £12 a week. The company has estimated that

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haemodialysis patients would need a CVC for an average of 132 days (estimated by the company based on Kwak et al. 2012, Crowley et al. 2017 and Hymes et al. 2017) until a more permanent form of vascular access is established. This results in a cost of £226 per person over this period.

2.7 Clinical experts said that the 'scrub the hub' disinfection practice is likely to continue, so alongside wipes the total cost is £247 for an average of 132 days of haemodialysis.

For more details, see the website for ClearGuard HD antimicrobial barrier caps.

3 Evidence

NICE commissioned an external assessment centre (EAC) to review the evidence submitted by the company. This section summarises that review. Full details of all the evidence are in the project documents on the NICE website.

Clinical evidence

The main clinical evidence comprises 6 studies

3.1 The company submitted 7 studies from its literature search, including 3 full-text papers (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 accepted 6, excluding Nitz et al. because the intervention and outcomes did not match the scope and because it felt it did not add to the decision problem. The 3 full-text papers included a total of 10,757 participants. For full details of the clinical evidence, see section 4 of the assessment report.

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The 2 prospective cluster randomised controlled trials are the most relevant to the decision problem

3.2 Brunelli et al. and Hymes et al. were the most relevant to the decision problem. Both were prospective, multicentre, open-label cluster randomised controlled trials, which included 40 sites each. Outcomes varied. Brunelli et al. compared ClearGuard HD caps with Tego (needleless connectors) plus Curos (disinfecting caps). Hymes et al. compared ClearGuard HD caps with standard central venous catheter (CVC) caps.

The other studies are observational and at high risk of bias

3.3 The remaining full-text paper (Weiss et al.) described a large retrospective analysis but was considered methodologically weak. The abstracts (Glennon et al., Li et al., Sibbel et al.) were all retrospective analyses with limited detail and do not add much more to the decision problem. The studies had largely homogenous populations. The proportion of men ranged from 51% to 53% and mean ages were 61.1 years to 62.8 years (except for Glennon et al., which studied children).

The pivotal trials report significantly reduced positive blood cultures

3.4 Most of the studies reported bloodstream infection rates, although they did not always use the same terminology. Positive blood cultures were the primary outcome in the randomised controlled trials. They both reported significantly lower positive blood culture rates for the ClearGuard group than in the comparator group. The incidence rate ratio (IRR) in Hymes was 0.44 (p=0.01) and in Brunelli 0.37 (p=0.001).

Other outcome measures included hospital admissions and mortality

3.5 Rates of hospital admission and stays were lower for the ClearGuard group in 3 studies (Brunelli et al., Hymes et al. and Sibbel et al.), although this was not significant in Brunelli et al. Not many of the studies reported length of hospital stay or rates of mortality. None of them reported intravenous antibiotic use or staff time.

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Nine adverse events are reported in MAUDE and none in the full-text papers

3.6 There are 9 records of adverse events on the US Food and Drug Administration's (FDA) MAUDE (Manufacturer and User Facility Device Experience) database. Two reported that the caps came off for 1 patient. Six reported that the caps became detached while the patients were asleep. One reported that the rod broke loose in the catheter. No patients were injured. None of the full-text papers reported adverse events. For full details of the adverse events, see section 6 of the assessment report.

Cost evidence

One abstract in the company's submission estimates costs

3.7 An abstract by Glennon et al. 2020 estimated total annual costs per patient for ClearGuard HD caps of £7,078, compared with £18,050 for antimicrobial lock solutions. This was estimated from 4 high-risk children having dialysis. The EAC noted that the authors did not do any sensitivity analysis to assess how robust the cost and rate were. It also noted that the applicability of the results to an adult setting was not certain.

The company's model compares ClearGuard HD caps against 4 comparators

3.8 The model included a decision tree that looked at cost savings with ClearGuard HD caps against 4 relevant comparators:

- standard CVC caps plus alcohol wipes for disinfection
- standard CVC caps plus antimicrobial lock solution and alcohol wipes for disinfection
- Tego needleless connectors plus Curos disinfecting caps (Tego plus Curos)
- Tego needleless connectors on their own, with manual decontamination of the catheter hub with alcohol wipes.

The model had a 1-year time horizon for cost and health outcomes. For full details of the cost evidence, see section 4 of the assessment report.

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The EAC's minor amendments to the model and parameters address mortality, comparators and disinfection protocols

3.9 The EAC agreed that the overall structure of the model, time horizon, population, most comparators, outcomes, and assumptions were acceptable and appropriate for the assessment. The EAC excluded the mortality branch, reporting that the cost of caps and cost of treating catheter-related bloodstream infections (CRBSI) was adequate without the need for the mortality branch. One comparator (scenario 5, Tego needleless connectors) was excluded, because it is a connector alone and therefore out of scope. The EAC provided additional analysis in the ClearGuard HD caps arm around disinfection protocols when using ClearGuard HD caps. This was based on discussions with clinical experts, who expected these disinfection protocols to still be used.

Sensitivity analysis shows cost savings are from baseline incidence rate of infection with ClearGuard, comparators and the cost of treating CRBSI

3.10 The EAC recommended that all parameters not validated by clinical data should be varied up and down by 50% in the sensitivity analysis. The EAC's results were similar to the company's. 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
- the average cost of treating CRBSI.

Cost savings remain even when CRBSI incidence rate is increased in the ClearGuard group

3.11 The company did 4 'worst case' scenario analyses, in which the base case baseline infection rate associated with each of the 4 comparators was at the lower end of the value range. The IRR of CRBSI with ClearGuard was at the upper end of the value range. For these scenarios, based on clinical expert opinion and varying clinical estimates from published studies, the EAC recommended varying the parameters up and

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down by 50%, or by a range informed by the evidence (rather than up and down by the 25% suggested by the company). ClearGuard remained cost saving in all the scenarios. Another scenario reduced the cost of antimicrobial lock solution: ClearGuard remained cost saving by £418.

Threshold analysis of baseline infections shows ClearGuard HD caps are still cost saving at infection rates that are clinically unlikely

3.12 The scenario analysis results are also supported by the EAC's threshold analysis. This reported cost neutral break-even points for different CRBSI incidence rates per 1,000 CVC days:

- 0.228 with standard caps (baseline rate was 0.7)
- 0.000001 with antimicrobial lock solution (baseline rate was 0.598)
- 0.111 with standard caps (baseline rate was 0.63).

ClearGuard HD caps remain cost saving when the cost of standard caps is reduced

3.13 Experts and committee members flagged discrepancies in agency costs of standard caps compared with the cost model, which were likely to be because of volume discounts in practice. The EAC input the reported value of £0.03 for the cost of standard caps into the model. ClearGuard remained cost saving compared with:

- standard caps and wipes by £351 (from £387)
- standard caps, antimicrobial lock solution and wipes by £1,096 (from £1,132).

ClearGuard HD caps are cost saving over all comparators in the EAC's update to the model

3.14 The final results showed ClearGuard HD caps were cost saving compared with all the 4 comparators. The company submission reports cost savings per patient of:

- £408 against standard caps and wipes

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- £1,167 against standard caps, antimicrobial lock solution and wipes.

The EAC's revised base case cost savings, with added disinfection costs in the ClearGuard HD caps arm, showed cost savings per patient of:

- £387 against standard caps and wipes
- £1,132 against standard caps, antimicrobial lock solution and wipes.

4 Committee discussion

Clinical evidence overview

Evidence shows that ClearGuard HD caps reduce the risk of catheter-related bloodstream infections

4.1 The committee noted that the literature consistently showed lower infection rates with ClearGuard compared with other options. It considered the 2 randomised controlled trials to be pivotal for decision making. While the studies had some risk of bias, the committee was reassured by the relatively large effect sizes. The way bloodstream infections were measured and reported varied across the evidence. Clinical experts said that this was a common problem in clinical studies and NHS practice. The primary end point in both randomised controlled trials was positive blood cultures. The committee understood that this end point was not specifically attributable to infections arising in the central venous catheters, but nevertheless it was satisfied by the overall weight of evidence that ClearGuard HD caps are likely to reduce the risk of catheter-related bloodstream infections (CRBSI).

The evidence is generalisable to children

4.2 A clinical expert discussed the potential benefit in children who may need a central line long term, and for whom recurrent infections could limit treatment options in the future. The clinical experts said they considered the incidence rates in the adult studies to be comparable and

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generalisable to children. They also highlighted some evidence of a benefit for children in Glennon et al. (2020), which was in high-risk children, although this evidence is lower quality because it was a retrospective analysis with limited detail and reported as an abstract only. On balance, the committee concluded that the evidence in adults could be generalised to children.

ClearGuard HD caps may benefit people who have haemodialysis at home

4.3 Clinical experts said that more central venous catheters were now being used, rather than surgical fistulas, because of the COVID-19 pandemic. They agreed that the aim was for more people of all ages to use home dialysis. But no evidence was identified on using ClearGuard HD caps at home. The committee felt that they could benefit people having dialysis at home and was encouraged by positive feedback provided by the company from users about their usability. Clinical experts said that in their experience these patients are motivated, and so they did not see any barriers to using the caps safely and effectively at home, as long as people were trained in how to use them.

Safety considerations

ClearGuard HD caps are safe and compatible with central lines used in clinical practice

4.4 The committee discussed the ClearGuard HD caps' compatibility with central lines. It was satisfied that the only central line that they were incompatible with was one that is seldom used. The company confirmed that the caps had been shown to be compatible with other line lock solutions, as part of US Food and Drug Administration (FDA) benchmarking assessments, including heparin-saline, saline and citrate. The committee discussed 1 adverse event reported on the FDA's MAUDE (Manufacturer and User Facility Device Experience) database, of rod detachment. The committee was reassured by the company that the cap

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had been examined, was not replicable, and that the problem has not been reported before or since.

The long-term implications for chlorhexidine allergy should be monitored

4.5 The rod and cap threads of ClearGuard HD caps are coated in chlorhexidine acetate, a broad-spectrum antimicrobial agent. Some people are allergic to chlorhexidine although, according to the clinical experts, this is unusual. The clinical experts reported that in their experience allergy shows more commonly as a skin reaction, although people can have anaphylactic reactions to chlorhexidine. The committee was concerned that we do not yet know the long-term effects of exposure to chlorhexidine acetate, and in particular if people could become sensitised to it. Because of this, the committee asked the company to proactively find out about adverse events and report them to the Medicines and Healthcare products Regulatory Agency (MHRA). The committee advised the company to provide a plan to monitor chlorhexidine sensitisation or allergies to address this gap in understanding for the future.

NHS considerations overview

The evidence is generalisable to NHS practice

4.6 The clinical evidence base was all from the US and North America. The clinical experts said that the baseline rates of catheter-related bloodstream infection in the US studies were broadly comparable to UK NHS practice. A difference between the US and UK is that high concentrate citrate is used as a catheter lock solution for adults in the UK. But it is not approved for use in this way in the US and therefore was not included in the evidence. The committee agreed that, although citrate's effect on reducing infection rates was uncertain, it was likely to be comparable to the antimicrobial line lock solution comparator in the evidence. The committee concluded that the evidence was broadly

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generalisable to NHS practice and was a reasonable basis for decision-making purposes.

No significant changes to infrastructure are needed

4.7 The clinical experts said that the 'scrub the hub' disinfection practice would continue regardless of the cap used during haemodialysis. The external assessment centre (EAC) acknowledged this in its minor amendments to the company model. The committee was satisfied that this accurately showed how the caps would be used in NHS practice. It agreed that no additional changes to NHS infrastructure would be needed to use ClearGuard HD caps in the NHS.

Cost evidence overview

The cost model for ClearGuard HD caps is well constructed and shows cost savings against all comparators

4.8 The cost model was well constructed, and the minor changes made by the EAC were appropriate and accepted by the committee. The committee concluded that the comprehensive sensitivity and scenario analysis supported cost savings against all comparators.

The model's main cost drivers are the comparators' infection incidence rate and ClearGuard HD caps' infection rate ratio

4.9 The main cost savings were from reduced CRBSI incidence rate. The committee discussed the uncertainty around incidence levels across comparators but concluded that the evidence was strong enough and backed by clinical expert opinion, indicating that there were likely to be costs savings in practice.

Sensitivity analysis adequately addresses the uncertainty around outcomes and comparators

4.10 The end points used in the pivotal clinical studies (positive blood cultures) introduced some uncertainty in the outcomes. However, the committee was satisfied that the EAC's extra sensitivity analysis adequately

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addressed the likely variation in incidence. There was some uncertainty around whether the model results were applicable to the NHS, when the evidence used to inform it did not include the comparator high concentrate citrate, which is used in the UK but not in the US (see section 4.6). The clinical experts said infection rates with high concentrate citrate were likely to be comparable to the antimicrobial line lock solution comparator used in the scenario analyses, which showed that even at low rates of baseline infection, ClearGuard HD caps were cost saving. The EAC's sensitivity analyses also showed cost savings at even lower rates of infection. The committee therefore concluded that the sensitivity analysis adequately addressed uncertainty around this comparator.

Cost savings

ClearGuard HD caps are likely to be cost saving against all comparators

4.11 Comprehensive scenario analyses, including 'worst case' scenarios, showed ClearGuard HD caps to be cost saving against all comparators. Additional threshold analysis reported cost neutral infection thresholds that clinical experts advised were clinically unlikely because they were so low. The committee was satisfied that the cost modelling evidence was robust and shows ClearGuard HD caps are cost saving against all comparators.

The EAC revised the base case cost savings, with added disinfection costs in the ClearGuard HD caps arm, and reduced standard caps costs because of volume discount, resulting in cost savings per patient of:

- £351 compared with standard caps and wipes
- £1,096 compared with antimicrobial line lock solution, standard caps and wipes
- £568 compared with Tego needleless connectors and Curos disinfecting caps.

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5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technologies advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more health technology assessment analysts (who act as technical leads for the topic), a health technology assessment adviser and a project manager.

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