NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

The 3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites

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 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's submission of evidence and with the EAC 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 7, following the summaries of the clinical and cost evidence.

This overview also contains:

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

1 The technology

The 3M Tegaderm CHG IV securement dressing (3M, 'Tegaderm CHG') is a sterile transparent semipermeable polyurethane adhesive dressing with an integrated gel pad containing a 2% concentration by weight of chlorhexidine gluconate (CHG). It is used to secure percutaneous devices and to cover and protect central venous and arterial catheter insertion sites with the aim of providing an effective barrier against external contamination. The dressing and the integrated gel pad are transparent to allow continual observation of the catheter insertion site. The integrated gel pad is designed to reduce skin and catheter colonisation in order to suppress regrowth of microorganisms commonly related to catheter-related bloodstream infections (CRBSI) at the catheter insertion site.

The 3M Tegaderm CHG IV securement dressing was CE-marked as a class 3 device in April 2009 to cover and protect catheter sites and to secure devices to the skin. There was a modification to the dressing design in 2011 to incorporate a breathable film.

2 Proposed use of the technology

2.1 Disease or condition

Catheter-related bloodstream infections (CRBSI) are estimated to account for 42.3% of all bloodstream infections, based on a 2006 prevalence survey. They are a significant cause of mortality and morbidity in critically ill patients. In these patients estimates of mortality attributable to CRBSI vary between 12% and 25%, and in those who survive, length of stay in hospital is increased by around 3 weeks.

2.2 Patient group

The Tegaderm CHG dressing was notified for use in critically ill adult patients in intensive care or high dependency units who need a central venous or

arterial catheter. Hospital Episodes Statistics data for 2012/13 show that there were 237,710 adult intensive care unit (ICU) episodes in England, 92,710 of which involved a stay of over 48 hours. Expert advice made available to the company suggests that a central venous catheter is used in 95% of adult ICU patients.

2.3 Current management

NICE's guideline on infection provides guidance on the use of dressings in adults and children with vascular access devices (central venous catheter or peripherally inserted central catheter) in primary and community care settings. The guideline recommends that the skin at the central venous catheter insertion site, and the surrounding skin during dressing changes, should be decontaminated with CHG in 70% alcohol and be allowed to air dry. Where the company's recommendations prohibit the use of alcohol with their catheters, an aqueous solution of CHG should be considered for use. It further recommends using a sterile, transparent semipermeable membrane dressing to cover the vascular access device insertion site, and that the dressing should be changed every 7 days or sooner if it is no longer intact or moisture collects under it. A sterile gauze dressing, covered with a sterile transparent semipermeable dressing, should be considered for use only if the patient has profuse perspiration, or if the vascular access device insertion site is bleeding or oozing. The guideline states that systemic antimicrobial prophylaxis should not be used routinely to prevent catheter colonisation or CRBSI, either before insertion or during the use of a central venous catheter. It makes no recommendations about the use of CHG impregnated dressings. However the full guidance document notes that they may be cost effective compared with sterile transparent semipermeable membrane dressings based on limited evidence from 1 study.

The Healthcare Infection Society's epic3 guideline on preventing healthcare-associated infections in NHS hospitals in England recommends using a sterile transparent semipermeable dressing to cover the intravascular insertion point

as best practice in both adults and children. The guideline recommends, based on high-quality evidence (grade A), a single application of 2% CHG in 70% isopropyl alcohol (or povidone iodine alcohol for patients with sensitivity to CHG) to clean the central catheter insertion site during dressing changes, and allow to air dry. The guideline also recommends, based on evidence of limited quality, that hospitals consider the use of a CHG-impregnated sponge dressing in adults with a central venous catheter, as a strategy to reduce CRBSI.

NICE's evidence update on infection concluded that the evidence on which the epic3 recommendation for the use of CHG-impregnated sponges is based is unlikely to have an impact on NICE's clinical guideline on infection, and that further research is needed to establish the efficacy of CHG dressings applied to CHG-prepped skin to prevent CRBSI in patients with venous access devices.

2.4 Proposed management with new technology

Tegaderm CHG was notified to the Medical Technologies Evaluation Programme for intensive care or high dependency unit patients needing a central venous or arterial catheter to reduce catheter-related infections, specifically CRBSI. It would be used in the current pathway where a sterile, transparent semipermeable membrane dressing is currently indicated.

2.5 Equality issues

No equality issues were identified.

3 Company's claimed benefits

The benefits to patients claimed by the company compared with standard care are:

- A 60% reduction in the incidence of catheter-related bloodstream infection (CRBSI) in critical care patients with intravascular catheters.

- Reduced risk of mortality due to catheter-related infections.
- Reduced incidence of skin and catheter colonisation during treatment with central venous catheters or arterial catheters.

The benefits to the health system claimed by the company compared with standard care are:

- Reduced length of stay in critical care/high dependency units.
- Reduced costs for diagnosis of CRBSI.
- Reduced material and staff costs for treatment of catheter-related infection.

4 Decision problem

Table 1 Summary of the decision problem

Population	Critically ill adult patients in intensive care or high dependency units who need a central venous or arterial catheter.
Intervention	Swabbing with 2% chlorhexidine gluconate (CHG) in alcohol and Tegaderm CHG IV securement dressing.
Comparator(s)	Swabbing with 2% CHG in alcohol and sterile semipermeable transparent dressing. Swabbing with 2% CHG in alcohol and CHG-impregnated dressing.
Outcomes	The outcome measures to consider include: • catheter-related bloodstream infection (CRBSI) and associated antimicrobial use • skin and catheter colonisation • length of stay in critical care/high dependency units • mortality caused by catheter-related infections • dermatitis • local site infection • quality of life • device-related adverse events, including adverse events caused by contact with CHG
Cost analysis	Two comparators will be considered: • Swabbing with 2% CHG in alcohol and a sterile semipermeable transparent dressing. • Swabbing with 2% CHG in alcohol and a CHG-impregnated dressing. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be done to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Special considerations, including issues related to equality	None identified.

No variations to the decision problem were proposed by the company.

5 The evidence

5.1 Summary of evidence of clinical benefit

The company carried out a literature review (figure 3, page 33 of the company's submission summarises the selection process) identifying 5 studies which met their inclusion criteria. Three studies, Maryniak et al. (2009), Olson et al. (2008) and Rupp et al. (2008), all reported nursing satisfaction scores on various aspects of dressing design and performance. The company excluded these on the grounds that the instruments or scales used could not be validated, and none included data on catheter-related bloodstream infection (CRBSI) rates. An unpublished study by Scoppettuolo et al. (2012) was also excluded. It reported interim results on a terminated study which involved both intensive care unit (ICU) and non-ICU patients so it was not in a format relevant to the patient population in the decision problem. These studies are discussed in detail on pages 37–41 of the company's submission.

The company presented the remaining study, which is a randomised controlled trial by Timsit et al. (2012). The External Assessment Centre (EAC) agreed with the inclusion of this study and the exclusion of the 4 remaining studies identified.

The EAC carried out a further literature search to identify all prospective comparative studies including at least 2 of the 3 dressing types in the scope: Tegaderm CHG, a standard dressing and a CHG-impregnated dressing. This search returned 1755 records of which 4 were considered relevant (page 41 of the assessment report). Two of the studies identified involved Tegaderm, one of which was presented by the company (Timsit et al. 2012), the second of which was identified as an ongoing study by the company (Karpanen et al. 2014), and had published interim results after the company's submission of evidence. The EAC considered the Timsit et al. (2012) study to be relevant to the decision problem despite the fact that both the intervention and control

groups were not swabbed with 2% chlorhexidine gluconate (CHG) in alcohol as specified in the decision problem. The other 2 studies (Timsit et al. 2009 and Roberts et al. 1998) compared a CHG-impregnated sponge dressing (Biopatch) and standard dressings, and were included by the EAC in order to provide an indirect comparison between Tegaderm CHG and a CHG-impregnated dressing (a comparator in the decision problem).

Details of the studies are summarised in table 2 and described in detail in tables 3.3–3.6 and pages 45 to 64 of the assessment report. Results from these studies are summarised below and discussed in more detail in table 3.9 and pages 66–76 of the assessment report.

Timsit et al. (2012) reported a large multicentre randomised controlled trial, based in 12 French ICUs, involving 1879 patients using 4163 catheters. Patients needing intravascular access were randomised to 1 of 3 groups: Tegaderm CHG (938 patients), standard dressing (Tegaderm Transparent Film Dressing; 476 patients) or highly adhesive dressing (Tegaderm HP Transparent Film Dressing; 465 patients). Assessors of suspected infection were blinded to dressing type. Included patients had their skin prepped with alcohol-PVI or alcohol chlorhexidine (0.5%). Dressings were replaced after 24 hours and then every 3–7 days according to centre, or as needed if there was leaking or soiling. The study follow-up period was 48 hours post discharge from ICU. Outcomes were reported on an intention to treat (ITT) basis. These were reported for each group, and comparative statistical analyses were done between the Tegaderm CHG group and the 2 non-CHG dressings groups combined (standard and highly adhesive), and between the standard dressing group and the highly adhesive dressing group.

Results showed that CRBSI rates were significantly lower in those who used Tegaderm CHG, at 0.5 days per 1000 catheter days compared with 1.3 for both the highly adhesive, and standard dressing groups (hazard ratio [HR] CHG compared with non-CHG 0.402; 95% confidence interval [CI] 0.306 to 0.556, p=0.02). Catheter and skin colonisation were significantly lower in the

Tegaderm CHG group at 4.3 per 1000 catheter days compared with 9.6 for the standard dressing group, and 12.5 for the highly adhesive group (HR [CHG compared with non-CHG] 0.412; 95% CI 0.306 to 0.556, p<0.0001). Major catheter-related infections were also significantly lower in those receiving Tegaderm CHG at 0.7 per 1000 catheter days compared with 2.3 for the standard dressing group and 1.9 for the highly adhesive (HR [CHG compared with non-CHG] 0.328; 95% CI 0.174 to 0.619, p=0.0006). Patients receiving a Tegaderm CHG dressing had a significantly higher rate of severe contact dermatitis needing removal of the dressing, 1.1% compared with 0.1% for the standard dressing and 0.5% for the highly adhesive dressing, p<0.0001. Also, abnormal International Contact Dermatitis Research Group (ICDRG) scores, measured at each dressing change and at catheter removal, were significantly higher for Tegaderm CHG at 2.3% , compared with 1% for the non-CHG dressings (0.7% for the standard dressing and 1.4% for the highly adhesive dressing), p<0.0001. No systemic adverse events were reported. The authors concluded that Tegaderm CHG was associated with a lower rate of major catheter-related infections.

Karpanen et al. (2014) reported interim results, in the form of a poster presentation, of a prospective comparative study of 273 ICU patients at University Hospitals Birmingham NHS Foundation Trust. Patients were randomised to Tegaderm CHG or a standard dressing (Tegaderm IV dressing). Patients in both groups had standard catheter care, including skin preparation with ChloraPrep, an antiseptic with 2% CHG in 70% alcohol. Based on interim results in the 273 patients, there were 10 (7.4%) instances of central venous catheter intradermal section colonisation in the Tegaderm CHG group compared with 22 (16.1%) in the standard dressing group, p=0.037. Ten instances of central venous catheter tip colonisation have been reported in the Tegaderm CHG group (7.4%) compared with 20 (14.6%) in the standard dressing group, p=0.08. Adverse events were not reported. The authors concluded that the adoption of Tegaderm CHG reduced bacterial

numbers on the skin, and reduced the bacterial load at the central venous catheter insertion site.

Studies on the comparator technologies

Timsit et al. (2009) reported on a multicentre, 2×2 factorial randomised controlled trial involving 1636 patients in 7 French ICUs. Patients were randomised to 1 of 4 groups by both dressing type (CHG-impregnated sponge [Biopatch] plus standard dressing or standard dressing alone) and frequency of dressing change (every 3 or 7 days). In all patients an antiseptic solution of 5% povidone iodine in 70% ethanol was applied and all dressings were changed 24 hours after catheter insertion. The follow-up period was 48 hours post discharge from ICU, and all outcomes were based on ITT analyses. The study had 2 aims: to assess the superiority of a CHG-impregnated disk in relation to major catheter-related infection; and to determine the impact on outcomes of a 3 or 7 day dressing change frequency.

Results from the study indicated that CRBSI rates were significantly lower in the CHG-impregnated sponge group at 0.4 per 1000 catheter days compared with 1.3 for the standard dressing group (HR 0.24; 95% CI 0.09 to 0.65, p=0.005). Catheter and skin colonisation rates were significantly lower in the CHG-impregnated sponge group, 0.6 per 1000 catheter days compared with 1.4 for standard dressing (HR 0.36; 95% CI 0.28 to 0.46), p<0.001). Major catheter-related infection rates were significantly lower in the CHG-impregnated sponge group, 0.6 per 1000 catheter days compared with 1.4 for the standard dressing (HR 0.39; 95% CI 0.16 to 0.93, p=0.03). There was no statistically significant difference in these outcomes between the 3 or 7 day dressing change interval groups. The rate of severe contact dermatitis needing removal of dressing was 0.53% for the CHG-impregnated sponge, 0% for the standard dressing (no statistical analyses reported). Abnormal International Contact Dermatitis Research Group ICDRG scores, measured at each dressing change and at catheter removal, were significantly higher for Biopatch at 1.49%, compared with 1.02% for the standard dressing, p=0.02.

No systemic adverse events were reported. The authors concluded that the CHG-impregnated sponge was associated with a reduction in risk of infection, even with low background infection rates.

Roberts et al. (1998) carried out a single-centre randomised controlled trial involving 32 patients with 40 catheters in an Australian ICU. Patients were randomised to receive a CHG-impregnated sponge (Biopatch) plus a standard dressing or a standard dressing alone (Opsite IV 3000, Smith and Nephew). Skin was prepared with 0.5% CHG in alcohol and dressings were changed every 3 days. There was 1 CRBSI in the CHG-impregnated sponge group, and 0 in the standard dressing group (p-value not reported). There were 2 instances of catheter colonisation on the central venous catheter tip, and 4 at the exit site in the CHG-impregnated sponge group compared with 1 and 3 respectively for the standard dressing group; neither difference was statistically significant. Adverse events were not reported. The authors noted that there was insufficient data to draw conclusions from this study.

Ease of use and performance

The EAC collated evidence from the company and its own searches relating to the ease of use of Tegaderm CHG and obtained expert advice on the ease of use and performance of the dressings.

Maryniak et al. (2009) reported a prospective observational study involving 217 inpatients or outpatients (107 Tegaderm CHG and 110 standard dressing). Olson et al. (2008) carried out a randomised controlled trial with 63 hospitalised patients (33 Tegaderm CHG and 30 standard care), some of whom were in ICUs. Finally, Rupp et al. (2008) completed a randomised controlled trial with 60 hospitalised patients (30 Tegaderm CHG and 30 standard care). All these studies were done in the USA, none of them considered critically ill patients specifically and satisfaction with the dressings was judged by the clinical staff. In summary, nurses were statistically significantly more satisfied with Tegaderm CHG than standard dressings in all 3 studies ($p<0.05$). Tegaderm CHG was reported to provide a more

satisfactory dressing securement, was easier to apply, and improved dressing adherence. There were mixed results in terms of nurse satisfaction with ease of correct application, transparency (site visibility) and ease of dressing removal, and reported patient discomfort levels. However, differences rarely reached significance.

The EAC identified a number of studies comparing the ease of use of Tegaderm CHG with a CHG-impregnated sponge. Eyberg at al. (2008) reported a randomised controlled trial comparing Tegaderm CHG with a CHG-impregnated sponge (Biopatch) in which 12 clinicians were randomly allocated to apply and remove one of the dressings to the left or right side of the neck in 12 healthy volunteers. There were 24 of each dressing applied and removed, with 48 (24 of each dressing) applied and removed in total. Clinicians found Tegaderm CHG to perform statistically significantly more favourably than the CHG-impregnated sponge across all parameters considered ($p<0.05$). These included overall performance, ease of correct application, ease of removal, ability to see the intravenous site, ease of training and intuitive application Two poster presentations (Zehrer at al. 2009 and Deschneau et al. 2008) reported on questionnaires that nurses completed after using Tegaderm CHG. In both studies Tegaderm CHG performed significantly better overall than the CHG-impregnated sponge.

Expert advice to specific questions raised during evaluation from 3 experts with experience of using both Tegaderm CHG and standard dressings stated that, in general, the use of Tegaderm CHG is similar to standard dressings (see correspondence log page 17). One expert mentioned that it takes longer to remove Tegaderm CHG and that there may be a few incorrect applications at first. The remaining 2 experts stated that the time taken is the same or similar for both Tegaderm CHG and standard dressings.

Two experts had experience of using both Tegaderm CHG and the CHG-impregnated sponge and reported minimal differences between the ease of use of the 2 types of dressings. One expert suggested that application and

removal of Tegaderm CHG is quicker than the CHG-impregnated sponge and another reported that some nurses placed the CHG-impregnated sponge upside down and therefore had to use a replacement.

Adverse events

The company searched the Medicines and Healthcare Products Regulatory Agency (MHRA) and Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) systems to identify surveillance reports relating to Tegaderm CHG, between 7 January 2000 and 29 July 2013. This revealed 1 result from the MHRA and 109 from MAUDE. The EAC repeated the company's search and identified the same number of records. The EAC extended the company's search to 28 November 2014 and identified a further 17 results. These results generally described local reactions within 48 hours of dressing application, and many were self-limiting. Two deaths were reported in MAUDE, but these were not directly linked to Tegaderm CHG. The company also did a search of the MHRA and MAUDE systems to identify surveillance reports for the Biopatch and Opsite IV 3000 (standard) dressings, but it did not report the search terms and dates used. The EAC conducted its own searches of these systems between 1 January 2012 and 30 November 2014. These searches identified 73 records for Biopatch, which were similar in nature but more numerous than the 29 for Tegaderm CHG over the same period, though this provides only a crude comparison because it does not allow for sales volumes. One of these was a reported death; however this was not directly linked to Biopatch. Only 1 minor, self-correcting adverse reaction was found for the Opsite IV 3000 dressing over this time period.

The company also searched their post market surveillance data for reported skin reactions. This identified a marked reduction in reports, both in numbers and relative to increasing sales, following a modification to the dressing design to incorporate a breathable film in 2011, see figure 9, page 93 of the company's submission.

EAC conclusions on the clinical evidence

The EAC critically appraised the methodologies of their and the company's included literature, the details of which can be found in pages 47–64 of the assessment report. In summary, the EAC judged that the studies by Timsit et al. (2012) and Timsit et al. (2009) were the most relevant and best conducted. The study by Roberts et al. (1998; not presented in the submission but identified in additional searches by the EAC) was underpowered to allow for the statistical significance of outcomes to be examined; provided few details on the methodology used; no details on how randomisation was achieved; and only provided information on age and gender of the study population at baseline. The poster presentation by Kapernan et al. (2014) contained insufficient detail for the EAC to fully appraise its methodology and accurately judge its relevance to the decision problem.

Overall, the EAC considered the company's submission to be reasonably consistent with the scope. The Timsit et al. (2012) study included by the company used internationally recognised definitions for catheter colonisation and CRBSI. Mortality caused by catheter-related infections, local site infection, and quality of life were not addressed in the company's submission. However, given international evidence for a link between CRBSI and mortality, the EAC considered it plausible that if Tegaderm CHG reduced CRBSI, it would have a positive impact on CRBSI-related mortality in practice. The EAC noted that the CRBSI rates reported in the study of 1.3 per 1000 catheter days were similar to those reported for the NHS in England in the Matching Michigan study of 1.48 per 1000 catheter days, making its results generalisable to the NHS. However, they also noted that the mortality of 31% for the French ICUs in the Timsit studies was substantially higher than the 9.1% mortality reported for adult critical care units in the NHS, suggesting that whereas their demographics were similar, the French ICUs likely had more severe illness than their UK counterparts. The skin preparation protocols followed by the French ICUs differed from those recommended for the NHS, as specified in the decision problem.

The EAC found that the company's search of the MAUDE and MHRA systems accurately reported, in detail, the adverse events records for Tegaderm CHG. Overall, they considered the company's search for adverse events to be robust and in line with NICE guidance.

Table 2 Characteristics of the company's and EAC's included studies

Abbreviations used: CRBSI: catheter-related bloodstream infections, CRI: catheter-related infections, CVC: central venous catheter, cfu: colony forming unit, ICU: intensive care unit, RCT: randomised controlled trial					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Full, peer-reviewed articles					
Tegaderm CHG dressing vs non CHG dressings					
Timsit et al. (2012)	RCT (France)	ICU patients older than 18 years expected to need intravascular catheterisation for 48 hours or longer	Tegaderm CHG versus standard dressing (Tegaderm IV) and highly adhesive dressing (Tegaderm HP Transparent Film Dressing)	Primary • Major CRI rate • Catheter colonisation rate Secondary • CRBSI • Skin colonisation • Rate of dressing change	The EAC's key concern with this study was that 156 patients were excluded with no reason provided. Other than this, the study was deemed to be at low risk of internal bias. Measurement of outcomes was well described and statistical significance of results reported.
CHG-impregnated sponge (Biopatch) dressing vs standard dressing					

Abbreviations used: CRBSI: catheter-related bloodstream infections, CRI: catheter-related infections, CVC: central venous catheter, cfu: colony forming unit, ICU: intensive care unit, RCT: randomised controlled trial					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Timsit et al. (2009)	RCT (France)	ICU patients older than 18 years expected to need intravascular catheterisation for 48 hours or longer	Biopatch plus standard dressing (Tegaderm IV) versus standard dressing (Tegaderm IV)	Primary • Major CRI rate • Catheter colonisation rate Secondary • CRBSI • Skin colonisation • Rate of dressing change	The EAC's key concern with this study was that 141 patients were excluded with no reason provided. Other than this, the study was deemed to be at low risk of internal bias. Measurement of outcomes was well described and statistical significance of results reported.
Roberts et al. (1998)	RCT (Australia)	All patients receiving CVCs in the adult ICU	Biopatch plus standard dressing (Opsite IV 3000) versus standard dressing (Opsite IV 3000)	Primary • Positive culture at CVC tip and exit site (skin) • CRI	The methodology of this study including randomisation, treatment allocation, similarity between groups and blinding was poorly reported. No intention-to-treat analysis was done. The study was judged to be at risk of performance and detection bias. Measurement of outcomes was well described and statistical significance of results sometimes reported.
Abstracts					
Karpanen et al. (2014)	RCT (UK)	Critical care adult patients who had a short-term	Tegaderm CHG versus standard dressing (Tegaderm IV)	Primary • Median number of bacteria recovered from the CVC insertion site, suture site and	The amount of information provided in this conference poster was not sufficient to fully assess levels of bias within the

Abbreviations used: CRBSI: catheter-related bloodstream infections, CRI: catheter-related infections, CVC: central venous catheter, cfu: colony forming unit, ICU: intensive care unit, RCT: randomised controlled trial					
Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
		CVC or Vascath (for haemodialysis) inserted for ≥3 days		sutures Secondary • Incidence of catheter segment colonisation (>15 cfu per catheter segment)	study. Measurement of outcomes was well described and statistical significance of results reported.

5.2 Summary of economic evidence

The company did a literature search and identified 5 studies that met their selection criteria. All of these studies used cost-benefit analyses. Three of these were done in the USA (Veenstra et al. 1999; Crawford et al. 2004; Ye et al. 2011), 1 in the UK (Hockehnull et al. 2008) and 1 in France (Schwebel et al. 2012). In 2 of the studies, the comparison was between an antiseptic-impregnated catheter and a standard catheter (Veenstra et al. 1999; Hockenhull et al. 2008). In the remaining 3 studies (Crawford et al. 2004; Schwebel et al. 2012; Ye et al. 2011), the intervention was a CHG-impregnated dressing and the comparator a standard dressing. None of the included studies involved the Tegaderm CHG dressing. Details of the company's search methodology are given in pages 97–102 of the company's submission, and further details on the studies identified are in section 8.2, pages 101–122 of the company's submission.

The EAC considered none of the company's identified studies to be relevant because they did not compare Tegaderm CHG to either of the comparators. It conducted additional searches and identified 4 economic studies, all of which used cost-benefit analyses and compared Tegaderm CHG with a standard dressing (Maunoury et al. 2013; Maunoury et al. 2014; Palka-Santini et al. 2014a; Palka-Santini et al. 2014b). All were published as conference abstracts after the company's searches, and are discussed in pages 91–94 of the assessment report. All of the studies were conducted from a French health service perspective, were written by the same authors, and used data from the Timsit et al. (2012) study. Each study used different model structures or reported different results, all involved a non-homogeneous Markov model, and were concerned with various measures of infection. No statistically significant differences were reported between the 2 dressings. The EAC was unable to extract any relevant data from the available reports.

De novo analysis

Model structure and assumptions

The company presented a cost analysis comparing Tegaderm CHG against a standard dressing (Tegaderm IV 1635). The costs of another commonly used but more expensive standard dressing (Opsite IV 3000) were also quoted, but not used in the model. The company did not include the CHG-impregnated sponge dressing in the model because of the lack of direct comparative clinical evidence. The economic model presented by the company was a decision tree with a short time horizon that involved the catheterisation period and any additional length of stay associated with CRBSI. The model used an NHS perspective. The decision tree simulated ICU patients on a pathway who had an absolute risk of acquiring CRBSI, local site infection or dermatitis. Each outcome was a separate health state and the model captured the number of patients in each state and the cost of being in that state (dressings and management costs).

Each time the model was run, Monte Carlo simulation was used to select values at random from the pre-specified distributions associated with each of the input parameters, apart from the unit cost of the dressings. This approach allowed for the effects of the joint uncertainty across the parameters of the model to be considered. The company's base-case results were probabilistic, based upon 1000 iterations of the model.

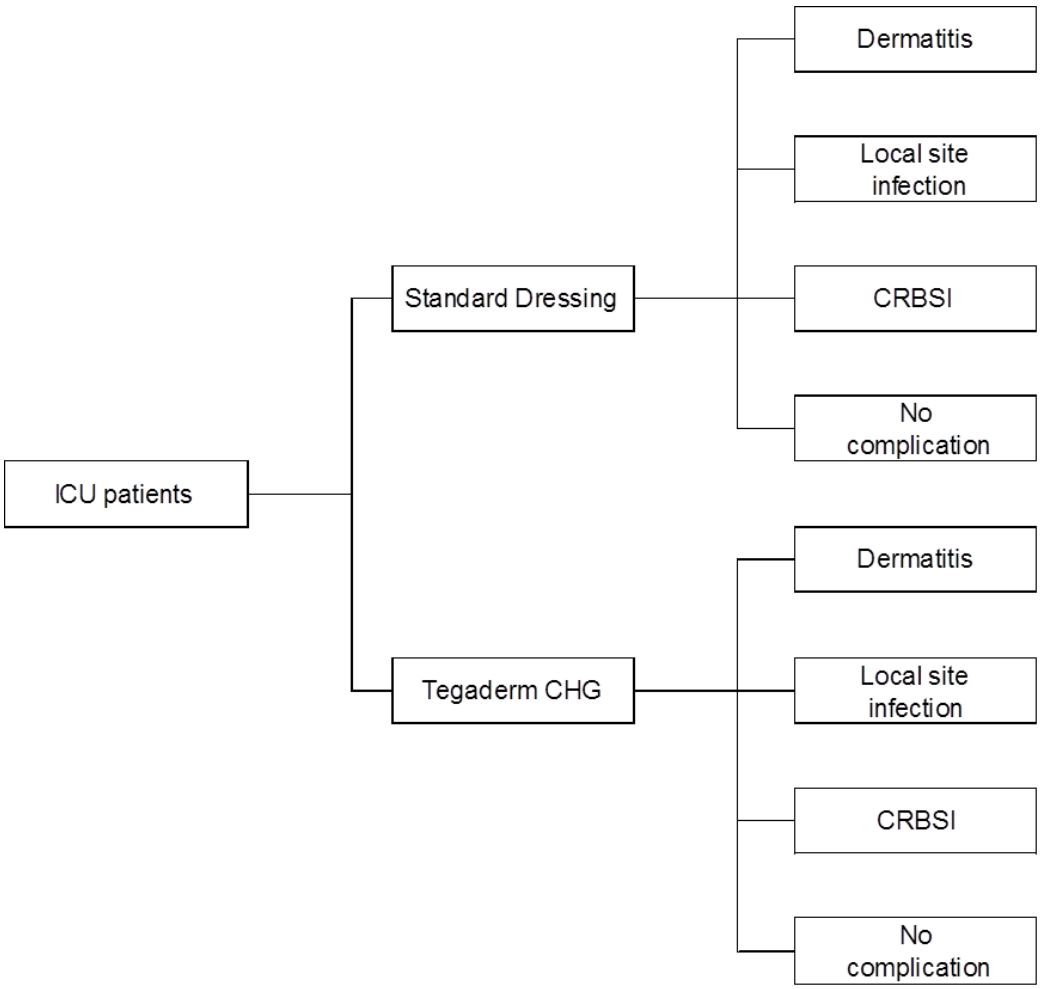

Figure 1 Company model structure with EAC amendment (addition of 'No complication' to both arms), reproduced from figure 4.1 assessment report page 98

The EAC considered the structure of the model was appropriate, capturing the main difference in reported clinical outcomes and cost differences between Tegaderm CHG and standard dressings. However it noted that the 3 end states did not account for patients who had no complications and it amended the model to include this state. The company did not report any structural assumptions but the EAC identified a number of structural assumptions in the model (see page 101 of the assessment report). These are:

- There is no difference in outcomes beyond the short time horizon of the study.

- The length of time a patient has a catheter is not influenced by whether or not they had an infection (CRBSI or local).
- The risk of having any of the study outcomes is mutually exclusive and independent.
- The dressings only affect actual outcomes and not suspected outcomes, which would also incur costs of investigation.
- Infection rates are assumed to be linear regardless of catheter dwell time.
- There are no organisational differences between the dressings such as time to apply and remove; wastage and training.

The EAC judged that these simplifying assumptions were unlikely to significantly bias the results of the company's model.

Model parameters

The company used data from its presented clinical study, Timsit et al. (2012), to populate the parameters for all the clinical end points in the model. The model's time horizon of 10 days was based on the mean length of catheterisation for critically ill patients reported in the study by Ye et al. (2012). Individuals who had a CRBSI incurred an additional length of stay of 3 days in ICU and 7 days in a ward and resource use cost based on figures reported in the Hockenhull et al. (2008) study. Baseline risks for the clinical end points were attained from a number of sources. Those for CRBSI (1.48 per 1000 catheter days) were taken from the Bion et al. (2012) paper based on 2010 final quarter figures from the Matching Michigan study; those for local site infection (0.1 per patient) from Ye et al. (2011); and for dermatitis (0.0026 per catheter) from Schwebel et al. (2012).

Table 3: Clinical parameters used in the company's and EAC's model

Variable	Company value (source)	EAC revised value if different (source)
Baseline CRBSI rate	1.48 per 1000 catheter days (Bion et al. 2012)	
Hazard ratio (HR) for CRBSI with Tegaderm CHG	0.402 (Timsit et al. 2012)	
Baseline local site infection rate	0.1 per patient (Ye et al. 2011)	0.14 per 1000 catheter days (NHS Wales data, 2013)
HR for local site infection with Tegaderm CHG	0.402 (Timsit et al. 2012)	
Baseline dermatitis risk	0.0026 per catheter (Schwebel et al. 2009)	0.0021 per catheter (Timsit et al. 2012)
Relative risk for dermatitis with Tegaderm CHG	4.4 (Timsit et al. 2012)	1 (Company, global event data report)
CRBSI: catheter-related bloodstream infection		

Costs and resource use

The company provides both the sources and a breakdown of the costs used in their model (see pages 134–142). The costs for the Tegaderm CHG and the standard dressing (Tegaderm IV 1635) were provided internally, and were £6.21 and £1.34 respectively. The cost for a CRBSI of £9900 was based on the figure reported in the health technology assessment paper by Hockenhull et al. (2010), inflated to 2012/13 prices. This value was used in NICE's guideline on infection. The company produced their own cost estimate for CRBSI based on resource usage identified through expert advice, which agreed with the £9900 figure. The cost of dermatitis of £150 used in the company's model was based on the cost of 4 standard dressings, removing the existing catheter, and replacing it with a new catheter. Local site infections were given a cost of £250 based on the US $400 figure reported in the study by Saint et al. (2000).

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

Variable	Company value (source)	EAC revised value if different (source)
Costs of Tegaderm CHG dressing	£6.21 (Company)	£6.26 (Company, weighted average of dressing sizes – sales data)
Tegaderm CHG dressing costs over a 10 day catheterisation period	£18.43 (Company)	£18.78 (Company, weighted average of dressing sizes – sales data)
Cost of standard dressing	£1.34 (Company)	£1.54 (NHS Supply Chain, weighted average)
Standard dressing costs over a 10 day catheterisation period	£4.02 (Company)	£4.62 (NHS Supply Chain, weighted average)
Cost for a CRBSI	£9900 (Hockenhull et al. 2010)	£9900 (Hockenhull et al. 2010)
Cost for a case of dermatitis	£150 (Schwebel et al. 2012)	£6 (Expert advice)
Cost of a local site infection	£250 (Saint et al. 2000)	£100 (Expert advice)
CRBSI: catheter-related bloodstream infection		

Company's base-case results

The company's base-case results reported an average per patient cost of £99.63 for those receiving a Tegaderm CHG group dressing compared with £176.89 per patient for those receiving a standard dressing, an average saving of £77.26 per patient if Tegaderm CHG were adopted. The probability of Tegaderm CHG having a cost saving over standard dressings was calculated at 98.5%. The parameter driving this cost saving was avoiding CRBSI through the use of Tegaderm CHG, saving on average £82.60 per patient.

Company's sensitivity analysis results

The company did univariate deterministic analysis on both the cost of CRBSI and its baseline risk, to see how robust their model was to changes in this key

variable. Based on a low estimate of CRBSI risk of 0.5 per 1000 catheter days, and a high estimate of 5.5 per 1000 catheter days, Tegaderm CHG had a cost saving of £23 and £135 respectively, per patient. Based on a low estimate of cost for treating a CRBSI of £5000, and a high estimate of £15,000, Tegaderm CHG generated cost savings of £36 and £119 respectively, per patient.

EAC's critique of the company's analysis

The EAC considered the company's economic model to be appropriate and robust, see pages 124–127 of the assessment report. The EAC identified 2 main weaknesses. Firstly, there was a lack of rationale for the choice of distributions and coefficients used in the probabilistic sensitivity analysis done by the company. The EAC noted however that this was not required as part of the submission template. Secondly, the company did not attempt to make any judgement on the comparative cost effectiveness of Tegaderm CHG and a CHG-impregnated sponge dressing. The EAC addressed both of these concerns in the assessment report.

EAC revisions to the company's model

Clinical parameters

The EAC reviewed the parameter values in the company's model and made a number of changes. These are discussed in table 4.5 and pages 105–110 of the EAC report.

The EAC revised the company's value for baseline local site infection risk based on 2013 audited rates for NHS Wales published by the Welsh Healthcare Associated Infection Programme (2014). The EAC judged it more appropriate to use the probability of 1 case of dermatitis per 476 patients reported in the Timsit et al. (2012) study rather than the rate used in the company's model from the Schwebel et al. (2012) study, which was based on figures from the Timsit et al. (2009) study.

The EAC revised the relative risk of dermatitis to 1, based on commercial-in-confidence global event data provided by the company on the rate of dermatitis after improvements in the breathability of the Tegaderm CHG dressing.

Whereas the EAC judged the company's value for baseline risk of CRBSI to be appropriate, it did carry out pragmatic and targeted literature reviews, as well as using general web search engines (Google) to find UK-specific rates, and to identify other published data on CRBSI rates (pages 105–107 of the assessment report). National CRBSI rates for 2013 were identified for both Wales (0.19 per 1000 catheter days) and Scotland (0.3 per 1000 catheter days), which were lower than those used in the company's model (1.48). The EAC noted that the figure for Scotland in 2010 had been 0.8 per 1000 catheter days, and that NHS England, Wales and Scotland all had similar bundles and practices for preventing infection when inserting and maintaining central venous catheters. The EAC therefore ran additional deterministic and probabilistic sensitivity analyses using the CRBSI rates reported for Scotland for 2013, 0.3 per 1000 days (95% CI 0.2 to 0.6).

Costs

The EAC reviewed the costs used in the company's model (pages 110–118 of the assessment report). They contacted clinical experts who validated the company's estimated resource use associated with CRBSI.

For the cost of a Tegaderm CHG dressing, standard dressing and CHG dressing, NHS Supply Chain costs were used. The EAC considered a weighted average cost, based on the proportionate sale figures for the 4 sizes of Tegaderm CHG dressing and 2 commonly used comparator dressings, to be most appropriate. Based on these calculations, the EAC produced higher estimates for all 3 dressing types than those in the company's model.

The EAC was advised by experts that it was not usual procedure to remove the catheter if patients had dermatitis. It therefore considered the company's

costs of the consequences of dermatitis to overstate the true cost. The EAC therefore estimated a lower value, which involved the costs of dressings only, but assumed that patients with dermatitis would need more frequent dressing changes and use more dressings. A total of 4 dressings was determined, as noted in the company's costing.

The study by Saint et al. (2000), which provided the cost for local site infection used in the company's model, provided no details on how that cost was generated. The EAC therefore sought expert advice to derive its own cost estimate which was lower than that used in the company's model.

The EAC also sought expert advice on the number of dressings used. This agreed with the company's estimate of 3 dressings over a 10-day catheterisation period.

The parameter values used in the company's model along with the EAC's commentary are presented in more detail in table 4.10, pages 119–122 of the assessment report. Those used in the EAC's analysis values along with changes made to the parameter values and their distributions are reported in table 4.14, pages 130–131 of the assessment report. These are summarised in table 3 below.

Results from EAC's revisions to the company model: Tegaderm CHG compared with standard dressing

The EAC re-ran the company's model with the above revisions to parameter values and distributions. They also ran an additional scenario in which the CRBSI rates for England were substituted with those reported for Scotland in 2013. Both deterministic and probability sensitivity analyses were done.

The EAC's deterministic base-case results using CRBSI data from England produced an average per patient cost of £77.75 for Tegaderm CHG and £151.29 for a standard dressing, a cost saving of £73.54. The key driver behind this cost saving was an average £87.62 difference in the cost of treating CRBSI.

When CRBSI data from Scotland were used, Tegaderm CHG had an average per patient cost of £30.79 and a standard dressing cost of £34.47; a cost saving of £3.68. CRBSI savings remained the main cost driver; however, these now amounted to an average of £17.76 per patient, only just offsetting the higher Tegaderm CHG dressing costs of £14.46.

The EAC did univariate probabilistic sensitivity analyses on all the parameters, which are reported in a series of Tornado diagrams. These show that for analyses using data from England on CRBSI (figure 4.3, page 134 of the assessment report) changing the parameter values individually between their distribution extremes resulted in no instances of Tegaderm CHG incurring costs. Using data from Scotland on CRBSI led to all parameters related to CRBSI (cost, hazard ratio and baseline rate) being cost incurring, as well as catheter dwell time and number of dressing changes (figure 4.4, page 136 of the assessment report). Tegaderm CHG became cost incurring when the hazard ratio of CRBSI was 0.526 or above and the cost of CRBSI was £8000 or below.

The EAC ran probabilistic sensitivity analyses varying all the model parameters using their ranges and distributions (see table 4.14 of the assessment report for values). Tegaderm CHG had a 97.8% probability of being cost effective using the baseline CRBSI risk from England, but this fell to 57.9% when figures from Scotland were used.

Cost analysis of Tegaderm CHG compared with CHG-impregnated sponge dressings

The EAC did a cost analysis of Tegaderm CHG compared with CHG-impregnated sponge dressings (pages 138 and 139 of the assessment report). The EAC concluded that from the limited clinical evidence available, and similar data on adverse events, it was plausible to assume for exploratory cost analysis that the 2 dressings had similar safety and efficacy. Due to the absence of hard data on outcomes this exploratory work relied on observational studies and expert opinion. This suggested that resource use

was similar between the 2 dressings, with any differences depending on acquisition cost. Based on NHS Supply Chain costs for Biopatch and the cheapest standard dressing (Tegaderm IV) the cost for CHG-impregnated sponge dressing was calculated at £8.13, compared with £6.26 for Tegaderm CHG. No sales data were available through the NHS Supply Chain and expert opinion indicated that trusts would likely purchase through other sources at a lower price than the NHS Supply Chain listed price. The EAC therefore ran additional costings using the price provided by the company for Biopatch of £5.16 per dressing. This resulted in a total price of £6.49, slightly more expensive than Tegaderm CHG.

6 Ongoing research

Two ongoing studies were identified by the company. The first was an unpublished health economics study comparing Tegaderm CHG with a sterile semipermeable dressing, which is based on the company's de novo cost model described here. The second was the Karpanen et al. (2014) study, which published interim results after the company's submission.

The External Assessment Centre (EAC) searched www.clinicaltrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform and the ISRCTN registry for ongoing studies. The searches identified 6 ongoing studies relating to Tegaderm CHG. Four of these had not reached their completion date and 2 have not had their information on the registry updated for over 2 years, and hence their status is unknown (see pages 27–29 of the assessment report).

The 4 ongoing studies consist of a randomised control trial in Japan comparing Tegaderm CHG with standard care in critically ill children needing a central venous catheter for more than 7 days (trial number: UMIN000007207). This study has catheter-related bloodstream infections (CRBSIs) as its primary end point, is funded by 3M and expected to complete in April 2015. A randomised controlled trial is being done in Germany on

cancer patients needing a central venous catheter, comparing Tegaderm CHG with Tegaderm Advanced IV dressing (trial number: NCT01544686). This has a primary end point of CRBSI and is expected to complete in October 2015. A randomised controlled trial is being conducted in the USA comparing Tegaderm CHG with a standard Tegaderm IV dressing in children needing intravascular access (trial number: NCT01955226). The primary end point is reductions in unscheduled central catheter dressing changes, with bloodstream infections being a secondary outcome. This study is expected to complete in January 2017. The final study is a randomised controlled trial in Switzerland currently recruiting patients needing implantation of an external ventricular drain (trial number: NCT02078830). The study is comparing Tegaderm CHG with Tegaderm Advanced IV and has a primary end point of difference in bacterial contamination at the external ventricular drain entry-site after 5 days. The estimated completion date is October 2016.

The 2 studies of which the status is unknown include a multicentre randomised controlled trial based in Italy comparing Tegaderm CHG with Tegaderm IV (trial number: NCT01142934). This study was expected to complete in October 2012 but is still shown as recruiting. The study is part funded by 3M who have indicated that the study was terminated due to the slow recruitment of participants. At termination some interim data were released but the EAC agreed with the company's view that there were no data relevant to the evaluation. The last study is a Spanish randomised controlled trial comparing Tegaderm CHG with Tegaderm IV in patients in an intensive care unit (ICU), which was due to complete in June 2013 but is shown as recruiting (trial number: NCT01733940). The company contacted the lead investigator who advised that the study concluded in 2012. Results were reported at the 2013 Congress of the Spanish Society of Preventive Medicine, and found that in the 126 patients Tegaderm CHG reduced the risk of catheter tip colonisation by 73% (95%CI 0.09 to 0.76, p=0.0013) compared with the standard dressing. Because this was reported in Spanish rather than English, this did not meet either the company or the EAC's inclusion criteria.

7 Issues for consideration by the Committee

Clinical evidence

Generalisability of the evidence to the decision problem

The External Assessment Centre (EAC) noted that with the exception of the study by Kapernan et al. (2014) all of the studies were done outside the UK, and did not follow UK NICE guidelines for skin preparation before application of a dressing, as specified in the scope. The EAC commented that had the scope been followed strictly in this sense, no published evidence on the technology would have been found. In addition, the EAC noted that patients in the Timsit et al. (2009) study appeared to be more unwell than those included in their 2012 study. In both studies the patients appeared on average to be more unwell than those in NHS intensive care units (ICUs), with higher mortality rates and longer length of stay. All of the evidence related to ICU or critical care and no evidence was found specifically relating to high dependency units (HDUs).

Identification of baseline catheter-related bloodstream infection (CRBSI) rates

The catheter-related bloodstream infection (CRBSI) rate in the Timsit et al. studies for standard dressings is 1.3 per 1000 catheter days, which is similar to the estimate in the NHS of 1.48 per 1000 catheter days, and so the EAC concluded that this was comparable to the NHS. The EAC also explored national CRBSI rates for use in the cost analysis. It used both CRBSI rates from England based on data from the Matching Michigan study, Bion et al. (2012), and 2013 national statistics from Scotland. Whereas the EAC acknowledges some concerns with the data from Scotland from 2013 (see page 106 of the assessment report), which may have led to underestimation of the true rate of CRBSI, the rate is nonetheless much lower than the figures

for England (1.48 per 1000 catheter days). The rate for Wales based on 2013 national data was also much smaller, at 0.19 per 1000 catheter days; however, no confidence intervals were placed on this value. The EAC notes that infection care bundles are similar across the UK.

Cost evidence

Tegaderm CHG compared with CHG-impregnated sponge dressing

The company did not do an analysis comparing Tegaderm CHG dressing and CHG-impregnated sponge dressing (which was a comparator in the decision problem). There are no direct comparative data on any clinical end points. The EAC carried out an analysis, assuming (largely in the absence of evidence to the contrary) that Tegaderm CHG and a CHG-impregnated sponge dressing are equivalent in terms of efficacy, safety and resource usage. The EAC estimated that Tegaderm CHG would cost £6.26 per dressing, £18.78 per patient for a 10-day catheterisation period compared with £6.49, £19.47 for a CHG-impregnated sponge dressing, an average saving of 69p per patient.

8 Authors

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NICE Medical Technologies Evaluation Programme

February 2015

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

A Details of assessment report:

- Jenks M, Craig J, Arber M, et al. The 3M Tegaderm CHG IV securement dressing for central venous and arterial catheter insertion sites, (January 2015)

B Submissions from the following companies:

- 3M Health Care

C Related NICE guidance

- Infection prevention and control. NICE quality standard 61 (2014). Available from: http://www.nice.org.uk/guidance/QS61
- Infection: Prevention and control of healthcare-associated infections in primary and community care. NICE clinical guideline 139 (2012). Available from: http://guidance.nice.org.uk/CG139
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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.

Mr James Bitmead
IV Lead nurse Infection control, Royal College of Nursing

Ms Lisa Dougherty
Nurse consultant, National Infusion and Vascular Access Society

Ms Annette Jeanes
Nurse consultant, Royal College of Nursing

Dr Linda Kelly
Lecturer, National Infusion and Vascular Access Society

Mr Maurice Madeo
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Ms Jackie Nicholson

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Mr Andrew Barton

Advanced Nurse Practitioner Vascular Access and IV therapy, Nursing and Midwifery Council

Dr Justin Roberts

Consultant in Intensive Care Medicine and Anaesthesia, Royal College of Anaesthetists

Dr Roland Black

Consultant Intensive Care Physician, Royal College of Anaesthetists

- Seven of the expert advisers had direct involvement with the technology. One expert indicated that they would like to use the technology but it is not currently available to them, and that they have managed patients on whom it is used on another part of their care pathway. The remaining expert did not complete this section but subsequent responses indicated that they did not have direct experience of the technology.
- Five experts thought that Tegaderm CHG is a significant modification of an existing technology, two that it was a minor variation, and two that it was thoroughly novel.
- The experts who provided justification for their choice largely identified visibility of the insertion site as the novel, or modification element, of the technology.
- Four experts identified the most appropriate use for the technology as being in patients at high risk of infection who have a central venous catheter.
- Eight of the experts identified Biopatch as a comparator or competing product. Two experts stated that the visibility of the CHG delivery mechanism at the catheter insertion site meant that the technology had no

direct equivalent. One was of the opinion that the CHG element made the technology unique and there was no comparator or competing technologies.

- A reduced risk of catheter-related bloodstream infections (CRBSI) was the most commonly cited patient benefit.
- All of the experts identified system benefits arising from reductions in catheter-related infections or CRBSI.

All of the experts indicated that there were minimal training requirements to use the technology safely and effectively.

Appendix C: Comments from patient organisations

The following patient organisations were contacted and no response was received.

- Brake
- British Kidney Patient Association (BKPA)
- British Red Cross
- Critical Care Patient Liaison Committee (CritPaL)
- ICU Steps
- Kidney Research UK
- Kidney Research UK
- National Kidney Federation (NKF)
- Royal College of Surgeons of England (RCSeng)
- Trauma Care
- Wound Care Alliance UK