External Assessment Centre report

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the sponsor's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

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

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Rider on responsibility for report

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

Contents

1 Summary

Scope of the sponsor's submission

The sponsor's submission is reasonably consistent with the scope of the decision problem. The population defined in the scope is critically ill adult patients in intensive care units (ICU) or high dependency units (HDU) who require a central venous or arterial catheter. The clinical evidence used in the sponsor's submission was from 12 French ICUs (1). Patients were expected to require intravascular catheterisation for at least 48 hours, which was not required in National Institute of Health and Care Excellence (NICE) scope and those with allergies to chlorhexidine or transparent dressings excluded. No subgroups are specified in the scope and the sponsor undertook no subgroup analyses.

The scope defines the intervention as swabbing with 2% chlorhexidine gluconate (CHG) in alcohol and Tegaderm CHG IV securement dressing. The 2 specified comparators are sterile semi-permeable transparent dressing (defined in this document as 'standard dressing') and CHG impregnated dressing. In both cases the scope requires swabbing with 2% CHG in alcohol. In the sponsor's clinical evidence, Tegaderm CHG was compared with standard dressings only, meaning no evidence was submitted on the relative efficacy of Tegaderm CHG IV securement dressing versus CHG impregnated dressing.

In the submitted clinical evidence, only catheters inserted in ICUs were included and French recommendations followed for catheter insertion and care. These recommendations are similar to recommendations made by NICE (2), with the main exception of skin preparation. In the clinical evidence, the skin was prepared any of a number of alcohol-based antiseptic solutions (1), whilst NICE specifically recommends the use of 2% CHG in alcohol. In addition, protocol within the clinical evidence was for an initial change of dressing 24 hours after catheter insertion. NICE recommend changing the dressing every 7 days unless there is a reason to change it sooner (2); however, experts advised that in some NHS trusts dressings are changed 24 hours after catheter insertion.

The sponsor's submission addressed 5 of the 8 outcomes listed in the scope using data from the clinical evidence. The definitions adopted in the clinical evidence for catheter related bloodstream infections (CRBSI) and catheter colonisation were internationally accepted. Outcomes were reported based upon patient follow-up for 48 hours after ICU discharge. The outcomes not addressed were: local site infection, quality of life and mortality caused by catheter related infection (CRI). The sponsor provided additional evidence relating to ease of use and performance of Tegaderm CHG, which were not specified in the scope.

Tegaderm CHG was compared with CHG impregnated dressings for skin colonisation only, based on a study that deviated from the scope and sponsor's selection criteria in that it was undertaken in healthy volunteers (3).

The cost analysis provided by the sponsor was largely consistent with the scope. The key exception to this was that no analyses were made comparing the cost-consequences of Tegaderm CHG with other CHG impregnated dressings. The unit costs of CHG impregnated dressings were, however, provided.

Summary of clinical evidence submitted by the sponsor

The sponsor undertook a high-quality literature search to identify published literature on the clinical effectiveness of Tegaderm CHG. Inclusion and exclusion criteria were applied to select studies, with 1 published study meeting the criteria. The study design was reported, an appropriate quality assessment undertaken and data on reported outcomes extracted accurately.

The included study, by Timsit *et al.* (2012), reported on a French randomised control trial (RCT) comparing Tegaderm CHG with standard dressings in 1,879 patients. Standard dressings comprised both Tegaderm standard dressings, 3M and Tegaderm highly adhesive dressings, 3M (1).

CRBSIs were reported to be statistically significantly lower in the Tegaderm CHG group than standard dressing group (0.5 versus 1.3 per 1,000 catheter days, p=0.02). The rate of catheter colonisation was also statistically significantly lower in the Tegaderm CHG group than the standard dressing group (4.3 versus 10.9 catheter colonisations per 1,000 catheter days, p<0.0001). The median length of stay in the intensive care unit similar across groups (either 9 or 10 days), with no p-value reported (1).

More adverse events occurred in the Tegaderm CHG group than the standard dressing group. This included statistically significantly greater incidence of severe contact dermatitis requiring the removal of the CHG dressing (1.1% versus 0.1% for standard dressings and 0.5% for highly adhesive dressings, $p<0.0001$) and statistically significantly greater incidence of abnormal International Contact Dermatitis Research Group scores (2.3% versus 0.7% for standard dressings and 1.4% for highly adhesive dressings, $p<0.0001$) (1).

The sponsor accurately reported, in detail, the 109 U.S. Food and Drug Administration (FDA) Manufacturer and User Facility Device (MAUDE) records that were identified relating to Tegaderm CHG between 7th January 2000 and 29th July 2013. The majority of these described local reactions occurring within 48 hours of dressing application, which in many cases were self-healing. The sponsor also provided an analysis of skin reactions to Tegaderm CHG in the UK, showing that reactions reduced following the introduction of a modified design of Tegaderm CHG with a high breathability film. The sponsor provided supplementary information relating to the ease of use of Tegaderm CHG compared with standard dressings.

Summary critique of clinical evidence submitted by the sponsor

The sponsor undertook sensitive searches using an appropriate PICO (Population, Intervention, Comparator and Outcome) framework to identify studies relevant to the decision question. The key weakness of the sponsor's clinical evidence submission was the use of restrictive selection criteria. Only studies comparing Tegaderm CHG to standard dressings were included. Therefore, evidence only related to 1 of the 2 comparators specified in NICE's decision problem. A second study comparing Tegaderm CHG with a CHG impregnated dressing was subsequently included; however this was not discussed until section 7.9 of the submission, which addressed interpretation of clinical evidence (3). There was no discussion of how this study was identified, nor of the quality of the study.

The External Assessment Centre (EAC) aimed to identify all prospective comparative studies conducting a head-to-head comparison of at least 2 of the 3 dressing types: Tegaderm CHG, standard dressing and CHG impregnated dressing. Reflecting the EAC's broader inclusion criteria, an additional literature search was conducted which aimed to identify all prospective comparative studies.

Three published studies (1, 4, 5), including the study identified by the sponsor (1), and 1 poster (6) met the EAC's inclusion criteria. The 2 additional published studies compared CHG impregnated dressing, in both cases a CHG sponge, to a standard dressing (4, 5). The conference poster (6) was published after the sponsor's search.

All 4 studies included by the EAC were undertaken in critically ill patients situated in an ICU (one of the patient groups stipulated in the decision problem). Two of the 4 studies were conducted in France (1, 4), 1 in Australia (5) and the study presented as a poster was set in the NHS (6). Three of the 4 studies were RCTs (1, 4, 5), with the remaining study being a prospective comparative observational study (6). No studies directly compared Tegaderm CHG with CHG sponge.

The sponsor provided a detailed and accurate description and critical appraisal of its included study (1). Weaknesses identified during critical appraisal of the study were unlikely to introduce bias. The EAC considered the generalisability of this study to the NHS largely through seeking expert opinion and comparison with clinical guidelines. Variation between study practice and the NHS existed in relation to the use of skin preparation solution and patient characteristics. The mortality rate of 31% in the study was substantially higher than the 9.1% rate reported for adult critical care units (CCU) in the NHS (7). It is likely that the age and gender of patients in the included studies generalised to the NHS; however, given the variation in mortality rates between study patients and the NHS ICU population, those reported in the clinical studies may have had more severe illness.

The first of the 3 additional studies included by the EAC was another French RCT (n = 1,653) comparing CHG sponges with standard dressings (4). This study was conducted by the same clinical group that conducted the later RCT (1). It was well reported, with both the internal bias and external validity similar to that of Timsit *et al.* (2012) (1). The applicability of Timsit *et al.* 2009 (4) to the NHS was limited in the same ways as the 2012 study (1).

The second additional RCT (n = 33) included by the EAC, reported by Roberts *et al.* (1998) compared CHG sponge with standard dressings (5). There was a paucity of information relating to the study methodology used, practice in hospital, and definition of endpoints, attrition rate and follow-up. Practice within the study also varied with that in the NHS in terms of skin preparation and dressing change intervals (5). This study thus has a high risk of internal bias and lacks external validity.

The final study included by the EAC was published as a conference poster and is the only study undertaken within the NHS (6). There is limited information on study design, inclusion criteria and conduct of the intervention making it difficult to assess levels of internal bias and generalisability to the patients specified in the decision problem. However, catheter insertion site protocols adopted in the study appear to be in line with those used in the NHS more widely.

The sponsor accurately reported results from its included study (1). The sponsor's results included statistical comparisons between Tegaderm CHG and a combined control of standard dressings and highly adhesive dressings. The comparative results that the sponsor presented were consistent with those reported in the study. The sponsor advised the EAC that the highly adhesive dressing (Tegaderm HP Transparent Film Dressing) is not listed on NHS Supply Chain nor widely used within the NHS. The EAC therefore judged that it would have been useful to also provide results for standard dressings alone. The results from the sponsor's included study (1) and the 3 additional studies included by the EAC (1, 5, 6) are now summarised.

Three papers reported the number of CRBSI. The poor quality and small sample size in Roberts *et al.* (1998) limits the usefulness of these results (5). The 2 studies by Timsit *et al.* provided robust and comparable rates that were homogenous in terms of definition of CRBSI, included patients and care package (1, 4). Timsit *et al.* (2012) reported a CRBSI rate of 0.5 per 1,000 catheter days for Tegaderm CHG and 1.3 per 1,000 catheter days for standard dressing (1). Timsit *et al.* (2009) reported a CRBSI rate of 0.4 per 1,000 catheter days for CHG sponge and 1.3 per 1,000 catheter days for standard dressing (4). The rate of CRBSI was statistically significantly lower with a CHG impregnated dressing (either Tegaderm CHG or CHG sponge) than a standard dressing ($p<0.05$). Applying a Z-test enabled the EAC to test whether the results from 2 studies (1, 4) indicated that the 2 products differed significantly in terms of impact on infection rates. The results reported no statistically significant difference between the effectiveness of Tegaderm CHG and the CHG sponge ($p=0.58$).

Given that the latest available estimate of CRBSI rates in the English NHS is 1.48 per 1,000 catheter days, which is similar to the rate of 1.3 per 1,000 catheter days for standard dressings (8), the results from the 2 studies by Timsit *et al.* are likely to be generalisable to the NHS.

Either skin or catheter colonisation results were provided in all 4 studies. The available evidence showed that catheter colonisation rates were lower with Tegaderm CHG compared with standard dressings. This result was statistically significant in the large RCT (1) and statistically significant in 1 area of the catheter (intradermal section) in the observational study ($p<0.05$) (6). Robust evidence comparing CHG sponge with standard dressings from Timsit *et al.* (2009) showed a statistically significant reduction in catheter colonisation with the CHG sponge ($p<0.01$) (4).

The median length of stay in ICU was similar across all treatment groups (between 9 and 12 days) in the 2 French RCTs, with no confidence estimates provided (1, 4).

Severe contact dermatitis reported in the 2 studies by Timsit *et al.* showed that both Tegaderm CHG and CHG sponges resulted in higher incidence rates than standard dressings. The higher incidence was statistically significant for Tegaderm CHG ($p=0.0005$), however statistical significance was not reported in the CHG sponge study (1, 4). The sponsor advised that, since the release of the latest more permeable Tegaderm CHG dressing, the rate of severe contact dermatitis has reduced, with data from 3M's global database of incident reports showing around [redacted]. Dermatitis was also reported a number of times in FDA MAUDE reports. These were often less severe cases than those in the RCTs, which often healed without treatment. An analysis of FDA MAUDE reports showed that incidents have reduced since the introduction of the highly permeable Tegaderm CHG dressing. No systemic adverse events were reported in any of the studies. Clinical experts advised that they had not had experience of any adverse events during their use of Tegaderm CHG.

The EAC collated evidence from the sponsor relating to the ease of use of Tegaderm CHG and expert advice on the ease of use and performance of the dressings. Tegaderm CHG was reported in these studies, and by the expert advisors, to be at least as easy to use as standard dressings and likely to be easier to use than the CHG sponge. Tegaderm CHG may be easier to use than the CHG sponge, due to the transparent nature of the dressing and because it is a single component.

The sponsor concluded that the clinical evidence shows that compared with standard dressings, Tegaderm CHG is associated with lower rates of CRBSI and catheter colonisation, but an increase in the incidence of dermatitis. The sponsor stated that the results of its included study are likely to be generalisable to other settings consistent with best practice for catheter insertion and care.

The EAC has not identified any further evidence to suggest that the conclusions drawn by the sponsor are invalid. Furthermore, consideration of studies comparing CHG sponges to standard dressings, supplemented by the Z-score analyses suggest that the rates of CRBSI and surrogate measures of infection, such as catheter colonisation, are likely to be similar with Tegaderm CHG and CHG sponges.

Summary of economic evidence submitted by the sponsor

The sponsor identified 5 studies that met its selection criteria for economic studies considering interventions aiming to reduce CRIs (9-13). A replicable literature search for these studies was not provided. The sponsor provided the EAC with a *de novo* economic model, written and executed in Microsoft Excel. The model adopted a decision tree structure, covering a short time horizon of the length of stay in an ICU plus any additional length of stay resulting from a CRBSI. The population within the model was critically ill adult patients requiring intravascular access. The model had two arms, which consisted of a current practice arm (standard dressing) and an intervention arm (Tegaderm CHG). The third dressing stipulated in the scope, CHG sponge, was not included within the *de novo* model. The decision tree simulated 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).

The model was run stochastically, meaning that distributions were specified for each input parameter, except the unit cost of the dressings, to represent uncertainty in their estimation. Monte Carlo simulation was then employed to select values at random from pre-specified distributions each time the model was run. This allowed for the effects of the joint uncertainty across all the parameters of the model to be considered (14). The sponsor's base case results were probabilistic, based upon 1,000 iterations of the model.

To populate its economic analysis, the sponsor utilised data from its included clinical study (1), 3 of its included economic studies (11-13) and sought advice from two clinical experts. The mean values adopted for absolute risks and relative risk reductions for each health state were referenced to relevant clinical studies. Mean values for unit costs were also obtained from published studies, with some supplementary validation provided using data from clinical experts. The ranges and distributions applied to each input parameter were largely based upon assumptions.

The sponsor reported that, in the base case, the introduction of Tegaderm CHG would lead to estimated cost savings to the NHS of £77.26 per patient

compared with standard dressings. Cost savings were generated with Tegaderm CHG in 98.5% of the 1,000 model iterations. The sponsor reported that baseline CRBSI risk and the cost of CRBSI were the key drivers of the analysis. Univariate sensitivity analyses were conducted around each of these inputs, which showed the results of the sponsor's analysis to be robust within the ranges examined.

Summary critique of economic evidence submitted by the sponsor

The EAC performed a literature review for economic studies comparing Tegaderm CHG to either standard dressings or CHG sponges. Four conference abstracts were identified (15-18) all reporting economic evaluations conducted from a French health care system perspective, which built on data from the French RCT comparing Tegaderm CHG with standard dressings (1). These studies were presented since the sponsor conducted its economic literature searches, but would have been excluded by the sponsor given the studies were reported as conference abstracts only. Given that these were abstracts, the limited information available precluded the EAC from making judgements around the generalisability of the studies to the English NHS. The results presented in each abstract reported that Tegaderm CHG was neither statistically significantly cost saving, nor statistically significantly cost incurring (15-18).

The EAC critiqued the sponsor's economic model and accompanying narrative. The model provided was easy to navigate and replicate and the sponsor's description of the model, inputs and results were clear. The EAC identified several strengths of the analysis including that:

- The model matched the scope of the decision problem well;
- The structure of the model was appropriate, capturing the main difference in reported clinical outcomes and cost differences between Tegaderm CHG and standard dressings;
- Sensitivity analyses were conducted that correctly identified that the baseline rate of CRBSI and the cost of CRBSI are the major cost drivers in the model;
- Although simplifying assumptions were made, the EAC considered that these were unlikely to introduce significant bias.

Mortality resulting from CRBSI was not included within the model, given the lack of UK specific CRBSI-related mortality data and lack of data to quantify the impact of Tegaderm CHG on CRBSI-related mortality. However, evidence from other countries shows that CRBSIs increase the risk of mortality. If it is accepted that Tegaderm CHG significantly reduces CRBSI rates compared with standard dressing, then it is plausible that Tegaderm CHG will have a positive impact on CRBSI-related mortality in practice.

The parameter values modelled for the absolute risk of CRBSI and dermatitis and their relative risk were from a well-conducted RCT (1), judged to generalise to the English NHS setting and consistent with the evidence presented in the clinical section of the sponsor's submission. The risk of local site infection came from a published study and the relative risk assumed to be the same as for CRBSI.

Resource use and unit costs were, in general, appropriate and from published sources. The published cost of CRBSI was also validated by clinical experts using a bottom-up approach.

The probabilistic sensitivity analysis (PSA) was also, in the main, well-conducted and although there were some concerns with the distributions adopted, these had a limited impact on the PSA results.

The key weakness of the analysis was the absence of any discussion regarding the comparative cost-consequences of Tegaderm CHG and CHG sponge. Although the lack of direct clinical evidence comparing the 2 dressings prevents a fully-informed analysis being made, a narrative comparison would have been welcome.

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

One clinical study was identified by the sponsor and was the main source of clinical evidence on the absolute risk of adverse events with standard dressing and relative risk reduction from using Tegaderm CHG in critically ill patients (1). This well conducted RCT compared Tegaderm CHG to standard dressings and was applicable to the decision problem. This study was used to inform the *de novo* economic model, which was well executed and verified by two clinical experts. These experts also validated the key cost driver being the cost of CRBSI.

The clinical experts nominated by NICE were asked by the EAC to validate the clinical pathway and related assumptions. Their responses were generally positive. These, together with wider reading conducted by the EAC, informed its judgment that the submitted evidence comparing Tegaderm CHG with standard dressings was robust.

No clinical evidence was submitted regarding the second comparator, CHG sponges, although some narrative comparison was provided. No cost-effectiveness analysis was provided comparing Tegaderm CHG with the CHG sponge which was a weakness.

Summary of any additional work carried out by the External Assessment Centre

The EAC conducted an independent search for clinical and economic evidence relevant to the scope. In light of the lack of clinical evidence comparing Tegaderm CHG with the CHG sponge, the EAC widened the scope of its clinical review to include studies comparing the CHG sponge with standard dressings to allow an indirect comparison to be made.

The EAC corrected a minor calculation error within the economic model and re-ran the analysis using inputs that it judged to be valid. This had a limited impact on the results of the base case analysis and Tegaderm CHG remained robustly cost saving versus standard dressings.

A scenario analysis was conducted by the EAC, in which more recent CRBSI baseline risk data from the NHS in Scotland were used. These data are subject to limitations resulting from the potential underreporting of CRBSI. The cost savings generated between Tegaderm CHG and standard dressings were modest (about £3 per patient) and sensitivity analyses showed the savings were subject to considerable uncertainty. In addition to the cost of CRBSI and hazard ratio of CRBSI with Tegaderm CHG the results were also sensitive to catheterisation time and the number of dressings required.

The confirmed incidence of CRBSI in Scotland used in this scenario analysis was low, at 0.3 CRBSI per 1,000 catheter days. For Tegaderm CHG to become cost incurring, the incidence of CRBSI had to be lower still, at 0.24 CRBSI per 1,000 catheter days, or below.

An exploratory analysis of the likely cost-effectiveness of Tegaderm CHG and the CHG sponge was conducted by the EAC. The EAC judged that, based on the limited clinical evidence available, it may be appropriate to adopt a cost minimisation appraisal. The weighted average cost of Tegaderm CHG is £6.26 per dressing, compared with the NHS Supply Chain price of £8.13 for CHG sponges (comprising the CHG patch plus standard dressing). There is

some uncertainty on the cost of CHG sponges; the sponsor advised a lower price of £6.50.

Abbreviations

CCU	Critical care unit
CFU	Colony-forming unit
CHG	Chlorhexidine Gluconate
cm	Centimetre
CRBSI	Catheter related bloodstream infection
CRI	Catheter related infection
CVC	Central venous catheter
DSA	Deterministic sensitivity analysis
EAC	External Assessment Centre
FDA	U.S. Food and Drug Administration
FOI	Freedom of Information
HDU	High dependency unit
HES	Hospital Episode Statistics
HMM	Homogenous Markov model
HR	Hazard ratio
HRG	Health Resource Group
HTA	Health Technology Assessment
ICDRG	International Contact Dermatitis Research Group
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive care unit
IQR	Inter-quartile range
ITT	Intention-to-treat
IV	Intravenous
MAUDE	Manufacturer and User Facility Device

MHRA	Medicines and Healthcare Products Regulatory Agency
NHMM	Non-homogenous Markov model
NICE	National Institute for Health and Care Excellence
NPSA	National Patient Safety Agency
NR	Not reported
NS	Not significant
OECD	The Organisation for Economic Co-operation and Development
PICC	Peripherally inserted central catheter
PICO	Population, Intervention, Comparator and Outcome
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PVI	Povidone iodine
RCT	Randomised control trial
RR	Relative risk

2 Background

Throughout this report, the EAC makes reference to specific sections within the sponsor's submission as: (section X.X, submission).

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

2.1.1 Critique of sponsor's description of the background condition

The sponsor provided a brief, accurate description of the group of patients for whom Tegaderm CHG is suitable taken from the scope produced by the National Institute for Health and Care Excellence (NICE). This included critically ill adult patients in an intensive care unit (ICU) or high dependency unit (HDU) who require either a central venous or arterial catheter. A more comprehensive description has been provided by the EAC in Section 2.1.2.

2.1.2 EAC overview of the condition and technology

Critically ill adult patients

Critically ill adult patients are usually treated within ICUs or HDUs. ICUs, also known as critical care units (CCUs), are departments within hospitals that are specifically staffed and equipped to provide support, monitoring and treatment for critically ill patients. Constant support and monitoring of patients using medical equipment is undertaken to help with functioning of at least one, and often multiple, organs. It is common for CCUs to specialise in certain areas of care, for example neonatal care, paediatric care or care of patients with trauma. Within some hospitals, condition-specific treatment units such as heart, liver, kidney, breathing, circulation or nervous disorders have CCUs attached (7).

Hospital Episode Statistics (HES) data report that there were 237,710 adult ICU episodes in England in 2012/13. The adult mortality rate in the ICU was 9.1% in England in 2012/13; however, the status at discharge of 28.5% of adults in the ICU is unknown. Adults were transferred to an ICU from the theatre in 44.2% of cases, from another non-CCU ward in 23.3% of cases and from accident and emergency in 16.1% of cases in England in 2012/13. Support provided in the ICU included cardiovascular, respiratory, renal, gastrointestinal, neurological, dermatological and liver support. This was provided for an average duration of 4.0 days in adult males and 3.9 days in adult females. Many patients require support in more than 1 area at a time. The average duration of stay for adults in CCUs in 2012/13 was 3.91 days (7). Although Tegaderm CHG is suitable for use in infants aged 2 months or above (19), children are outside of the scope issued by NICE due to the lack

of evidence relating to the efficacy and safety of Tegaderm CHG in this population. Critically ill children up to the age of 16 are usually treated in paediatric ICUs. The care and support provided in paediatric ICUs is similar to that provided in adult ICUs, with children usually entering an ICU from children's inpatient services, operating theatres, neonatal units or accident and emergency (20).

Catheterisation in critically ill adult patients

Clinicians managing critically ill, adult patients frequently require vascular access through either an arterial or central venous catheter (CVC) for haemodynamic monitoring or access to enable the administration of drugs.

Arterial catheters are used to take an accurate blood pressure measurement and to obtain samples for arterial blood gas measurements. It consists of a thin hollow tube that is placed in an artery, usually at the wrist (via radial artery) or groin (via femoral artery). Patients with either low or high blood pressure require monitoring in order to inform treatment decisions (21).

CVCs can be used to provide access, for example, to administer drugs or parenteral nutrition, or facilitate extracorporeal blood circuits, or for haemodynamic monitoring and interventions (22). These catheters have a tip that sits in either the proximal third of the superior vena cava, the right atrium, or the inferior vena cava. CVCs are inserted via a peripheral vein or a proximal central vein, such as the internal jugular, subclavian, or femoral vein (22). It is estimated that at least 78% of critically ill patients have some form of CVC (23).

Complications with catheters can be classified as mechanical, embolic or infectious. Incidence of mechanical and embolic complications can be reduced by correct insertion technique, correct line-tip positioning and subsequent use (22).

Infections in critically ill patients

The susceptibility of infection in critically ill patients is higher than the general population and further, patients within an ICU are exposed to risk factors including invasive treatments and monitoring. Using catheters breaches the mucosal immune system, which is a front-line section of the immune system that attends the mucosal membranes such as those found in the gastrointestinal and upper respiratory tracts. The breaching of this system can provide ready access for pathogens in an already immunocompromised patient. Infections in these critically ill patients can be further complicated by the fact that clinical signs may be absent or hidden by signs of co-existing disease (23).

Infections occur when catheters become colonised by microorganisms, and this can take place either during insertion of the catheter, or when routine care of the catheter is being undertaken. It is believed up to 25% of catheters inserted are colonised, and there is also evidence that there is a statistically significant increase in the rate of colonisation, when dressing disruptions occur. Therefore, if protocols can be implemented in which the number of dressing disruptions is reduced, this is likely to improve practice by reducing the number of colonisations. Although the colonisation itself has no serious clinical effect, it can lead to catheter related blood stream infection (CRBSI) in an estimated 5% of catheterised patients (23).

NICE (2012) provide the following definition for a CRBSI:

"The presence of 1 or more CVC at the time of the blood culture, or up to 48 hrs following removal of the CVC, and 1 of the following:

i. A positive semiquantitative (>15 colony-forming units (CFU)/catheter segment) or quantitative (>10^3 CFU /ml or >10^3 CFU/catheter segment) culture whereby the same organism (species and antibiogram) is isolated from blood sampled from the CVC or from the catheter tip, and peripheral blood;

ii. Simultaneous quantitative blood cultures with a >5:1 ratio CVC versus peripheral CRBSI can be diagnosed where a patient has both a positive peripheral blood culture within 48 hours of catheter removal, a positive catheter-tip culture and no other explanation of the positive blood culture (2)."

CRBSI occurs when bacteria or fungi present following colonisation, migrate along the extraluminal catheter surface and into the bloodstream (24). This leads to a systematic infection, which in turn causes a severe immune response that can lead to septic shock and multiple organ failure, increasing the risk of death. The risk of CRBSI increases following the occurrence of thrombus (i.e. a blood clot), and the thrombus itself can become infected, which generally causes a more severe form of the disease that is treatment resistant (25).

In 1 recent case series of ICU patients, crude mortality rates for patients with a CRBSI ranged from 35% to 53%. ICU and hospital length of stay were also prolonged by an estimated 7.5 to 25 days and 4.5 to 32 days respectively (26). Clinical experts and national data provide a range of mortality rates in CCUs generally, from 9% (7) to 31%, the rate reported by Timsit *et al.,* 2012 (see correspondence log).

In terms of quality of life, the experts noted that CRBSI has a significantly detrimental effect over the short term. No details were given on the longer-term impact on quality of life.

Where a CRBSI is suspected, removal of the catheter may be sufficient to facilitate recovery. If the CRBSI is more severe, patients will be treated with broad spectrum antibiotics until laboratory results provide information on the organism causing the infection. A specific treatment regimen can then be tailored to the individual patient based upon antibiotic sensitivity and resistance profiling (23).

A number of measures can be undertaken to reduce the risk of CRBSI and local infections at the catheter entry site. NICE guidelines on infection (clinical guideline 139) recommend decontaminating the skin at the insertion site with chlorhexidine gluconate in 70% alcohol before inserting a central catheter and using a sterile, transparent semipermeable membrane dressing to cover the venous access device insertion site. A sterile gauze dressing covered with a transparent semi-permeable dressing should only be considered where patients have perfuse perspiration, or the access site is bleeding or oozing. The guidelines recommend changing the transparent semipermeable membrane dressing covering a central venous access device insertion site every 7 days, or sooner if the dressing is no longer intact or moisture collects under it. During dressing changes, the CVC insertion site and surrounding skin should be decontaminated, using chlorhexidine gluconate in 70% alcohol, and allowed to air dry (2).

A National Patient Safety Agency (NPSA) initiative known as 'Matching Michigan' was introduced into the NHS in April 2009 and run for 2 years. The purpose of this initiative was to draw on the lessons learnt in Michigan in tackling CVC-related bloodstream infections (referred to as CRBSI within this report). A reduction in CRBSIs from 7.7 to 1.4 CRBSIs per 1,000 CVC-days was achieved in Michigan. The initiative comprised 3 interventions:

- Technical interventions - to ensure consistent use of evidence-based measures for reducing risks of CRBSI;
- Non-technical interventions to address culture and systems within trusts and departments;
- Establishment of a standardised national reporting system.

Ninety-seven per cent of acute trusts in England participated in Matching Michigan and data were collected until March 2011. The CRBSI rate in adult ICUs fell from 3.7 CRBSIs per 1,000 catheter days in the first quarter of the study to 1.48 CRBSIs per 1,000 catheter days in the final quarter ($p<0.0001$). Infection rates for paediatric ICUs changed from 5.65 to 2.89 CRBSIs per 1,000 catheter days ($p=0.625$) (8). The findings included that infections rates were already trending down before the Matching Michigan programme. Further, the observed reduction in infection rates could be attributable as much to improvement efforts outside of the programme and to the awareness-raising effect of a nationwide programme as to any specific component of the programme itself (8). The EAC undertook a pragmatic literature review and identified no evidence relating to CRBSI within the NHS in England that was more recent than the results reported in Matching Michigan (Section 4.2.3).

Technology: Tegaderm CHG

Tegaderm CHG IV securement dressing, shortened to Tegaderm CHG (3M Health Care), is a transparent securement dressing used to cover and protect catheter sites and secure devices to the skin. Tegaderm CHG is a single device which comprises both a transparent adhesive dressing and an integrated gel pad. The gel pad absorbs fluid and contains an antiseptic agent (2% w/w chlorhexidine gluconate (CHG)) that is antimicrobial and antifungal. The aqueous gel is positioned over the insertion site and is readily active for delivery onto the skin. The transparent adhesive dressing acts as a barrier against external contamination and protects the catheter insertion site. Tegaderm CHG is breathable (allowing moisture vapour exchange) and transparent, meaning the insertion site can be observed continually (19).

The main advantage of Tegaderm CHG, over other CHG-impregnated dressings available to the NHS (Biopatch), are the transparent gel pad that allows for the observation of the catheter infection site, and the single component aspect that allows for potentially easier application. Photographs of Tegaderm CHG and Biopatch are shown in Figure 2.1.

The dressing is available in 4 shapes and sizes. These sizes and the proportion of total sales in the UK as provided by the sponsor (see correspondence log) are:

- 7 x 8.5 centimetre (cm) comprising less than 5% of total sales;
- 8.5 x 11.5 cm comprising 85% of total sales. These are largely used with CVC;
- 10 x 15.5 cm comprising 13% of total sales. These are largely used with PICC;
- 10 x 12 cm comprising less than 5% of total sales.

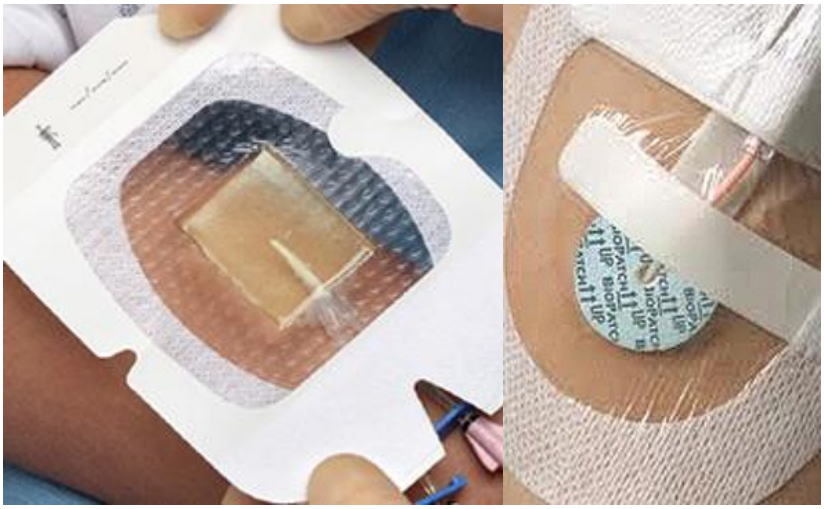
The average amount of CHG per dressing is dependent on the size of the dressing and varies between 15 mg and 78 mg (19). Different sizes and shapes of dressings (as outlined above) are required dependent upon the type of catheter being inserted. The shelf life of a Tegaderm CHG dressing is currently 2 years. The dressing is undergoing an aging and validation process to determine if this can be extended beyond 2 years (see correspondence log).

Common applications of Tegaderm CHG include central venous and arterial catheters, other intravascular catheters and percutaneous devices. The dressing should not be used on premature infants or infants younger than 2 months of age (19).

[redacted]. The sponsor also stated that the dressing is used outside of CCU and HDU, in haematology and renal dialysis, with its highest use in renal dialysis (see correspondence log).

Tegaderm CHG is an alternative or replacement to standard transparent semipermeable dressings. The antiseptic properties of the dressing are intended to reduce skin and catheter colonisation and hence incidence of CRBSI. The sponsor claims if successful, this will reduce the risk of mortality, reduce length of stay in ICU or hospital, improve quality of life and reduce costs associated with infection.

Figure 2.1: Tegaderm CHG (left) and Biopatch (right) dressings (27, 28)



Comparator: Sterile semi-permeable transparent dressing

Sterile semi-permeable transparent dressings are standard of care in most NHS hospitals. Such dressings are similar to Tegaderm CHG in that they are used to cover and protect catheter sites and secure devices to the skin, aiming to provide a barrier against external contamination. Advice from the sponsor and clinical experts (see correspondence log) suggests that the most commonly used standard dressings are those manufactured by 3M (Tegaderm IV) and those manufactured by Smith and Nephew (Opsite IV 3000). The shelf life of a Tegaderm IV dressing is 3 years.

Comparator: CHG impregnated dressing

CHG impregnated dressings are also used as standard of care in some NHS hospitals. CHG impregnated dressings comprise a CHG impregnated sponge, such as Biopatch (Johnson and Johnson), and a standard dressing (Figure 2.1). There are 3 key differences between Biopatch and Tegaderm CHG. First, Biopatch requires 2 separate items - a CHG sponge and an additional standard dressing. Second, CHG sponges are fully opaque and cover a 2 cm diameter around the insertion site meaning the insertion site cannot be observed continually. Finally, Biopatch contains 18% dry CHG which requires humidity from the skin in order to be released. In 'Matching Michigan', 17% of respondents used a CHG impregnated patch (likely to be either Biopatch or Tegaderm CHG) at the insertion site (8).

NHS Supply Chain dressing sales

A freedom of information request from NHS Supply Chain provided information on the volume of sales of Tegaderm CHG and its comparators in 2011/12 and 2012/13 (see correspondence log). In 2012/13 there were 108,200 Tegaderm CHG dressings sold across the various sizes (substantially higher than the 84,900 sold in 2011/12). Of the 2012/13 sales, 82,075 units were 8.5 x 11.5 cm dressings. As part of the sponsor's economic submission, they reported that the 10 x 12 cm IV 3000 dressing and the 8.5 x 10.5 Tegaderm IV dressing are the most often used standard dressings. This corroborated with expert opinion of the brands of standard dressings used within the NHS. In 2012/13, sales of these were 740,500 and 258,850 respectively. There were no sales of Biopatch recorded by NHS Supply Chain in either 2011/12 or 2012/13. However, it is highly plausible that all brands of dressings are sold in elsewhere to NHS Supply Chain.

2.1.3 Overview of relevant clinical guidelines

The sponsor correctly identified 3 clinical guidelines as being relevant to the decision problem. These included a NICE clinical guideline on Infection (CG139) (2) and an epic3 guideline on preventing healthcare-associated infections in NHS hospitals (29) as described in section 1.5 of the scope. The final guideline identified by the sponsor was "The Guidelines for the Prevention of Intravascular Catheter-Related Infections" (30). This guideline is United States specific.

The sponsor provided a description of the recommendations described in all 3 guidelines, which the EAC considered accurately represented their contents and was a satisfactory description of optimal clinical practice. It should be noted that, although all 3 guidelines recommend the use of sterile semi-permeable transparent dressing in patients with venous access devices, none are specific to critically ill patients. There is no suggestion in any of the guidance that practice in these patients should differ to the wider population.

In addition, the sponsor notes that the epic3 guideline recommends consideration of the use of CHG impregnated sponge dressings in adult patients with a CVC as a strategy to reduce CRBSI (29). The sponsor also notes that CG139 was reviewed in September 2014 following the release of the epic3 guidelines, however, it was decided that the guidance should not be updated at that time, noting further research is required to establish the efficacy of CHG dressings when applied to CHG-prepared skin.

2.1.4 Clinical care pathway

The clinical care pathway for vascular access device site care is described in Section 4.2.4.3 of the NICE clinical guideline on Infection (CG139) (2). The guideline recommends following the clinical care pathway as shown in Figure 2.2.

Figure 2.2: Clinical care pathway for vascular access device site care (adapted from NICE, 2012)

1. Decontaminate the skin at the insertion site with chlorhexidine gluconate in 70% alcohol before inserting a peripheral vascular access device or a peripherally inserted central catheter.

2. Use a sterile, transparent semipermeable membrane dressing to cover the vascular access device insertion site.

3. Consider a sterile gauze dressing covered with a sterile transparent semipermeable membrane dressing only if the patient has profuse perspiration, or if the vascular access device insertion site is bleeding or oozing. If a gauze dressing is used:
- **a.** Change it every 24 hours, or sooner if it is soiled and
- **b.** Replace it with a sterile transparent semipermeable membrane dressing as soon as possible.

4. Change the transparent semipermeable membrane dressing covering a central venous access device insertion site every 7 days, or sooner if the dressing is no longer intact or moisture collects under it.

5. Leave the transparent semipermeable membrane dressing applied to a peripheral cannula insertion site in situ for the life of the cannula, provided that the integrity of the dressing is retained.

6. Dressings used on tunnelled or implanted central venous catheter sites should be replaced every 7 days until the insertion site has healed, unless there is an indication to change them sooner.

7. Healthcare workers should ensure that catheter-site care is compatible with catheter materials (tubing, hubs, injection ports, luer connectors and extensions) and carefully check compatibility with the manufacturer's recommendations.

8. Decontaminate the central venous catheter insertion site and surrounding skin during dressing changes using chlorhexidine gluconate in 70% alcohol, and allow to air dry. Consider using an aqueous solution of chlorhexidine gluconate if the manufacturer's recommendations prohibit the use of alcohol with their catheter.

9. Individual sachets of antiseptic solution or individual packages of antiseptic-impregnated swabs or wipes should be used to disinfect the dressing site.

The clinical care pathway outlined in this guidance is not specifically for critically ill adult patients who require a central venous or arterial catheter; however, the evidence on which the recommendations are based is largely from patients with intravenous access via catheters. The clinical care pathway described in Figure 2.2 applies to the patients in the decision problem that this report addresses.

2.1.5 Changes to current services

In its clinical evidence submission, section 3.5, the sponsor has stated that "the proposed pathway would not differ in any way from the current pathway and the Tegaderm CHG dressing replaces sterile, transparent, semi permeable dressings in the protocol of care".

The EAC confirmed with experts that the use of Tegaderm CHG will not materially alter the care pathway described in Figure 2.2. The only change being that Tegaderm CHG specifically, rather than a sterile, transparent semipermeable membrane dressing would be used within step 2.

2.2 Overview of sponsor's description of ongoing studies

The sponsor undertook a search of a trial registry (ClinicalTrials.gov) to identify ongoing studies of relevance to the decision problem. The sponsor identified no studies following this search. However, 2 ongoing studies were noted within the sponsor's submission, 1 comparative clinical and 1 health economics. As these were not identified via the trial registry search, it is likely the sponsor noted them due to prior knowledge of them.

The 2 ongoing studies identified by the sponsor were described as:

- A health economic analysis comparing Tegaderm CHG to sterile semi-permeable transparent dressing has been prepared and is currently awaiting journal acceptance. The sponsor advised the *de novo* model reported in this submission is largely based upon this analysis (see Section 4);

- A comparative study at a major clinical centre in the UK is ongoing. A poster presentation containing the results of the initial data analysis of a comparative study in 273 ICU patients was presented at The Hospital Infection Society Conference, Lyon, Nov. 2014. This study was not powered to detect differences in CRBSI and the primary objective was comparing skin colonisation at the insertion site of the intravascular catheter, comparing Tegaderm CHG dressing with a sterile semi-permeable film dressing. All patients were swabbed with 2% CHG in alcohol.

Since the sponsor's clinical evidence review was undertaken, a poster presenting results of the comparative clinical study has been published (6). This study was identified during the EAC's literature review (Section 3).

The EAC searched Clinicaltrials.gov, WHO International Clinical Trials Registry Platform and ISRCTN registry for ongoing studies as described in Appendix 2. One hundred and fifty four unique studies were identified, of which 6 were ongoing studies relating to Tegaderm. Four of the 6 studies have not yet reached their completion date and these are now described.

1. *Investigation of Tegaderm Chlorhexidine Dressing for the Prevention of Catheter Associated Blood Stream Infection in Paediatric Intensive Care Units (Trial number: UMIN000007207) (31)*

This Japanese randomised control trial (RCT) is comparing Tegaderm CHG to standard care in critically ill children requiring a CVC for more than 7 days, with CRBSIs being the primary end point. The trial is expected to complete in April 2015. This is funded by 3M.

2. *Antimicrobial Catheter Securement Dressings for the Prevention of CVC-related Bloodstream Infections in Cancer Patients/ Chlorhexidine Containing Iv-securement Dressings for the Prevention of Central Venous Catheter-related Blood Stream Infections in Neutropenic Patients: a Randomized Trial (Trial number: NCT01544686) (32)*

Neutropenic cancer patients requiring CVC are being recruited into a RCT, conducted in Germany, comparing Tegaderm CHG to Tegaderm Advanced IV (a standard dressing). The primary end point is CRBSI. The study is expected to complete in October 2015.

3. *CHG Dressings in Children With Central Lines (Trial number: NCT01955226) (33)*

This RCT, set in the USA, compares Tegaderm CHG with a standard Tegaderm IV dressing in children requiring intravascular access. The primary end point is reduction in unscheduled central catheter dressing changes, with blood stream infections being a secondary outcome. It is due to complete in January 2017.

4. *A Prospective Randomised Microbiological Study for Use of 3M™ Tegaderm™ Chlorhexidinegluconate Dressing at Entry Site of EVD's to Reduce EVD-associated Infections (Trial number: NCT02078830) (34)*

This Swiss RCT is recruiting patients requiring the implantation of an external ventricular drain (EVD) and compares Tegaderm CHG to standard dressing (Tegaderm Advanced IV). The primary end point is difference in bacterial contamination at the EVD entry-site after 5 days. The estimated completion date is October 2016.

The register has not received information for over 2 years on either of the 2 other studies, hence their status is shown as 'unknown'. A description of each of these studies is provided.

1. *Trial on the Efficacy of Tegaderm Chlorhexidine Gluconate (CHG) in Reducing Catheter Related Bloodstream Infections (Trial number: NCT01142934)*

This multicentre, Italian RCT of hospitalised patients is comparing Tegaderm CHG with Tegaderm IV (standard dressing). The study, funded in part by 3M, was anticipated to be completed in October 2012; however the trial is shown as "recruiting". No results of the study were identified by the EAC. The sponsor reported in section 7.3.2 of its submission that this study has been terminated due to slow recruitment of participants. At termination, some interim data was released; however, CRBSI rates were not provided for critically ill patients alone. Therefore, the sponsor correctly judged that this study could not be utilised further.

2. *Efficacy of Tegaderm-CHG® Dressing vs. Tegaderm-IV® Dressing (Trial number: NCT01733940)*

This Spanish RCT comparing Tegaderm CHG with Tegaderm IV (standard dressing) in patients in ICU was due to complete in June 2013; however it is shown as "recruiting". No results of the study were identified by the EAC. The sponsor contacted the lead investigator of the study who provided a report of the study and its results. The study was conducted and finished during 2012. The lead investigator advised that the results of the study had been presented at the 2013 Congress of the Spanish Society of Preventive Medicine. The sponsor reported that the RCT of n=126 patients found Tegaderm CHG reduced the risk of catheter tip colonisation by 73% (95%CI: 0.09 to 0.76, p = 0.0013) compared with standard dressing (see correspondence log). Given that this study is reported in Spanish, rather than English, it would not have met the inclusion criteria for either the EAC's or sponsor's clinical evidence review.

2.3 Critique of sponsor's definition of the decision problem

The sponsor, on the whole, has used the decision problem provided in the scope and no deviation from the scope was described by the sponsor in submission, table A1. There are, however, some variations between the sponsor's submission and the decision problem, which are now described. Some of these deviations were acknowledged by the sponsor in 'extra table C' of the submission. This compared the parameters defined in the scope with those adopted in the 1 RCT (1) included by the sponsor in the clinical evidence section.

Population

The population was described in the scope as "Critically ill adult patients in intensive care or high dependency units who require a central venous or arterial catheter". The clinical evidence submission provided by the sponsor largely matches this patient population. The only deviation from this occurs where skin colonisation in healthy volunteers is considered for 1 of the comparators. This is described in detail in this section under 'outcomes'.

The *de novo* economic model provided by the sponsor is consistent with the population defined in the scope.

Intervention

The intervention described in the scope is swabbing with 2% CHG in alcohol and Tegaderm CHG IV securement dressing, shortened to Tegaderm CHG. The sponsor's submission is in line with the scope in that the evidence provided by the sponsor relates to Tegaderm CHG. The evidence meeting the sponsor's inclusion criteria did not include swabbing with 2% CHG in alcohol prior to application of Tegaderm CHG, however. Instead, skin was swabbed with 1 of a number of alcohol-based antiseptic solutions (5% povidone iodine (PVI) in 70% ethanol; 0.5% CHG in 67% ethanol; 0.25% CHG in 0.025%; or benzalkonium chloride, 4% benzyl alcohol). The sponsor has acknowledged this discrepancy and provided an additional ongoing study in which skin preparation included swabbing with 2% CHG in alcohol (6). This study has been published as a poster since the sponsor's clinical evidence review was undertaken. The economic model is populated using the sponsor's clinical evidence and, therefore, relates to Tegaderm CHG, with no swabbing with 2% CHG in alcohol.

The sponsor provided the EAC with the relevant CE (Conformité Européenne) documentation (CE certificate number No. CE 525600), which shows that a CE mark was received for Tegaderm CHG in April 2009. The sponsor stated in its submission that the authorisation was updated in February 2014 to include reduction in CRBSI as an indication. The CE mark covers all 4 sizes of Tegaderm CHG. An ISO 13485: 2003 certificate (FM 68740) as evidence of the sponsor implementing and maintaining a quality management system was provided (see correspondence log).

Comparator(s)

Two comparators are described in the scope:

- Swabbing with 2% CHG in alcohol and sterile semi-permeable transparent dressing (described henceforth as standard dressing);
- Swabbing with 2% CHG in alcohol and CHG impregnated dressing (described henceforth as CHG sponge).

The clinical study (n=1,879) identified by the sponsor as meeting its inclusion criteria compared Tegaderm CHG to standard dressings (1). The brands of standard dressing used within this study were Tegaderm HP Transparent Film Dressing, a highly adhesive dressing, and Tegaderm Transparent Film Dressing, a standard breathable hypoallergenic dressing. The sponsor provided justification for the inclusion of highly adhesive dressings as a comparator. In line with the intervention, preparation in the comparator patients involved swabbing with 1 of a number of antiseptic solutions prior to dressing application. The sponsor acknowledged that this deviated from the scope. The study reported in the poster by Karpanen *et al.* (mentioned by the sponsor, but published after its review) compared Tegaderm CHG with a standard dressing (n=273). Patients in this study were swabbed with 2% CHG in alcohol. (6).

No studies meeting the sponsor's inclusion criteria compared Tegaderm CHG with a CHG sponge. In the submission, extra table C, the sponsor stated that maintenance of reduction in of skin colonisation is similar between Tegaderm CHG and CHG sponge based upon a study in healthy volunteers (3). A justification of this source of comparative evidence was not provided.

The economic model utilised the comparative clinical evidence identified by the sponsor's clinical evidence review and as such, only standard dressings are included within sponsor's *de novo* economic model.

Outcomes

The scope lists 8 clinical outcomes as relevant to the decision problem. The sponsor has addressed 5 of these for Tegaderm CHG and standard dressings based on data provided in Timsit *et al.*, 2012 (1). The remaining 3 outcomes (mortality caused by catheter related infections (CRI), local site infections and quality of life) were not addressed in either Timsit *et al.*, 2012 or the sponsor's submission.

The only outcome considered for CHG sponge was skin colonisation. This was based on a study in 32 healthy adult volunteers, rather than critically ill adult patients (3). Table 2.1 displays the outcome measures suggested in the scope and those included in the submission.

Table 2.1: Outcomes scope and sponsor's submission

Outcomes to consider in scope issued by NICE:	**Outcomes considered in submission:**
• 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 CRI; • Dermatitis; • Local site infection; • Quality of life; • Device-related adverse events, including adverse events caused by contact with chlorhexidine.	<u>Outcomes compared for Tegaderm CHG and standard dressing:</u> • Catheter related bloodstream infection (CRBSI); • Skin and catheter colonisation; • Length of stay in critical care/high dependency units; • Dermatitis; • Device-related adverse events, including adverse events caused by contact with chlorhexidine; • Ease of use. <u>Outcomes compared for Tegaderm CHG and CHG sponge</u>: • Skin colonisation.

Cost analysis

The economic analysis provided by the sponsor, including the *de novo* model, largely matched that of the scope (see section 4). The only deviation from the scope was that "swabbing with 2% CHG in alcohol and a CHG impregnated dressing", i.e. CHG sponge, was not included as a comparator within the sponsor's economic model. The sponsor justified this given the lack of evidence available to populate the model for Tegaderm CHG compared with CHG sponge. In the economic submission, the sponsor provided details regarding the cost of the CHG sponge within the NHS.

Subgroups

No subgroups were specified in the scope and none have been included in the sponsor's clinical evidence submission or economic model.

Special considerations, including issues related to equality

No special considerations including issues related to equality were specified in the scope and sponsor has not identified any additional issues.

Tegaderm CHG is not appropriate for use in people with an allergy to CHG. Clinical experts advised that the proportion of patients with an allergy to CHG is very low. One expert advised that, although rare, allergic reactions to CHG may be increasing due to an increase in exposure to the antiseptic (see correspondence log).

The sponsor provided additional information on the number of reported incidents suggestive of severe contact dermatitis. [redacted].The experts noted that severe contact dermatitis will impact on quality of life, but only during the period in which the symptoms of the condition appear.

The clinical experts also advised that CRBSIs are more common in certain critically ill patients, specifically oncology patients who have low neutrophil count and patients with haematological cancers. In these patients, CHG impregnated dressings which have the potential to reduce CRBSI may be of particular benefit.

Conclusions on sponsor's submission in relation to the decision problem

The sponsor provided a transparent and concise submission with relevance to the decision problem dictated by the evidence available from its included RCT (1). This study, on the whole, aligned with the decision problem, with the key gap in evidence relating to information around the CHG sponge. The other limitation of the sponsor's submission was the lack of information on ongoing studies relating to Tegaderm CHG. A short description of ongoing studies, including those that were not necessarily within scope of this assessment, would have been welcome.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

3.1.1: Critique of the sponsor's search strategy

The Peer Review of Electronic Search Strategies (PRESS) Checklist was used to inform the critique of the sponsor's search strategy (35). The PRESS checklist is an evidence-based tool to critically appraise literature search strategies. The PRESS project was funded by the Canadian Agency for Drugs and Technologies in Health (CADTH) and this approach to peer reviewing search strategies is supported by the Cochrane Collaboration's Information Retrieval Methods Group (36).

The sponsor conducted 3 separate searches: a single concept search on Tegaderm CHG; a 2 concept search on comparators and CVC; and a 2 concept search on comparators and arterial catheters. The sponsor stated that the search was designed to retrieve all studies relating to the technology and relevant comparators (including standard care dressings). The highly sensitive search approach taken was appropriate to this aim.

Searches were not restricted by date or language (though the submission selection criteria restricted to English language studies). No study design filter was used; this is appropriate for a search which aims to retrieve evidence on adverse effects. The main databases searches were carried out in July and October 2013; a more recent search would have improved the currency of the submission.

The databases searched for clinical evidence and adverse events were in line with NICE's guidance as stated on the submission template; MEDLINE, MEDLINE In-Process, Embase, and Cochrane Library, with additional searches using Econlit, Conference Proceedings Citation Index - Science, Clinicaltrials.gov, MAUDE, EuroScan, MHRA, and EMEA. In addition, key investigators were contacted for information about unpublished or on-going studies. It is not clear if the search on comparators and arterial catheters included a search of ClinicalTrials.gov, MAUDE, EuroScan, MHRA or EMEA as neither result numbers or strategies are reported. The providers for each database were listed. Though the range of resources was appropriate for the research question, the search for unpublished literature would have been enhanced by the inclusion of additional key trial registers such as WHO International Clinical Trials Registry Platform (ICTRP), and a hand-search of key conference abstracts. Methods guidance (37) and research (38) suggests that both ClinicalTrials.gov and ICTRP should be searched when looking for ongoing and unpublished trials. Restricting the search for studies

presented at conferences to the 2 sources which index conference abstracts (Embase and the Conference Proceedings Citation Index – Science) increases the risk of missed relevant studies.

Dates of searching were given in the submission, though there was some inconsistency. On page 25 for example, the search date for the published studies search was given as July 23rd 2013, whereas in appendix 10.1, submission, the search dates for the published studies search on comparators and arterial catheters was given as October 29th 2013.

The search strategies were reported in section 10 and appendices 1 and 2 of the submission. The EAC could not fully reproduce the sponsor searches as strategies were not reported in full for all searches (e.g. the comparator searches in MAUDE, EuroScan, EMEA, MHRA and Clinicaltrial.gov). The main database strategies were reported in detail, although comparison of the EAC re-run sponsor searches with the result numbers reported in the results summary table (page 135 in the submission) indicated several possible reporting errors e.g. unreported search lines (Embase Tegaderm strategy), wrong line combinations reported (Cochrane comparator and CVC search – line 26; Cochrane comparator and ACs search – line 34), wrong database segment reported (Web of Science Tegaderm search). Where this occurred, the EAC was led by the reported result numbers and strategy logic, and has assumed the error lay in the methods reporting, rather than the actual strategy as run.

The strategies were clearly structured into search concepts, Boolean operators were used appropriately and where database functionality allowed, the strategies included both subject heading searches and free-text searches. Search lines appear to be combined correctly, though on occasion due to reporting issues (detailed above) it is difficult to be certain.

While fundamentally adequate in construction, sensitivity could have been improved in a number of ways. In the Tegaderm MEDLINE strategy for example, a free-text search on ‘chlorhexidine’ alone (rather than ‘chlorhexidine gluconate’) would have enhanced the strategy, as would the inclusion of relevant potential alternatives to ‘dressing’ (e.g. ‘pad’). A search on the Unique Ingredient Identifier (UNII) for chlorhexidine gluconate using the Registry Number/Name of Substance (RN) field in the Tegaderm strategy would also have been a useful addition to the strategy. At times, a wider range of subject headings could have been used. In the Embase search on comparators and CVCs for example, the free-text searches in lines 8 and 10 indicate that Hickman catheters and peripheral inserted CVCs are of interest, yet relevant subject headings (‘peripherally inserted central venous catheter’, ‘Hickman catheter’) were not included in the strategy. Similarly, in the

Embase search on comparators and arterial catheters, the subject heading of ‘arterial line’ was not included. In the searches on comparators and CVCs, a wide range of terms for dressings and related concepts were included, but certain terms which would also seem relevant (e.g. ‘pad’, ‘sponge’, ‘disc’) were not. The use of truncation was mostly appropriate, though the strategies would have been improved by additional use in some instances (e.g. truncation of ‘tegaderm’ to retrieve variants such as ‘tegadermTM’, truncation of catheter names such as ‘Hickman’ to retrieve variants such as ‘Hickman’s catheter’, truncation of catheter location terms such as ‘chest’, ‘neck’, ‘wrist’, ‘elbow’.)

The way in which syntax was used in Cochrane Library searches means that parts of the strategy are unlikely to function as the searcher intended, increasing the risk of missed relevant studies. One single search was carried out across the Cochrane Library for all databases and non-MeSH search lines were limited to the title / abstract / keyword fields. This limit is not appropriate for a search of the DARE, HTA and NHS EED databases, as it does not include a search across abstracts in these resources; in effect for these 3 databases the strategy searched in the title and keyword fields only. There is also a problem with the way proximity operators were used in the Cochrane Library searches. The sponsor search used the syntax ‘next’ for proximity e.g. ‘next/3’. In Cochrane only ‘NEAR’ is designed to be used in this way; the ‘NEXT’ term in Cochrane does not support the /x parameter (39). It is likely, therefore, that proximity searches did not work as intended, for example, the search in line 7 of *‘((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw’* would not retrieve many results which include the phrase “hickman catheters”. Occasionally, absence of proximity syntax adversely impacts on the precision of the search. In the Cochrane Library arterial catheter search for example, phrases such as such as ’art line’ or ‘a line’ were not specified as such through the use of quotation marks. As a result, these phrases would be interpreted by the interface as (art AND line) or (a AND line). Although this would not impact on search sensitivity, it could return excessive non-relevant results. For example, the search (*art line or a line):ti,ab,kw* as run by the sponsor retrieves 11,819 records in Cochrane, whilst the search *("art line" or "a line"):ti,ab,kw* retrieves just 166 records (search run 10/12/14).

The sponsor's searches for published and unpublished evidence were re-run by the EAC. Searches were run exactly as reported, apart from when a comparison of the re-run sponsor searches with the result numbers reported in the submission results summary table indicated possible reporting errors, as described above. In these instances the EAC amended the strategy in the way that the reported result numbers and the search logic indicated appropriate. Where insufficient information was provided to enable replication, the EAC did not run searches. The strategies used when re-running the sponsor's search and the volume of results identified, are fully reported in Appendix 1. The EAC search identified 6,831 unique titles and abstract, compared to 6,895 records identified by the sponsor, a broadly similar yield.

3.1.2: EAC's additional searches

A *de novo* literature search was undertaken by the EAC. This search aimed to identify all prospective comparative studies conducting a head-to-head comparison of at least 2 of the 3 dressing types: Tegaderm CHG, standard dressing and CHG impregnated dressing. The purpose of this search was to a) identify any studies on Tegaderm CHG that may have been missed by the sponsor's search strategies and b) identify any studies relevant to the broader inclusion criteria applied in the EAC review.

A strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through assessment of the sponsor strategy, discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi).

The search comprised 3 concepts:

- Catheters;
- Dressings;
- CHG.

The concepts were combined as follows: 'Catheters AND dressings AND CHG'. An additional line searched on the brand names for the 2 known interventions of interest ('Tegaderm' and 'Biopatch'). This was designed to capture any records that may have been missed by the 3 concept approach.

Reflecting the inclusion criteria, searches were limited to English language studies. The strategy also excluded animal studies using a standard algorithm. No date limits were applied and the search was not restricted by study design.

The sensitivity of the MEDLINE strategy was assessed by checking successful retrieval of the relevant studies listed on the manufacturer's webpages (40, 41) and of the studies included in 2 relevant systematic reviews (42, 43). All relevant studies which were indexed in MEDLINE were retrieved by the strategy.

The MEDLINE strategy was translated appropriately for other search sources. The strategy for MEDLINE is shown in Figure 3.1. Full strategies (including search dates) for all search sources and volume of results returned are provided at Appendix 2.

Figure 3.1: EAC search strategy for Ovid MEDLINE and MEDLINE In-Process

1	Catheterization/ (47106)
2	Catheterization, Central Venous/ (12212)
3	exp Catheterization, Peripheral/ (8822)
4	Cardiac Catheterization/ (40962)
5	exp Catheters/ (19630)
6	Catheter-Related Infections/ (2264)
7	(catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kf. (195245)
8	(CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs).ti,ab,kf. (5442)
9	((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (103)
10	(central adj3 (venous or pressure)).ti,ab,kf. (21893)
11	(central adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (10248)
12	(peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (5819)
13	((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (22893)
14	((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (6890)
15	(art line$1 or a line$1 or IAC or IACs).ti,ab,kf. (9422)
16	(CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (831)
17	(access$ adj3 (device$ or site or sites or route$1)).ti,ab,kf. (9310)
18	((invasive or percutaneous) adj3 device$).ti,ab,kf. (2294)
19	(CVA or CVAD or CVADs or VAD or VADs).ti,ab,kf. (8146)

20	(IVD or IVDs).ti,ab,kf. (1454)
21	(hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1).ti,ab,kf. (6679)
22	or/1-21 (319106)
23	Bandages/ (14372)
24	Occlusive Dressings/ (3632)
25	exp Gels/ (36117)
26	exp Surgical Sponges/ (2955)
27	(dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag$ or gel or gels or film or films or secur$).ti,ab,kf. (579803)
28	(transparen$ or see-through or permeable or semipermeable).ti,ab,kf. (51475)
29	or/23-28 (650615)
30	Chlorhexidine/ (6430)
31	(chlorhexidine$ or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1).ti,ab,kf,rn. (9288)
32	(3M or 3MTM).ti,ab,kf. (4684)
33	("johnson & johnson$" or "johnson and johnson$").ti,ab,kf. (798)
34	ethicon$.ti,ab,kf. (904)
35	or/30-34 (15568)
36	22 and 29 and 35 (180)
37	(tegaderm$ or biopatch$).ti,ab,kf. (161)
38	36 or 37 (328)
39	exp animals/ not humans/ (4094649)
40	(editorial or comment or case reports).pt. (2605322)
41	case report.ti. (166720)
42	38 not (39 or 40 or 41) (259)
43	limit 42 to english language (236)
44	remove duplicates from 43 (230)

Key to Ovid symbols and commands

.ti,ab,kf.	Restricts search to title, abstract and keyword headings fields
.rn.	Restricts search to Registry Number/Name of Substance field
/	Restricts search to Medical Subject Headings (MeSH)
exp	Explodes the Medical Subject Heading (MeSH) search
$	Truncation symbol
adjn	Words must appear with n words of each other
.pt.	Restricts search to publication type field

The EAC searched all of the resources reported by the sponsor. The EAC also searched additional resources including 2 additional trial registers and a selection of relevant conferences and websites The selection of conferences to search was identified through discussion with the research team, the manufacturer and NICE. The selection of websites to search was informed by the list of external organisations identified on the NICE final scope document for the technology.

3.2 Critique of the sponsor's study selection

The study selection applied by the sponsor adopted a PICO (Population, Intervention, Comparator, Outcomes) framework which was appropriate and generally in line with the scope specified by NICE. Both Tables B1 and B2 within its submission were completed, identifying the same selection criteria were used for published and unpublished studies.

The population was limited to adult patients in an ICU or critical care setting requiring an intravascular catheter (CVC or arterial catheter) after admission for at least 48 hours. This patient population is in line with the scope, with the exception of catheter dwell time, which is not specified within the scope. The sponsor excluded studies in children and studies in adults who were not in a critical setting or admitted to such a setting with a catheter in place or had the catheter for less than 24 hours.

The intervention was appropriately limited to chlorhexidine-containing Tegaderm dressing (Tegaderm CHG dressing). The scope defines a more specific intervention - swabbing with 2% CHG in alcohol and Tegaderm CHG IV securement dressing. However, had the sponsor limited included studies to those swabbing with 2% CHG in alcohol prior to applying Tegaderm CHG no studies would have been included.

The following comparators were defined by the sponsor:

- Chlorhexidine-sponge dressing (Biopatch);
- Any transparent film dressing including Tegaderm non-medicated dressings, IV 3000;
- Gauze and tape, etc.;
- No dressing.

Only the first 2 comparators listed were specified in the scope, as these represent standard of care within the NHS. The sponsor, however, was attempting to identify all comparative literature relating to Tegaderm CHG and hence included all plausible comparators including those used outside of the UK.

The sponsor listed 3 categories of outcomes, those relating to effectiveness, those relating to safety and those relating to performance. These outcomes are broadly in line with those specified in the scope (see Table 2.1).

Inclusion according to study design varied with category of outcomes. For effectiveness outcomes (CRBSI, skin and catheter colonisation), only randomised controlled trials that compared Tegaderm CHG with 1 or more of the comparators listed were included. For safety and performance outcomes (such as securement), comparative studies were included provided that there were at least 10 patients recruited and less than 50% were lost to follow up. Again, Tegaderm CHG had to be compared with one, or more, of the comparators listed.

The sponsor followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology to report on the studies identified and justify any inclusions and exclusions. Its submission included a description of the study selection process, a fully completed PRISMA diagram and supplementary file specifying the reason for exclusion of papers at the full paper review stage. The selection was conducted by 2 reviewers who were not independent; rather the second reviewer checked the selections made by the first and disagreements were resolved by discussion.

3.3 Included and excluded studies

3.3.1: Sponsor's included and excluded studies

Of the retrieved records (6,898), the sponsor included 1 study (see Table 3.1) which met its selection criteria. This published study, by Timsit *et al.* (2012), was within scope and hence included appropriately. The included study was a RCT, set in 12 French ICUs, included patients aged 18 years or older and expecting to require intravascular catheterisation for 48 hours or longer. Tegaderm CHG was compared with both a highly adhesive dressing, Tegaderm HP transparent film dressing, and a standard dressing, Tegaderm transparent film dressing (1).

Data were extracted by the sponsor from 4 additional studies in the sponsor's submission tables B3 and B4 (44-47). Three of these studies reported on nursing satisfaction with Tegaderm CHG and were subsequently excluded as they did not report appropriate outcomes based upon a validated tool (44-46). The final study, an unpublished clinical trial, was excluded as both critically ill and non-critically ill patients were included within the study and results were not reported for critically ill patients independently (47). Further information on the 3 studies reporting on nursing satisfaction is provided in Section 3.6.2.

Table 3.1: List of included studies identified by the sponsor

Primary study reference	Population	Intervention	Comparator
Timsit *et al.* (2012) (1)	Critically ill patients in ICU	Tegaderm CHG	1. Standard dressing (Tegaderm Transparent Film Dressing); 2. Highly adhesive dressing (Tegaderm HP Transparent Film Dressing).

The EAC applied the sponsor's inclusion criteria to the 6,831 unique records identified during the replication of the sponsor's search (Section 3.1.1); 1 record was selected for inclusion. The exclusion of the 4 additional studies was appropriate given the criteria adopted. The included study matches the study included by the sponsor (1).

In 'extra table C' of the sponsor's submission, the sponsor provided brief information from a comparative study of Tegaderm CHG and other CHG containing dressings (3). The EAC judged that this study was not applicable to the decision problem given the participants were healthy volunteers.

3.3.2: EAC's included and excluded studies

The EAC undertook an additional search, which returned 1,742 records (reduced to 1,215 following deduplication). Broader inclusion criteria than those utilised by the sponsor were applied to sift the 1,215 titles and abstracts (Section 3.1.2). This additional search was more focused than the sponsor's search, which resulted in a lower number of titles to sift. This additional search aimed to identify all prospective comparative studies conducting a head-to-head comparison of at least 2 of the 3 dressing types: Tegaderm CHG, standard dressing and CHG impregnated dressing. This was conducted to gain a greater understanding of efficacy of the Tegaderm CHG compared with CHG impregnated dressings, given the lack of comparative evidence identified by the sponsor.

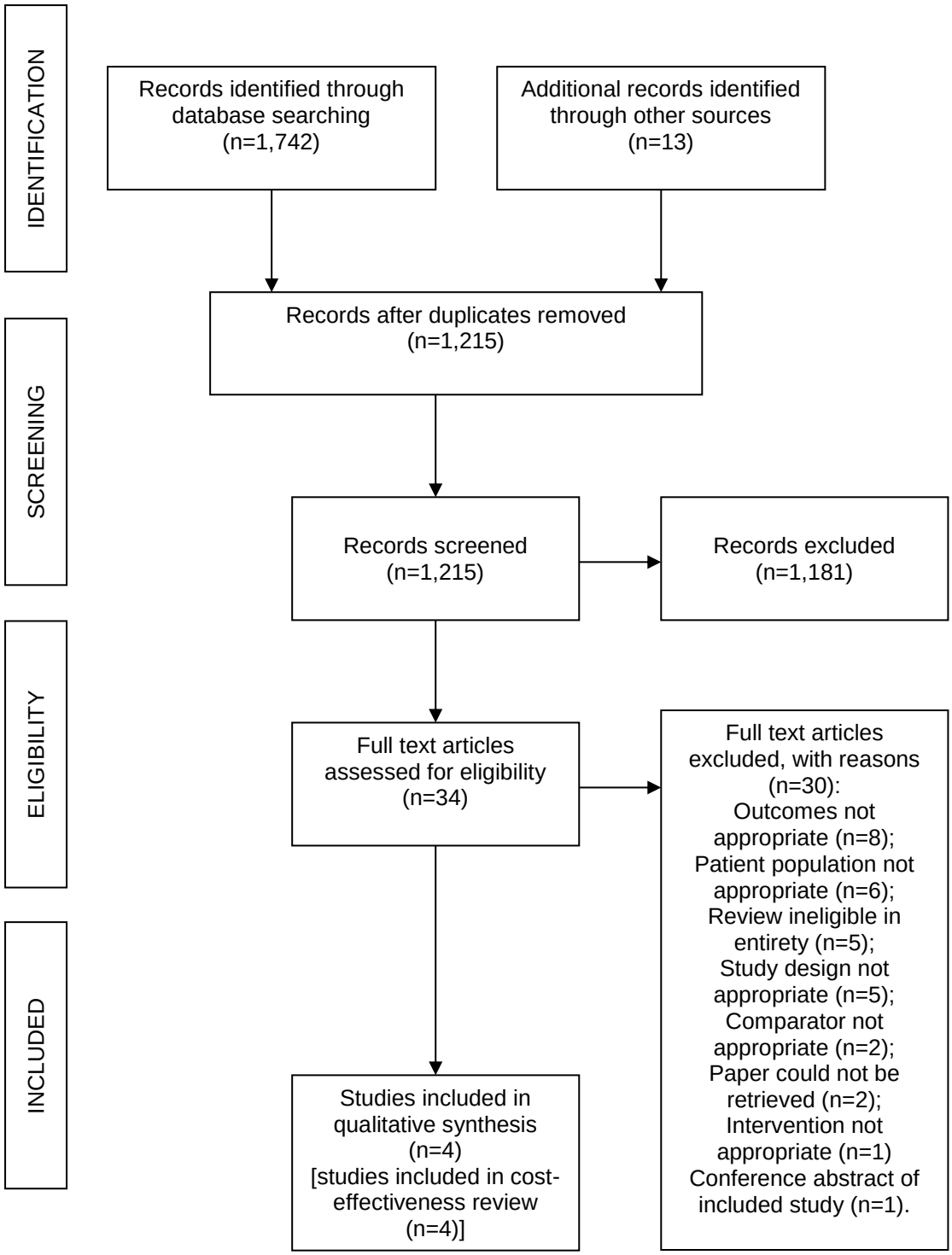
The selection criteria are described in Table 3.2. The criteria are in line with scope issued by NICE with the exception of the skin preparation solution. The scope specifies that prior to catheter insertion skin should be prepared with 2% CHG in alcohol solution as defined in the NICE clinical guideline on infection (2). In order to maximise sensitivity, the skin preparation solution was not specified within the selection criteria.

Table 3.2: EAC selection criteria for comparative studies

Inclusion criteria	
Patients	Adult patients (18 years or older) in ICU/CCU or HDU requiring CVC or atrial catheter insertion
Intervention	Tegaderm CHG IV securement dressing
Comparator	CHG impregnated dressing (e.g. Biopatch); Sterile semi-permeable transparent dressing (e.g. Tegaderm IV).
Outcomes	As specified in scope: • 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 chlorhexidine. To inform economic modelling: • Length of stay in hospital; • Number of dressings per patient/catheter (to inform economic model).
Study design	Prospective comparative head-to-head studies including RCTs and observational studies (published and unpublished). Studies must compare either: Tegaderm CHG v. CHG impregnated dressing; Tegaderm CHG v. Sterile semi-permeable transparent dressing; CHG impregnated dressing v. Sterile semi-permeable transparent dressing.
Language restrictions	English only
Search dates	No limit
Exclusion criteria	
Population	Animal and in vitro studies; Patients in a non-ICU, CCU or HDU setting; Paediatric populations (under 18 years old).
Interventions	Studies where the dressing used is unclear or unspecified; Studies where an interim dressing is used prior to Tegaderm CHG or CHG impregnated use; Studies where dressing is used as part of a multifaceted intervention aimed at reducing infection rate, e.g. change in skin preparation, change in equipment used and education of staff.
Study design	Non-comparative studies Retrospective studies or studies making a retrospective comparison

The 1,215 records were screened by 2 independent reviewers (MJ and WG). Disagreements were resolved between the 2 reviewers, or where required by consulting a third reviewer (JC). Following a review of titles and abstracts the full papers of 34 articles were requested. Thirty studies were excluded at this stage, with the remaining 4 studies meeting the selection criteria. A further 4 studies were included in the EAC's cost-effectiveness review as reported in Section 4.1. A PRISMA diagram of record selection by the EAC is provided in Figure 3.2 and the reason for exclusion of full papers provided in Appendix 3.

Figure 3.2: PRISMA flow diagram showing studies assessed during the EAC review



The 4 studies that met the EAC's inclusion criteria (see Table 3.3) included the study identified by the sponsor (1), plus 3 additional studies (4-6). The study by Karpanen *et al.* (2014) (6) was identified by the sponsor within its submission as an ongoing study, but at the date of submission had not been published. Results from the study have subsequently been published as a conference abstract. Information for the EAC's review utilised the full poster presentation, which was provided by the sponsor. Had this conference abstract been published prior to the sponsor's search for evidence, the sponsor would have excluded the study given that it is not a RCT.

Table 3.3: List of included studies identified by the EAC

Primary study reference	Population	Intervention	Comparator
Timsit *et al.* (2012) (1) (Note also identified by the sponsor)	Adults in ICU	Tegaderm CHG	**1.** Standard dressing (Tegaderm Transparent Film Dressing); **2.** Highly adhesive dressing (Tegaderm HP Transparent Film Dressing).
Timsit *et al.* (2009) (4)	Adults in ICU	Biopatch plus standard dressing (Tegaderm IV)	Standard dressing (Tegaderm IV)
Roberts *et al.* (1998) (5)	Adults in ICU	Biopatch plus standard dressing (Opsite IV 3000)	Standard dressing (Opsite IV 3000)
Karpanen *et al.* (2014) (6)	Adults in critical care	Tegaderm CHG	Standard dressing (Tegaderm IV dressing)

3.3.3: Description of included studies

Timsit *et al.* (2012) (1) reported on a large multicentre RCT of 1,879 patients using 4,163 catheters. Patients requiring intravascular access in 12 French ICUs were randomised to 1 of 3 groups: Tegaderm CHG, standard dressing (Tegaderm Transparent Film Dressing) or highly adhesive dressing (Tegaderm HP Transparent Film Dressing). Assessors of suspected infection were masked 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 to 7 days according to centre, or as required due to leaking or soiling. The authors concluded that Tegaderm CHG was associated with lower rate of major CRI, and a higher rate of dressing detachment.

Timsit *et al.* (2009) (4) reported on a multicentre, 2 x 2 factorial RCT of 1,636 patients with 3,778 catheters undertaken in 7 French ICUs. Patients were randomised to 1 of 4 groups by both dressing type (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% PVI in 70% ethanol was applied and all dressings were changed 24 hours after catheter insertion. The study was designed to assess superiority of Biopatch dressings in relation to major CRIs and non-inferiority of 3 or 7 day dressing changes. It was concluded that Biopatch was associated with a reduction in risk of infection, even with low background infection rates.

Roberts *et al.* (1998) (5) undertook a single-centre RCT involving 32 patients with 40 catheters in an Australian ICU. Patients were randomised to receive Biopatch (CHG sponge) plus a standard dressing or a standard dressing alone. The standard dressing utilised in this study was Opsite IV 3000 (Smith and Nephew). In this study, skin was prepared with 0.5% CHG in alcohol and dressings were changed every 3 days. The authors noted that there were insufficient data to draw conclusions from this study.

Karpanen *et al.* (2014) (6) undertook a prospective comparative study of 273 patients at University Hospitals Birmingham NHS Foundation Trust. The study is ongoing and interim results have been reported as a poster presentation. The study is comparing Tegaderm CHG with a standard dressing (Tegaderm IV dressing). Patients in both groups received standard catheter care, including skin preparation with ChloraPrep®, an antisepsis with 2% CHG in 70% alcohol. The authors concluded that the adoption of Tegaderm CHG reduced bacterial numbers on the skin, and reduced the bacterial load at the CVC insertion site.

Table 3.4 provides a summary of the key points from the 4 included studies.

Table 3.4: Key points from included studies

Study	Patient population	Setting	Study design and aim	Sample size and age
Timsit *et al.* (2012) (1)	Adult patients in an ICU requiring intravascular access	12 French ICUs	RCT to determine if CHG or strongly adhesive dressings decrease catheter colonisation and CRI rates	N=1,879 patients and n=4,163 catheters. Median age 64 years
Timsit *et al.* (2009) (4)	Adult patients in ICU requiring intravascular access	7 French ICUs	To assess superiority of Biopatch regarding the rate of major CRIs and noninferiority of 7-day vs 3-day dressing changes	N=1,636 patients and n=3,778 catheters. Median age 62 years.
Roberts *et al.* (1998) (5)	Adult patients requiring a CVC in an ICU	Sir Charles Gardiner Hospital, Perth, Western Australia	To determine the effect of Biopatch dressings on the rates of CVC-tip and exit-site infection and colonisation	N=32 patients with n=40 catheters. Median age in standard dressing arm 61 years and 58 years in Biopatch
Karpanen *et al.* (2014) (6)	Critical care adult patients requiring a CVC or Vascath for haemodialysis inserted for ≥3 days. Under 10% received Vascath	University Hospitals Birmingham NHS Foundation Trust	Non-randomised comparative study to evaluate the antimicrobial activity of the Tegaderm CHG IV dressing on the number of micro-organisms at the CVC insertion site	N=273 patients. Median age 64 years in standard dressing arm and 59 years in Tegaderm CHG arm

3.4 Overview of methodologies of all included studies

The sponsor provided a thorough and accurate description of the methodology used within its included study (1) in section 7.4.1 and table B5 of its submission. The information provided by the sponsor, and similar information extracted by the EAC on its 3 additional studies, is shown in Tables 3.5 and 3.6.

Timsit *et al.* (2012), Timsit *et al.* (2009) and Roberts *et al.* (1998) were RCTs (1, 4, 5) with the remaining study by Karpanen *et al.* (2014) being a prospective observational study published as a conference poster (6). The 2 Timsit studies recruited sufficient patient numbers to achieve 80% statistical power, whilst the Robert *et al.* paper was underpowered. Two RCTs compared a CHG sponge, Biopatch, plus a standard dressing with a standard dressing alone (4, 5). The remaining RCT (1) and 1 observational study (6) compared Tegaderm CHG with standard dressings. The sales of the dressing used in the RCT (1) (Tegaderm HP film dressing) are low in England, but significant in France (see correspondence log).

All 4 studies recruited critically ill adult patients requiring intravascular access within an ICU or CCU setting. The type of intravascular access varied between studies. CVC were included in all 4 studies, whilst arterial catheters were also included in 2 of the 3 RCTs, 1 studying Tegaderm CHG (52.9% of catheters) (1) and the other considering the CHG sponge (45.7% of catheters) (4). In the observational study by Karpanen *et al.*, patients requiring a vasocath (a specialised CVC used for kidney dialysis) were included, but comprised fewer than 10% of the included patients. Further, in this study over 50% of the catheters were inserted in theatre, with the remainder mainly in CCU (6). In Timsit *et al.* (2012) all catheters were inserted in an ICU setting (1). In the remaining 2 studies, it was unclear where in the hospital catheter insertion took place (4, 5).

Two studies excluded patients with a known allergy to CHG or transparent dressings (1, 4). The same studies reported that microbiologists processing the skin and catheter cultures and to the adjudication committee were blinded to treatment group (1, 4), whilst the remaining 2 studies did not report on exclusion criteria or blinding.

Follow-up times varied between studies, with 2 studies following patients until catheter removal (5, 6), and the remaining 2 studies for 48 hours after ICU discharge (1, 4). There was also variation in the catheter related care approach taken between studies. In 1 study, the skin was prepared with 0.5% CHG in alcohol (5); in another a variety of antiseptic solutions were used, including 0.5% CHG in alcohol (1); the third study used 0.5% PVI in ethanol (4); whilst 2% CHG in alcohol was used in the outstanding study (6). Skin preparation with 2% CHG in alcohol is in line with current NICE guidelines(2). In all 4 studies a sterile dressing was applied following catheter insertion. Dressings were reported to be changed and attended to with CHG in alcohol every fifth day in 1 study (5). In 2 studies patients dressings were changed after 24 hours and then either every 3 or 7 days, depending on randomisation or local hospital protocol. Where dressings were soiled or leaking they were

changed immediately (1, 4). The final study did not report on the dressing change protocol (6).

There were no significant differences between the baseline characteristics of patients in each group within each study. There did, however, appear to be differences in included patients between studies. Both studies by Timsit *et al.* provided enough detail on patient's characteristics to make a comparison between patients included in the 2 studies (1, 4). Patients in the 2009 study appeared to be sicker than those in the 2012 study, with a higher number of patients on mechanical ventilation (86.9% versus 71.1%), a longer median length of stay in the ICU (11 days versus 9 days) and a higher mortality rate (39.4% versus 31.2%) (1, 4). In both studies, the patients appeared, on average, to be sicker than those in NHS ICUs, with higher mortality rates and length of stay (7).

CRBSI were reported in 3 of the 4 studies (1, 4, 5). Two studies defined CRBSI as a combination of 1 or more positive peripheral blood cultures sampled immediately before or within 48 hours after catheter removal; a positive quantitative catheter-tip culture positive or a blood-culture differential time-to-positivity of 2 hours or more; and no other infectious focus explaining the positive blood cultures (1, 4). The third study defined CRI as "any infection in which the organism isolated from CVC tip and/or exit site was the same as that isolated from a clinical isolate associated with clinical signs; that is, raised temperature and white cell count". Patients with CRBSI also had a positive blood culture (5).

Catheter colonisation rates were provided in all 4 studies and skin colonisation rates in 1 (5). Both catheter and skin colonisation were generally defined as a positive culture from either the catheter tip or the catheter exit site.

Major CRI rates were provided in 2 studies (1, 4). This outcome was not defined in the scope, but has been extracted as there were data on this for all 3 dressing types. Major CRI was defined in both studies as catheter related clinical sepsis either with, or without, blood infection. Therefore, CRBSI are included within major CRI.

The median length of stay in an ICU, CCU or HDU was reported in 2 studies (1, 4). The same 2 studies also reported on condition of patient's skin. This was defined using the International Contact Dermatitis Research Group (ICDRG) score. The ICDRG system scores the condition of skin as follows: 0, normal skin; 1, mild redness; 2, red and slightly thickened skin; 3, intense redness and swelling with coalesced large blisters or spreading reaction (1).

The final outcome considered is the number of dressing changes per catheter. Although not included in the scope, this information was extracted in order to inform the EAC's critique of the sponsor's *de novo* economic modelling. No data were available in any of the 4 studies on the following outcomes defined within the scope: local site infections, quality of life, device related adverse events (with the exception of dermatitis) and mortality caused by CRBSI.

Treatment groups at baseline were compared using various statistical methods. Two studies used chi squared or Mann-Whitney tests, as deemed appropriate by the authors (1, 4). One study (6) used Kendall's tau-b or Fisher's exact test, as appropriate and the remaining study used Wilcoxon signed rank testing (5). Kaplan-Meier curves were used in 2 studies to plot the risk of CRIs and the same 2 studies used the marginal Cox model to model clustered data (i.e. the effect of multiple catheters per patient) (1, 4). Catheter colonisation differences between groups was assessed using Fisher's exact test in 1 study (6) and Chi-squared testing in another (5).

All 4 studies reported catheter colonisation rates and provided p-values around the significance of differences between groups. The 3 RCTs also reported on skin colonisation and CRBSI (1, 4, 5). Three studies provided information on the frequency of dressing changes (1, 4, 6).

In all 4 studies at least some funding was provided by manufacturers. This was 3M in the Tegaderm CHG studies (1, 6), together with Ethicon in 1 study (4), with Johnson & Johnson Medical and B. Braun Medical Products Division providing sponsorship and dressings respectively (5).

Table 3.5: Methodologies of included RCTs

	Timsit *et al.* (2012) Tegaderm CHG v. Standard dressing (1)	**Timsit *et al.* (2009) CHG sponge v. Standard dressing (4)**	**Roberts *et al.* (1998) CHG sponge v. Standard dressing (5)**
Objectives	To determine if CHG or strongly adhesive dressings decrease catheter colonisation and CRI rates	To assess superiority of CHG sponge regarding the rate of major CRIs and non-inferiority of 7-day vs 3-day dressing changes	To determine the effect of CHG sponge on the rates of CVC-tip and exit-site infection and colonisation in an adult ICU
Location	12 French ICUs	7 French ICUs	Australian ICU
Design	Multicentre RCT	Multicentre RCT	Single-centre RCT
Duration of study	13 months	17 months	7 weeks
Sample size	1,879 patients, 4163 catheters, 34,339 catheter-days	1,636 patients, 3,778 catheters, 28,931 catheter-days	32 patients, 40 catheters (with data available on 33 of these)
Inclusion criteria	ICU patients older than 18 years expecting to require intravascular catheterisation for 48 hours or longer	ICU patients older than 18 years expecting to require intravascular catheterisation for 48 hours or longer	All patients receiving CVCs in the adult ICU
Exclusion criteria	Patients with known allergies to CHG or transparent dressings. The following catheter types: Pulmonary arterial, haemodialysis, PICCs, and catheters inserted before ICU admission.	Patients with known allergies to CHG or transparent dressings. The following catheter types: Pulmonary arterial, haemodialysis and PICCs	Not reported (NR)
Method of randomisation	Web-based random-number generator producing permuted blocks of 8, with stratification on ICU	Web-based random-number generator producing permuted blocks of 8, with stratification on ICU	NR

	Timsit *et al.* (2012) Tegaderm CHG v. Standard dressing (1)	Timsit *et al.* (2009) CHG sponge v. Standard dressing (4)	Roberts *et al.* (1998) CHG sponge v. Standard dressing (5)
Method of blinding	Microbiologists processing skin and catheter cultures and the adjudication committee were blinded from the treatment group	Microbiologists processing skin and catheter cultures and the adjudication committee were blinded from the treatment group	NR
Intervention(s) (n =) and comparator(s) (n =)	Tegaderm CHG: n = 2108 catheters, n = 938 patients; Tegaderm highly adhesive (HA): n = 988 catheters, n = 465 patients; Tegaderm IV (standard): n = 1,067 catheters, n = 476 patients	CHG sponge (Biopatch plus Tegaderm IV): n = 1953 catheters, n=817 patients; Standard dressing (Tegaderm IV): n = 1825 catheters, n=819 patients	CHG sponge (Biopatch plus Opsite IV 3000): n = 17 patients; Standard dressing (Opsite IV 3000): n = 16 patients
Baseline differences	Baseline differences were reported but without p values, so it is not clear if there were statistical differences. A review of the table shows no major differences	Baseline differences were reported but without p values, so it is not clear if there were statistical differences. A review of the table shows no major differences	Baseline differences and p-values are reported. The only significant difference was for mean (range) days catheter line was in place: CHG sponge = 7 (5-10); Standard = 8 (5-14) ($p<0.05$)
Duration of follow up, lost to follow up	Duration of follow-up: 48 hours after ICU discharge. Lost to follow-up simply reported as "few patients and catheters were lost to follow-up"	Duration of follow-up: 48 hours after ICU discharge Lost to follow-up simply reported as "few patients and catheters were lost to follow-up"	Duration of follow-up: not relevant since endpoint was catheter removal. No patients were lost to follow-up
Statistical tests	Analyses were stratified by ICUs and used an intention-to-treat approach.	Analyses were stratified by ICUs and used an intention-to-treat approach	Wilcoxon signed rank testing was used to compare demographic data between

	Timsit *et al.* (2012) Tegaderm CHG v. Standard dressing (1)	Timsit *et al.* (2009) CHG sponge v. Standard dressing (4)	Roberts *et al.* (1998) CHG sponge v. Standard dressing (5)
	Treatment groups compared using chi squared or Mann-Whitney tests. Risk of major-CRI and catheter colonisation plotted using Kaplan-Meier curves. Marginal Cox model used to model clustered data (i.e. effect of multiple catheters per patient)	Treatment groups compared using chi squared or Mann-Whitney tests, Risk of major-CRI and catheter colonisation plotted using Kaplan-Meier curves. Marginal Cox model used to model clustered data (i.e. effect of multiple catheters per patient)	groups; Chi-squared testing (with Yates correction as appropriate) was used to compare the number of positive CVC tips and positive exit-site swabs in the 2 groups
Primary outcomes	• Major CRI rate; • Catheter colonisation rate	• Major CRI rate; • Catheter colonisation rate.	• Positive culture at CVC tip and exit site (skin); • CRI.
Secondary outcomes	• CRBSI; • Skin colonisation; • Rate of dressing change.	• CRBSI; • Skin colonisation; • Rate of dressing change.	NR
Funding source	3M Company	French Ministry of Health. Ethicon Inc donated Biopatch dressings used in this study	Johnson & Johnson Medical Inc provided Biopatch and B. Braun Medical Products Division provided catheters

Table 3.6: Methodology of included observational study

	Karpanen *et al.* (2014) Tegaderm CHG v. Standard dressing (6)
Objective	To evaluate the antimicrobial activity of the Tegaderm CHG IV dressing on the number of micro-organisms at the CVC insertion site
Location	University Hospitals Birmingham NHS Foundation Trust
Design	Prospective, comparative observational study
Duration of study	NR
Patient population	Critical care adult patients who had a short term CVC or Vascath (for haemodialysis) inserted for ≥3 days
Sample size	273 patients
Inclusion criteria	NR
Exclusion criteria	NR
Intervention(s) (n =) and comparator(s) (n =)	• Tegaderm CHG IV dressing (n = 136 patients); • Tegaderm IV dressing (n = 137 patients).
Baseline differences	Baseline differences were recorded and there were no significant differences at p<0.05.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	• Duration of follow-up: NR • No patients were lost to follow-up
Statistical tests	• Differences in baseline characteristics were assessed using Kendall's tau-b and Fisher's exact test as appropriate. • Differences in bacteria recovered were assessed using Mann-Whitney test as appropriate. • Differences in catheter colonisation were assessed using Fisher's exact test.
Primary outcomes (including scoring methods and timings of assessments)	• Median number of bacteria recovered from the CVC insertion site, suture site and sutures
Secondary outcomes (including scoring methods and timings of assessments)	• Incidence of catheter segment colonisation (>15 cfu per catheter segment)
Funding source	3M Health Care (Neuss, Germany)

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor completed table B7 of its submission (critical appraisal of randomised control trials) for its included study (1). The critical appraisal was appropriate. The EAC undertook its own critical appraisal of the sponsor's included study and generally agreed with the sponsor's appraisal. The EAC's judgement differed to the sponsor's on 2 of the 7 study questions. First, the sponsor answered 'yes' to the question 'Was the concealment of treatment allocation adequate?'. Both the sponsor and the EAC agreed that the method of concealment was not discussed in the paper. The sponsor's positive response was based on the following statement "The investigators were unaware of the block size and permutation procedure". However, the EAC judged this not be sufficient to confirm adequate treatment allocation concealment, given that the method of concealment was not explicitly reported.

Second, the sponsor answered 'yes' to 'Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?' The EAC answered 'no' to this question as neither patients nor ICU staff were blinded to treatment. However, given the nature of the intervention this would have been very difficult and the bias introduced by the lack of blinding is likely to be very low. Moreover, the primary objective was not subjective, limiting the potential for bias further. Microbiologists assessing clinical outcomes were blinded to treatment.

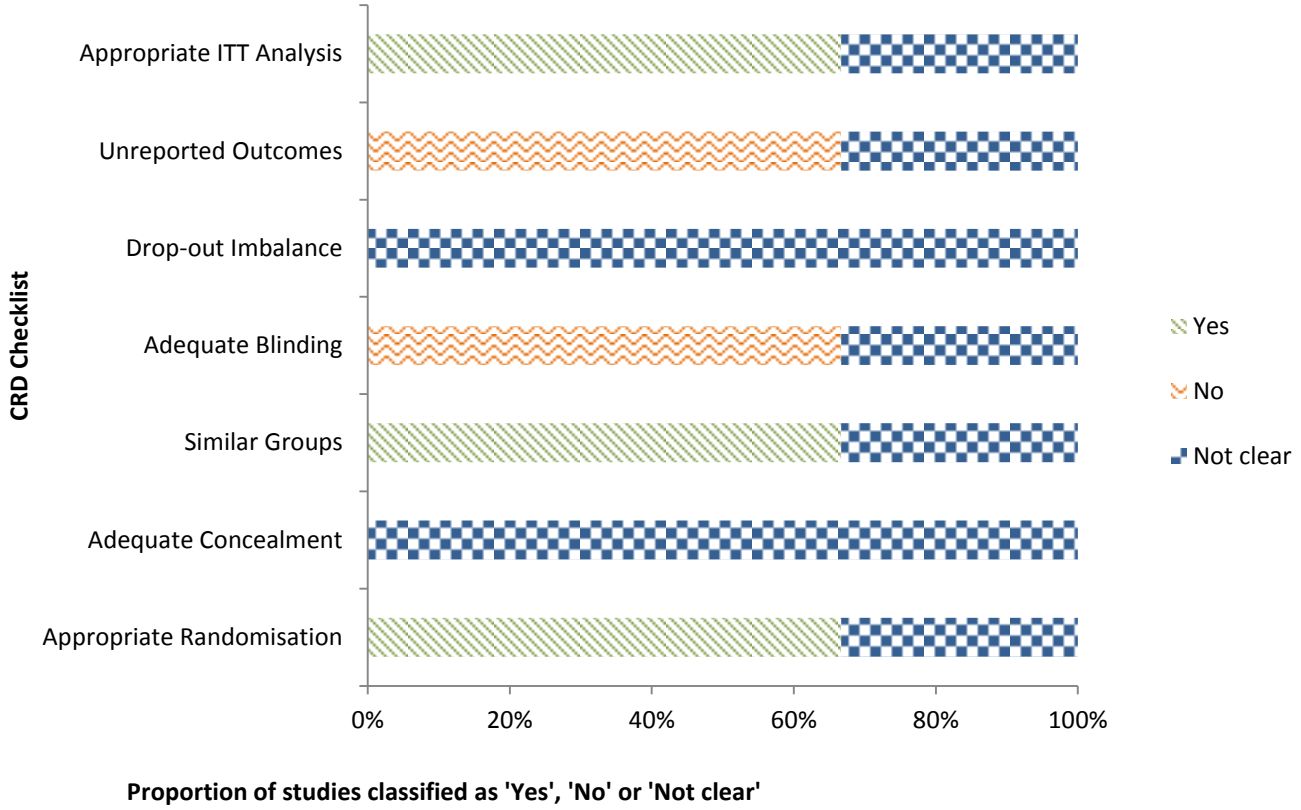
Table 3.7 provides the EAC's fully completed checklist for the 3 studies (1, 4, 5) and Figure 3.3 provides a graphical presentation of the completed checklist for the same 3 studies. This checklist was based on criteria proposed by the Centre for Reviews and Dissemination. Critical appraisal was not carried out for the study published as a conference poster, due to the limited information available on this study (6).

Table 3.7: Critical appraisal of RCTs

	Timsit *et al.* (2012) Tegaderm CHG v. Standard dressing (1)	Timsit *et al.* (2009) CHG sponge v. Standard dressing (4)	Roberts *et al.* (1998) CHG sponge v. Standard dressing (5)
Was randomisation carried out appropriately?	**Yes:** Web-based random-number generator producing permuted blocks of 8, with stratification on ICU.	**Yes**: Web-based random-number generator producing permuted blocks of 8.	**Not clear**: Technique not reported.
Was the concealment of treatment allocation adequate?	**Not clear:** Method of concealment is not discussed. However, it is noted that "investigators were unaware of the block size and permutation procedure", suggesting they were concealed from treatment allocation.	**Not clear**: Not reported.	**Not clear**: Not reported.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	**Yes**: Baseline differences were recorded in Table 1, but without p values. A review of the table appears to show no major differences, but without p values it is difficult to assess with full confidence.	**Yes**: Baseline differences were recorded in Table 1, but without p values. A review of the table appears to show no major differences, but without p values it is difficult to assess with full confidence.	**Not clear**: Insignificant differences in patient characteristics estimated. However, only age and sex were reported, suggesting all potential differences were not accounted for.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	**No**: Blinding of patients is not discussed; however, as patients are in the ICU they are unlikely to have sufficient cognitive awareness to allow them to be influenced by knowledge of the treatment. ICU staff were not blinded, but this would be difficult given the nature of the intervention, and the level of potential bias is judged low. Microbiologists processing the cultures were blinded, along with an independent adjudication committee.	**No**: Blinding of patients is not discussed; however, as patients are in the ICU they are unlikely to have sufficient cognitive awareness to allow them to be influenced by knowledge of the treatment. ICU staff were not blinded, but this would be difficult given the nature of the intervention, and the level of potential bias introduced is judged low. Microbiologists processing the cultures were blinded, along with an independent adjudication committee.	**Not clear**: This is not well reported, however it appears both participants and providers were not blinded. This is unsurprising, given the nature of the intervention, and blinding of participants in particular, is unlikely to bias the results (due to the severity of their condition). It was not reported whether investigators (i.e. those undertaking blood cultures) were blinded. It simply states "standard laboratory protocol" was followed, suggesting no blinding occurred.

	Timsit *et al.* (2012) Tegaderm CHG v. Standard dressing (1)	Timsit *et al.* (2009) CHG sponge v. Standard dressing (4)	Roberts *et al.* (1998) CHG sponge v. Standard dressing (5)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	**Not clear**: Drop-outs are not well reported within the article, with only the following reference made "few patients and catheters were lost to follow-up". Patients were followed until 48 hours after ICU discharge which may have caused some patients to be 'lost' but the potential bias is not judged likely to have a material impact on the results.	**Not clear**: Drop-outs are not well reported within the article, with only the following reference made "few patients and catheters were lost to follow-up". Patients were followed up followed until 48 hours after ICU discharge which may have caused some patients to be 'lost' but the potential bias is not judged likely to have a material impact on the results.	**Not clear:** 40 catheters were included in the study but data were reported on 33, with no reason provided on why data were missing. This is an 18% loss, which is concerning. The missing data were balanced across both arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**: Reported outcomes match those listed on the clinical trials registry, with the exception of cost which is not reported.	**No**: Reported outcomes match those listed on the clinical trials registry.	**Not clear**: No clinical trial registry or trial protocol identified.
Did the analysis include an intention-to-treat (ITT) analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes**: ITT analysis was undertaken. However, the methodology used was not reported and, therefore, it is difficult to assess its appropriateness. Further, 175 patients were excluded from the eligible population with no reason given for 156 of them. Therefore, there is a risk the results of the trial are biased, if these patients are inherently different to those included.	**Yes**: A modified ITT analysis was undertaken where those who withdrew consent after randomisation were not included (17/1,653). The methodology used was generally not well reported and, therefore, it is difficult to assess its appropriateness. Further, 141 patients were excluded from the original eligible population with no reason other than "Investigator did not include" given. Therefore, there is a risk the results of the trial are biased, if these patients are inherently different to those included.	**Not clear**: Forty catheters were included, but data were only available for 33. No reason for the discrepancy was provided. Hence an ITT analysis was not undertaken.

Figure 3.3: Graphical presentation of study quality and reliability following critical appraisal with the CRD checklist



The 2 RCTs by Timsit and colleagues (1, 4) were generally well reported allowing an appraisal of the level of bias for each of the 7 parameters shown in Table 3.7. The study by Roberts *et al.* was not well reported and therefore making judgements regarding the bias that existed in this study is difficult (5).

Randomisation was carried out appropriately in 2 of the 3 studies using a web based number generator to obtain blocks of 8 (1, 4). The method of randomisation in the third study was not reported (5). In all 3 studies, the method of concealment of treatment allocation was unclear. Timsit *et al.* (2012) stated that "investigators were unaware of the block size and permutation procedure", however, suggesting that treatment allocation was concealed but without giving the methodology used (1). Neither of the other 2 studies provided any information on concealing treatment allocation (4, 5).

All 3 studies provided information on the baseline patient characteristics in each group. In the study by Roberts *et al.*, however, this was limited to age and gender, making it impossible to inform a judgement on whether there are underlying differences between groups that could have introduced bias (5). In the 2 remaining clinical trials, the treatment groups appeared to be similar in terms of age, gender, chronic disease status, simplified acute physiology score and sequential organ failure assessment (1, 4).

Timsit and colleagues reported in both of their RCTs that the patients and ICU staff were not blinded to treatment, but that microbiologists processing the skin and catheter cultures were blinded to treatment type. Given the nature of the treatment it would have been very difficult to blind patients or ICU staff to dressing type. Further, given the severity of illness of participants, not blinding patients or ICU staff is unlikely to have introduced performance bias (1, 4). Roberts and colleagues do not report any blinding of participants, nurses, laboratory staff or investigators (5). If laboratory staff and/or investigators were aware of dressings used, detection bias may have been introduced meaning that the knowledge of the dressing received, rather than solely the cultures may have influenced outcome measurement.

Patient drop out was not well reported in any of the 3 studies. However, given that patients were in an ICU and patient drop out numbers were low, it is unlikely that attrition bias would have been introduced through systematic differences in drop out between groups.

The outcomes reported in both papers by Timsit *et al.* were in line with those specified on the clinical trial registry (1, 4). The only exception to this was that costs were not reported in Timsit *et al.* (2012) but were stated as an outcome on the trial registry (1). No study protocol or trial registry listing could be identified for Roberts *et al.* (1998) and therefore it is impossible to judge whether all outcomes were reported (5).

Intention-to-treat analysis was undertaken in 2 of the 3 studies; however, the methodology used was not well reported making it difficult to assess its appropriateness. In both of these studies a substantial number of patients (n=156 and n=141 from study (1) and (4) respectively) were excluded from the initial eligible population with no reason provided. As these patients were excluded prior to randomisation this will not introduce any internal bias. The external validity of the studies may be somewhat compromised, however. Roberts and colleagues provided no information to account for the 7 of 40 missing catheter data (5).

A narrative of the internal bias and external validity in terms of generalisability to the decision problem of all 4 studies is now provided.

Timsit *et al.* (2012) (1)

The study by Timsit *et el.* (2012) was a multicentre RCT comparing Tegaderm CHG to a standard dressing (Tegaderm IV) and a highly adhesive dressing (Tegaderm HP) in adult ICU patients requiring intravascular access. The RCT was well reported and therefore internal bias could be assessed. The study was considered to be at low risk of internal bias, as even where domains had not been met, these were unlikely to introduce bias.

The generalisability of this study to the NHS was considered largely through seeking expert opinion and comparison with clinical guidelines on whether:

a. Patient characteristics in the French study setting generalise to the NHS;

b. Protocol for inserting and removal of catheters is consistent with NHS practice;

c. Protocol for dressing changes are consistent with NHS practice.

There were 3 areas of concern regarding the external validity of this study. First, the experts advised that skin preparation with 2% CHG in 70% alcohol is standard practice within the NHS. Timsit *et al.* (2012) undertook skin preparation a number of antiseptic solutions including 0.5% CHG in alcohol; note the 2% CHG solution is not commercially available within France. Thus, the skin preparation in this study is a deviation from the scope. Second, 156 patients (out of 2,054) meeting the inclusion criteria were excluded with no reason provided. It is possible that these excluded patients were inherently different to included patients and the ICU population in general. This, in turn, may impact upon the generalisability of the study. Third, Timsit *et al.* reported a mortality rate of 31%. One expert advised that this rate is consistent of ICUs within the UK, however, the national Health and Social Care Information Centre statistics adult ICU mortality rate is reported to be 9.1% (7). The seemingly high mortality rate in the study (1) suggests that the included patients may be more severely ill than patients within NHS ICUs.

The experts advised that the characteristics of included patients within Timsit *et al.* (2012) in terms of median age, proportion on mechanical ventilation and median length of stay were consistent with those managed in ICU's in the NHS. National data were available on the average number of support days by critical care period. This was substantially lower at 4 days than the median length of stay in ICU of 9 days reported by Timsit and colleagues (1, 48).

The reason for ICU admission from the study was compared with national statistics relating to the number of critical care records. Admissions for coma and trauma reported by Timsit *et al.* (2012) could not be compared with critical care records as these are catch all terms covering multiple Health Resource Group (HRG) chapters. *De novo* respiratory failure accounted for 26% of ICU admissions in the study, nationally, within the UK, 14% of critical care records relate to the respiratory system. Timsit *et al.* (2012) reported that 17.8% of patients were admitted to the ICU due to septic shock. In the UK, 6% of critical care records relate to the nervous system, under which septic shock would be included. Cardiogenic shock was the main reason for admission to ICU in 6.8% of study participants, whilst 20% of UK critical care records refer to cardiac surgery and primary cardiac conditions. The study patients appear to differ to adults in CCUs within the UK, however, comparisons are difficult given the variation in categories for admission between the study and UK national statistics (1, 48).

The dressing change protocol in the RCT was to change all dressings after 24 hours and then every 3 or 7 days as per local protocol. Where there was soiling or dressings became loose, they were changed sooner. Advice from the expert advisors indicated that there is variation in practice across the NHS, with a change of dressing 24 hours after catheter insertion standard practice in some trusts, but not in others. NICE guidelines stipulate that dressings should be changed every 7 days unless there is reason to be changed sooner (2).

Three dressings, all manufactured by 3M, were compared within Timsit *et al.* (2012). These were Tegaderm CHG, Tegaderm IV (standard dressing) and Tegaderm HP (highly adhesive dressing). The sponsor advised (see correspondence log) that the highly adhesive dressing is not currently widely used within England and therefore the results relating to this dressing are not relevant to the decision problem. Further, a modified design of the Tegaderm CHG dressing has been introduced since this study, meaning the adverse event results relating to dermatitis may not generalise to the current NHS. This is discussed in Section 3.7.

Timsit *et al.* (2009) (4)

The study by Timsit *et al.* (2009) compared a CHG sponge (Biopatch) with standard dressing (Tegaderm IV) to standard dressing alone. The study was well reported, with both the internal bias and external validity similar to that of Timsit *et al.* (2012) (1) given the similarity in study designs. As with Timsit *et al.* (2012), although some domains were not certain, this was unlikely to introduce bias into the study.

This study is judged to be partly applicable to the decision problem and the current NHS. The main reason for limited generalisability is this; the study did not include the intervention described in the scope. Variations to NHS practice existed in relation to the skin preparation solution used (0.5% PVI in ethanol), exclusion of 141 patients by the investigator and mortality rate of 33.6% plus higher ventilation in this one. The patient characteristics in terms of median age and median length of stay in an ICU within Timsit *et al.* (2009) were consistent with both those in Timsit *et al.* (2012) (1) and expert advice of ICU's in the NHS. The median length of stay in an ICU of 11 days reported by Timsit *et al.* 2009 was longer than the 4 day average number of support days by critical care period reported in UK national statistics (4, 48).

The reasons for admission to the ICU in Timsit *et al.* (2009) were compared with national UK data (4). As with Timsit *et al.* (2012), comparisons could not be made for all admission reasons (1). Timsit *et al.* (2009) reported that 21.3% of patients were admitted to the ICU with septic shock. In the UK, 6% of critical care records relate to the nervous system, under which septic shock would be included. *De novo* respiratory failure accounted for 19.9% of study ICU admissions, nationally, within the UK, 14% of critical care records relate to the respiratory system. Finally, cardiogenic shock was the main reason for admission to ICU in 9.5% of study participants, whilst 20% of UK critical care records refer to cardiac surgery and primary cardiac conditions. Again, the study patients appear to differ to adults in CCUs within the UK, however, comparisons are limited.

Roberts *et al.* (1998) (5)

Roberts *et al.* undertook a single-centre RCT comparing CHG sponge (Biopatch) plus a standard dressing to a standard dressing alone. The standard dressing in use was Opsite IV 3000 (Smith and Nephew) which is widely used in NHS trusts. There was also a paucity of information relating to the methodology used. There is, therefore, the potential that this study is biased. Moreover, the randomisation method was not described; hence selection bias could have occurred due to inadequate concealment of dressing allocation. In addition, differences between treatment groups were not well described (only age and gender were provided) and no blinding of study participants was described. These may have introduced performance bias in that patients were treated differently dependent on their dressing assignment and also detection bias in measuring outcomes, due to microbiologists and/or study investigators being influenced by dressing type.

In terms of external validity, as with Timsit *et al.* (2009) did study did not contain the intervention outlined in the scope, and furthermore, compared with both Timsit studies it was underpowered with a small sample size. More generally, the limited information provided makes assessment difficult. Skin was prepared with 0.5% CHG in alcohol and dressings were changed every 5 days. As specified previously, the NICE guidelines state that skin should be prepared with 2% CHG in alcohol and dressings changed every 5 days (2). Patients within this study had a median age of 58 years (CHG sponge group) or 61 years (standard dressing group). This is consistent with expert advice relating to the median age of patients in ICUs in the NHS. Information on admission diagnosis was provided for study participants. The most frequent diagnosis was intracranial events (35%), which could not be compared UK CCU records as it straddled multiple HRG chapters. Other frequent diagnosis included abdominal surgery (17.5%), respiratory failure (12.5%) and vascular surgery (12.5%). The proportion of CCU records in the UK relating to the

digestive system (15%), respiratory system (14%) and cardiac surgery (20%) were similar to those reported by Roberts *et al.* (5, 7).

Karpanen *et al.* (2014) (6)

The study by Karpanen *et al.* compared Tegaderm CHG to a standard dressing (Tegaderm IV) in adult patients in critical care who required a CVC. Preliminary results were published as a conference poster and it is therefore difficult to assess levels of bias within the study given the limited information available.

In terms of external validity, this study represents the only included study set in the NHS. Skin preparation is carried out using 2% CHG in 70% alcohol which is in line with NICE guidelines (2) and expert experience (see correspondence log). The median age of patients in this study was 64 years in the standard dressing group and 59 years in the Tegaderm CHG groups. Clinical experts advised that this is in line with their experience of patients in ICU. No inclusion or exclusion criteria are provided making it difficult to advise if the results from this study generalise to the patients specified in the decision problem.

Summary

A summary of the findings of the critical appraisal performed by the EAC is reported in Table 3.8.

Table 3.8: Summary of critical appraisal in relation to decision problem

Study	Internal validity	External validity	Usefulness to decision problem
Timsit *et al.* (2012) Tegaderm CHG v. Standard dressing (1)	Weaknesses in a number of domains were unlikely to introduce bias.	Treatment regime and patient characteristics are partially applicable to scope.	High, most relevant and highest quality study on Tegaderm CHG.
Timsit *et al.* (2009) CHG sponge v. Standard dressing (4)	Weaknesses in a number of domains were unlikely to introduce bias.	Treatment regime and patient characteristics are partially applicable to scope.	High, most relevant and highest quality study on CHG sponge.
Roberts *et al.* (1998) CHG sponge v. Standard dressing (5)	Generally poor across all domains and poorly reported.	Treatment regime is partially applicable to the scope. Lack of information on patient characteristics.	Low.
Karpanen *et al.* (2014) Tegaderm CHG v. Standard dressing (6)	Certain weaknesses noted, e.g. observational so there is no randomisation. Overall, difficult to assess as results are published as a conference poster only.	NHS treatment regime is applicable to scope. Lack of information on patient characteristics.	Medium.

3.6 Results

3.6.1: Critique of sponsor's report of results

The sponsor completed table B9 accurately and provided a detailed description of the results in its included study (1). The results included within section 7.6.1 of the submission included information from both the main paper and the supplementary material provided alongside the publication. The sponsor's results included statistical comparisons between Tegaderm CHG and a combined control of standard dressings and highly adhesive dressings. The comparative results that the sponsor presented were in line with those analysed in the study. The sponsor provided justification of the combined control group by citing 2 RCTs that found no statistically significant difference in CRBSI between standard and highly adhesive dressings (49, 50).

The sponsor advised the EAC that the Tegaderm highly adhesive dressing (Tegaderm HP Transparent Film Dressing) is not listed on NHS Supply Chain and the only UK account is with a Welsh hospital (see correspondence log). The EAC therefore judged that given highly adhesive dressings are not used within England (but are a standard care option within France where the study was undertaken) it would have been useful to also provide results for standard dressings alone. The results for Tegaderm CHG and Tegaderm IV (standard dressing) have greater applicability to the decision problem, than those which also include the highly adhesive dressing. The EAC acknowledges that many of the statistical comparisons were only undertaken for CHG containing versus non-CHG containing dressings.

The study included in 'extra table C' of the sponsor's submission which was undertaken in healthy volunteers, suggested that the reduction of skin colonisation between Tegaderm CHG and a CHG sponge compared with a standard dressing is similar (3). The EAC have reported the results from studies deemed more applicable in Section 3.6.2.

The sponsor provided information in a supplementary file of its submission on the relative ease of use of Tegaderm CHG compared with standard dressings and CHG sponge. Data were extracted from 3 RCT's (44-46) which provided useful supplementary information about Tegaderm CHG. This is discussed further in Section 3.6.2.

3.6.2: EAC's report of results

Outcomes considered

The primary results from all 4 studies included by the EAC are summarised in Table 3.9. Results from each study were extracted for 6 outcomes. The definitions provided in each of the included studies for each outcome are reported in Section 3.4. To recap, no data were available in any of the 4 studies on the following outcomes defined within the scope: local site infections, quality of life, device related adverse events (with the exception of dermatitis) and mortality caused by CRBSI.

Table 3.9: Summary of reported results from included studies

Study	Catheter related bloodstream infection (CRBSI)	Catheter and skin colonisation	Major catheter related infection	Length of stay in ICU/HDU - days	Adverse events	No. of dressing changes per catheter
Timsit *et al.* (2012), N = 1,879 patients Tegaderm CHG = 938 patients; Standard = 476 patients; Highly adhesive = 465 patients. Follow up: 48 hours after ICU discharge	*Per 1,000 catheter days* Tegaderm CHG = 0.5; Standard = 1.3; Highly adhesive = 1.3. <u>CHG vs non-CHG:</u> HR = 0.402 (0.186-0.868), p = 0.02.	*Catheter colonisation per 1,000 catheter days* Tegaderm CHG = 4.3; Standard = 9.6; Highly adhesive = 12.5. <u>CHG vs non-CHG:</u> HR = 0.412 (0.306-0.556), p < 0.0001.	*Per 1,000 catheter days* Tegaderm CHG = 0.7; Standard = 2.3; Highly adhesive = 1.9. <u>CHG vs non-CHG:</u> HR = 0.328 (0.174-0.619), p = 0.0006.	*Median (IQR)* Tegaderm CHG = 9 (5-20); Standard = 10 (5-20); Highly adhesive = 9 (5-18), p= NR.	*Rate of abnormal ICDRG score* Tegaderm CHG = 2.3%; Standard = 0.7%; Highly adhesive = 1.4%. <u>Comparison among 3 groups</u> P = 0.0005 *Severe contact dermatitis requiring removal of dressing (% of catheters)* Tegaderm CHG = 1.1%; Standard = 0.1%; Highly adhesive = 0.5%. <u>CHG vs non-CHG:</u> p < 0.0001 *Systemic adverse reactions:* None reported	*Median (IQR)* Tegaderm CHG = 2 (1-4); Standard = 3 (1-5); Highly adhesive = 2 (1-4).

Study	Catheter related bloodstream infection (CRBSI)	Catheter and skin colonisation	Major catheter related infection	Length of stay in ICU/HDU - days	Adverse events	No. of dressing changes per catheter
Timsit *et al.* (2009), N = 1,653 patients CHG sponge = 817 patients; Standard = 819 patients. Follow up: 48 hours after ICU discharge	*Per 1,000 catheter days* CHG sponge = 0.4; Standard = 1.3. <u>CHG vs Standard:</u> HR = 0.24 (0.09-0.65), p = 0.005.	*Catheter colonisation per 1,000 catheter days* CHG sponge = 6.3; Standard = 15.8. <u>CHG vs Standard:</u> HR = 0.36 (0.28-0.46), p < 0.001.	*Per 1,000 catheter days* CHG sponge = 0.6; Standard = 1.4. <u>CHG vs Standard:</u> HR = 0.39 (0.16-0.93), p = 0.03.	*Median (IQR)* CHG sponge = 12 (5-25); Standard = 10 (5-21).	*Rate of abnormal ICDRG score* CHG sponge = 1.49%; Standard = 1.02%; p = 0.02. *Severe contact dermatitis requiring removal of dressing (% of catheters)* CHG sponge = 0.53%; Standard = 0%; p = NR. *Systemic adverse reactions:* None reported	*Median (IQR)* CHG sponge = 3 (1-5); Standard = 3 (1-5).

Study	Catheter related bloodstream infection (CRBSI)	Catheter and skin colonisation	Major catheter related infection	Length of stay in ICU/HDU - days	Adverse events	No. of dressing changes per catheter
Roberts *et al.* (1998), N = 40 catheters randomised (data available for 33 catheters) CHG sponge = 17 catheters; Standard = 16 catheters. Follow up: NR	*Incidents* CHG sponge = 1; Standard = 0; p = NR.	*Incidents* <u>CVC Tip:</u> CHG sponge = 2; Standard = 1; p < NS. <u>Exit Site (skin):</u> CHG sponge = 4; Standard = 3; p < NS.	NR	NR	NR	NR

Study	Catheter related bloodstream infection (CRBSI)	Catheter and skin colonisation	Major catheter related infection	Length of stay in ICU/HDU - days	Adverse events	No. of dressing changes per catheter
Karpanen *et al.* (2014), N = 273 patients Tegaderm CHG = 136 patients; Standard = 137 patients. Follow up: NR	NR	*Incidents* <u>CVC Intradermal Section Colonisation:</u> Tegaderm CHG = 10 (7.4%); Standard = 22 (14.6%); p = 0.037. <u>Positive CVC Tip:</u> Tegaderm CHG = 10 (7.4%); Standard = 20 (16.1%); p = 0.080 (NS).	NR	NR	NR	*Median (range)* Tegaderm CHG = 1 (0-5); Standard = 1 (0-5).
Abbreviations: ICDRG = International Contact Dermatitis Research Group; HR = Hazard ratio; IQR = inter-quartile range; NR = not reported; NS = not significant.						

CRBSI results

CRBSI infections were reported in 3 of the 4 studies, 1 comparing Tegaderm CHG (1) to standard dressing and the other 2 comparing CHG sponge to standard dressing (4). The study by Roberts *et al.* reported a higher incidence of CRBSI in the CHG sponge group (n=1) compared with the standard dressing group (n=0) (5). Given the limitations of this study and the small sample size it is not possible to draw any conclusions from this study.

Both studies by Timsit *et al.* reported a statistically significant decrease (at $p<0.05$) in CRBSI with CHG impregnated dressings, be that Tegaderm CHG or CHG sponge. Timsit *et al.* (2012) reported a CRBSI rate of 0.5 per 1,000 catheter days for the Tegaderm CHG and a CRBSI rate of 1.3 per 1,000 catheter days for the standard dressing group. The p-value of 0.02 was provided for Tegaderm CHG versus non-CHG dressings (comprising standard and highly adhesive dressings) (1). Timsit *et al.* (2009) reported a CRBSI rate of 0.4 per 1,000 catheter days for the CHG sponge and a CRBSI rate of 1.3 per 1,000 catheter days for the standard dressing group ($p=0.005$) (4).

A Z-test was performed to estimate whether the CRBSI rate reported for Tegaderm CHG was statistically significantly different to that reported for the CHG sponge. Z-tests can be used to determine whether a difference between 2 proportions is significant. In order to undertake the Z-test, the total number of catheter-days for each treatment group was obtained from the study authors (see correspondence log). In Timsit *et al.* (2012), 9 CRBSI occurred in 17,303 catheter days for patients in the Tegaderm CHG group (1). In Timsit *et al.* (2009), 6 CRBSI occurred in 15,479 catheter days for patients in the CHG sponge group (4). The Z-test was performed and a score of 0.56 obtained, with a p-value of 0.58.

Therefore, it is estimated that there is no statistically significant difference in the CRBSI rate between Tegaderm CHG and the CHG sponge. This suggests that where baseline CRBSI rates are at 1.3 per 1,000 catheter days, both Tegaderm CHG and CHG impregnated sponges are effective in reducing CRBSI, but that there is insufficient evidence to demonstrate that one is more effective than the other.

Catheter and skin colonisation

Catheter colonisation rates were reported in all 4 studies, whilst skin colonisation rates were only reported in 1 study (5). Both studies comparing Tegaderm CHG to standard dressings reported a reduction in catheter colonisation rates. Timsit *et al.* (2012) reported a reduction from 9.6 to 4.3 catheter colonisations per 1,000 catheter days. This reduction was statistically significant with $p<0.0001$ (note significance was only reported where standard dressings were grouped with highly adhesive dressings) (1). Karpanen *et al.* reported a statistically significant fall in CVC intradermal section colonisation incidence ($p=0.037$) and a reduction in positive CVC tip colonisation. The latter did not reach statistical significance (6).

Timsit *et al.* (2009) found catheter colonisation rates to be statistically significantly lower in the CHG sponge group compared with standard dressing (6.3 per 1,000 catheter days versus 15.8 per 1,000 catheter days, $p<0.001$) (4). Roberts *et al.* reported a non-significant higher incidence of both catheter and skin colonisation with CHG sponge compared with standard dressings (5).

Major catheter related infection

Timsit *et al.* (2012) defined a major CRI as CR sepsis with or without CRBSI. The rate was reported in 2 of the 4 included studies (1, 4). A statistically significantly lower rate of major CRI was reported with Tegaderm CHG (0.7 per 1,000 catheter days) compared with standard dressings (2.3 per 1,000 catheter days) ($p = 0.0006$ for non CHG dressings versus Tegaderm CHG) (1). Likewise, a statistically significantly lower major CRI rate was reported with a CHG sponge (0.6 per 1,000 catheter days) than with a standard dressing (1.4 per 1,000 catheter days) ($p = 0.03$) (4).

Length of stay in ICU, CCU or HDU

The median (and IQR) length of stay in ICU was reported in 2 studies (1, 4). No studies reported the length of stay in hospital more generally. The ICU length of stay reported by Timsit *et al.* (2012) was 9 days (5-20 days) in the Tegaderm CHG group and 10 days (5-20 days) in the standard dressing group (1). Timsit *et al.* (2009) reported the median ICU length of stay as 12 days (5-25 days) in the CHG sponge group and 10 days (5-21 days) in the standard dressing group (4). Neither study reported whether any statistically significant differences existed between groups.

Adverse events

No systemic adverse reactions to CHG were reported in any of the 4 studies. This was explicitly stated in 2 studies (1, 4). In both studies patients with known allergies to CHG were excluded from the study, which may compromise the generalisability of adverse reactions in the studies to the NHS more generally.

Severe contact dermatitis requiring removal of the dressing was reported in 2 studies (1, 4). Timsit *et al.* (2012) reported the incidence of 1.1% in Tegaderm CHG dressed catheters was statistically significantly higher than the 0.1% in standard dressed catheters (p=0.0005) (1). Timsit *et al.* (2009) reported that severe contact dermatitis occurred in 0.53% of CHG sponge dressed catheters and 0% of standard dressed catheters. Statistical significance was not reported (4).

Damage to the skin, measured by abnormal ICDRG scores, was reported in the 2 studies by Timsit *et al.* The skin was inspected at each dressing change and at catheter removal. The rate represents the total number of times an abnormal score was recorded, divided by the total number of checks for all patients at all dressing changes including at catheter removal. Abnormal scores occurred with a rate of 2.3% in the Tegaderm CHG group and 0.7% in the standard dressing group. This difference was statistically significant (p=0.0005) (1). In the 2009 study, abnormal scores occurred with a rate of 1.49% in the CHG sponge group and 1.02% in the standard dressing group. This difference was again statistically significant (p=0.02) (4).

Number of dressing changes per catheter

Information on the number of dressing changes per catheter was provided in 3 of the 4 studies and extracted to potentially inform the *de novo* economic modelling critique (section 4.2) (7, 8, 19). Table 3.10 shows the median number of dressing changes per catheter and the median days per catheter from each of the 3 studies. No confidence measures were provided in any of the 3 studies.

Table 3.10: Duration of catheter and dressing changes per catheter

	Dressing changes per catheter			Catheter dwell time (days)		
Study	**Tegaderm CHG**	**CHG sponge**	**Standard dressing**	**Tegaderm CHG**	**CHG sponge**	**Standard dressing**
Karpanen *et al.* (2014) (6)	*Median (range)* 1 (0-5)	N/A	*Median (range)* 1 (0-5)	*Median (range)* 6 (3-24)	N/A	*Median (range)* 5 (3-17)
Timsit *et al.* (2012) (1)	*Median (IQR)* 2 (1-4)	N/A	*Median (IQR)* 3 (1-5)	*Median (IQR)* 6 (4-11)	N/A	*Median (IQR)* 7 (4-12)
Timsit *et al.* (2009) (4)	N/A	*Median (IQR)* 3 (1-5)	*Median (IQR)* 3 (1-5)	N/A	*Median (IQR)* 6 (4-10)	*Median (IQR)* 6 (4-10)

Ease of use and performance

The sponsor provided supplementary information from 3 studies on the performance of Tegaderm CHG compared with a standard dressing (either Tegaderm IV or IV 3000) (44-46). Satisfaction of the dressings was judged by clinical staff. Maryniak *et al.* (2009) enrolled 217 inpatients or outpatients (107 Tegaderm CHG and 110 standard dressing) into a prospective observational study. Olson *et al.* (2008) undertook an RCT with 63 hospitalised patients (33 Tegaderm CHG and 30 standard care), some of whom were in ICUs. Finally, Rupp *et al.* (2008) completed an RCT with 60 hospitalised patients (30 Tegaderm CHG and 30 standard care). None of the submitted supplementary studies considered critically ill patients specifically.

In summary, nurses reported being statistically significantly more satisfied with Tegaderm CHG than standard dressings in all 3 studies (at $p<0.05$). Tegaderm CHG was reported to provide a more satisfactory dressing securement, be easier to apply and improve dressing adherence. There were mixed results in terms of nurse satisfaction with ease of correct application, transparency (site visibility) and ease of dressing removal, however, differences rarely reached significance. Patients reported slightly higher

discomfort levels with Tegaderm CHG in 2 studies, however, again this did not reach statistical significance (at $p<0.05$) (46).

The EAC identified a number of studies comparing the ease of use of Tegaderm CHG with a CHG sponge. To recap, as explained in Section 2.1.2 CHG sponges are used in conjunction with a standard dressing. One RCT compared Tegaderm CHG to a CHG sponge in healthy volunteers and reported that clinicians found Tegaderm CHG to perform statistically significantly more favourably than the CHG sponge across all parameters considered ($p<0.05$). These included overall performance, ease of correct applications, ease of removal, ability to see IV site, ease of training and intuitive application (51). A further 2 studies published as poster presentations reported on questionnaires that nurses completed after using Tegaderm CHG. In both studies Tegaderm CHG was significantly better than the CHG sponge in terms of overall performance (52, 53).

Expert advice 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). One expert mentioned that it takes longer to remove Tegaderm CHG and that there may be a few incorrect applications at first. Another said that there may be minimal differences in time taken to apply and remove dressings. The remaining 2 experts stated that the time taken is the same for both Tegaderm CHG and standard dressings.

Two experts had experience of using both Tegaderm CHG and the CHG sponge. Again, there were 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 sponge and another reported that a number of nurses place the CHG sponge upside down and had to, therefore, use a replacement.

3.6.3: Summary of results

As described in Section 3.4 no studies included all 3 dressing types defined in the scope. All studies were carried out in patients in an ICU or CCU, rather than a HDU. A summary of the results in each of the 4 studies and their applicability to the decision problem is provided.

Timsit *et al.* (2012) undertook a RCT in critically ill patients in French ICUs requiring intravascular access. The study was judged to be at low risk of bias and to be partially applicable to the decision problem. Statistically significantly lower rates of CRBSI, catheter colonisation and major CRIs were reported in the Tegaderm CHG group compared with patients receiving dressings with no

CHG ($p<0.05$). Significantly more cases of dermatitis were reported in the Tegaderm CHG group, however (1). However, the EAC notes that subsequent to this study the product has been modified. The reduction in CRBSI was from a baseline infection rate of 1.3 per 1,000 catheter days. The sponsor correctly identified that this is similar to the UK infection rate for adult patients in ICUs of 1.48 per 1,000 catheter days reported in the Matching Michigan study (8).

Timsit *et al.* (2009) reported on a RCT comparing a CHG sponge to standard dressing in patients in French ICUs. The study was judged to be at low risk of bias and to be partially applicable to the decision problem. The group dressed with CHG sponges had statistically significantly lower rates of CRBSI, catheter colonisation and major CRI than the standard dressing group ($p<0.05$). They also had a non-significantly higher incidence of dermatitis (4). Again, the reduction in CRBSI was from on a baseline rate of 1.3 per 1,000 catheter days, similar to the more recently reported rate within the NHS from the Matching Michigan study (8).

Roberts *et al.* carried out a RCT that was judged to be at high risk of bias and to be partially applicable to the decision problem. The study was undertaken in a small number of ICU patients in Australia who required a CVC. Patients were randomised to receive a CHG sponge or standard dressing. Non-significant increases in skin and catheter colonisation and CRBSI were reported with the CHG sponge (5).

Karpanen *et al.* compared Tegaderm CHG and standard dressings in critically ill adult patients requiring CVC in the NHS. As the study has thus far been published as a poster only, making judgements about its quality is difficult. The study is, however, deemed to be applicable to the decision problem. A reduction in the incidence of catheter colonisation was reported. This was statistically significant in the CVC intradermal section, but did not reach significance in the CVC tip ($p<0.05$). The number of dressing changes was equal in both groups (6).

Expert advice and information taken from studies reporting on surveys of clinicians suggest that Tegaderm CHG is at least as easy to use as a standard dressing and may be preferable in terms of ease of use over the CHG sponge. No information was available on the remaining outcomes listed in the scope, which comprised local site infections, quality of life, device related adverse events (with the exception of dermatitis) and mortality caused by CRBSI.

3.7 Description of the adverse events reported by the sponsor

The sponsor provided accurate information on the adverse events reported in Timsit *et al.* (2012). The EAC has summarised the adverse events occurring in all 4 studies in Table 3.9 and provided an overview of these in Section 3.6.2.

The sponsor also undertook searches of both the Medicines and Healthcare products Regulatory Agency (MHRA) website and US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database. The term "Tegaderm" was searched for on MHRA. On FDA MAUDE the 3M was inserted into the manufacturer field and "Tegaderm CHG" into the brand name field. The sponsor obtained 1 relevant result from MHRA and 109 from FDA MAUDE. The sponsor provided a copy of each of the 109 FDA MAUDE reports (extra table B, submission) and a summary of the adverse events reports. The EAC independently searched FDA MAUDE using the terms provided by the sponsor and set the report dates from 7th January 2000 to 29th July 2013 in line with the sponsor. The EAC yielded the same results as the sponsor. The EAC undertook an additional search to 28th November 2014. An additional 17 results were retrieved, which were similar to those reported previously.

To summarise the adverse events described by the sponsor, the reports identified on FDA MAUDE tended to describe local reactions occurring within 48 hours of dressing application. These included redness and irritation that was sometimes severe. In many cases adverse reactions were self-healing, however, there were 7 reports that stated that an eschar had occurred. This is dead tissue that is shed from healthy skin, usually resulting from a burn or pressure wound. Two deaths were reported on FDA MAUDE, however, these were not directly linked to Tegaderm CHG.

The EAC undertook additional searches of both FDA MAUDE and MHRA, the details of which are provided in Appendix 2. The EAC searched FDA MAUDE from 1st January 2012 to 30th November 2014 for adverse reactions relating to both "Biopatch" (CHG sponge) and "Opsite IV 3000" (standard dressing). The sponsor also searched FDA MAUDE for these dressings, however information in the terms used and dates searched were not provided. The EAC searched for records reported over the last 3 years in an attempt to ensure that only those records relating to currently used versions of the dressings were retrieved. For Opsite IV 3000, 1 event referring to a minor, self-correcting adverse reaction was found.

Seventy three records relating to Biopatch were identified. These reports were similar to the reports that were identified for Tegaderm CHG, with around half relating to local reactions occurring after Biopatch application. These reports varied in severity with some describing redness or itching at the dressing site and others more severe reactions similar to chemical or second degree burns. A third of the reports referred to patients who had experienced infection (either local site infections or systemic infection) despite the use of Biopatch. Nine of the reports concerned product malfunctions including separation of 2 sections of the sponge or foreign objects appearing in the packaging. One report noted a patient had died; however, this was not directly linked to Biopatch. In summary, the reports submitted to FDA MAUDE about Biopatch are similar in nature but higher in number to those reported about Tegaderm CHG. For reference, there have been 29 reports relating to Tegaderm CHG over the same time frame, however, it is difficult to infer anything from this information given the likely variation in sales volume of the dressings

The sponsor searched the MHRA website on 29th July 2013, using the term 'Tegaderm', and returned 2 results. The first was a report into the assessment of LMX4 Lidocaine 4% WW cream. This product contains Tegaderm occlusive dressing, and not Tegaderm CHG, and is therefore irrelevant here. The second result related to a 'Medical Device Alert' issued by the MHRA, warning of a risk of anaphylactic reactions for products containing chlorhexidine gluconate. As this relates to all chlorhexidine gluconate products it is relevant to both Tegaderm CHG and CHG sponge. Six actions were identified including the need to record known allergies in patient notes; check labels and instructions for use to establish if products contain chlorhexidine prior to use on patients with a known allergy; if a patient experiences an unexplained reaction, check whether chlorhexidine was used; and report allergic reactions to products containing chlorhexidine to the MHRA (54).

The EAC replicated the sponsor's search of MHRA on the 10th December 2014 and this yielded 3 results. The first 2 results matched those identified by the sponsor. The third result again relates specifically to Tegaderm occlusive dressing, and is therefore irrelevant here. This record was not identified by the sponsor as it was published on the 31st March 2014, after the sponsor undertook its search.

[redacted]

[redacted]

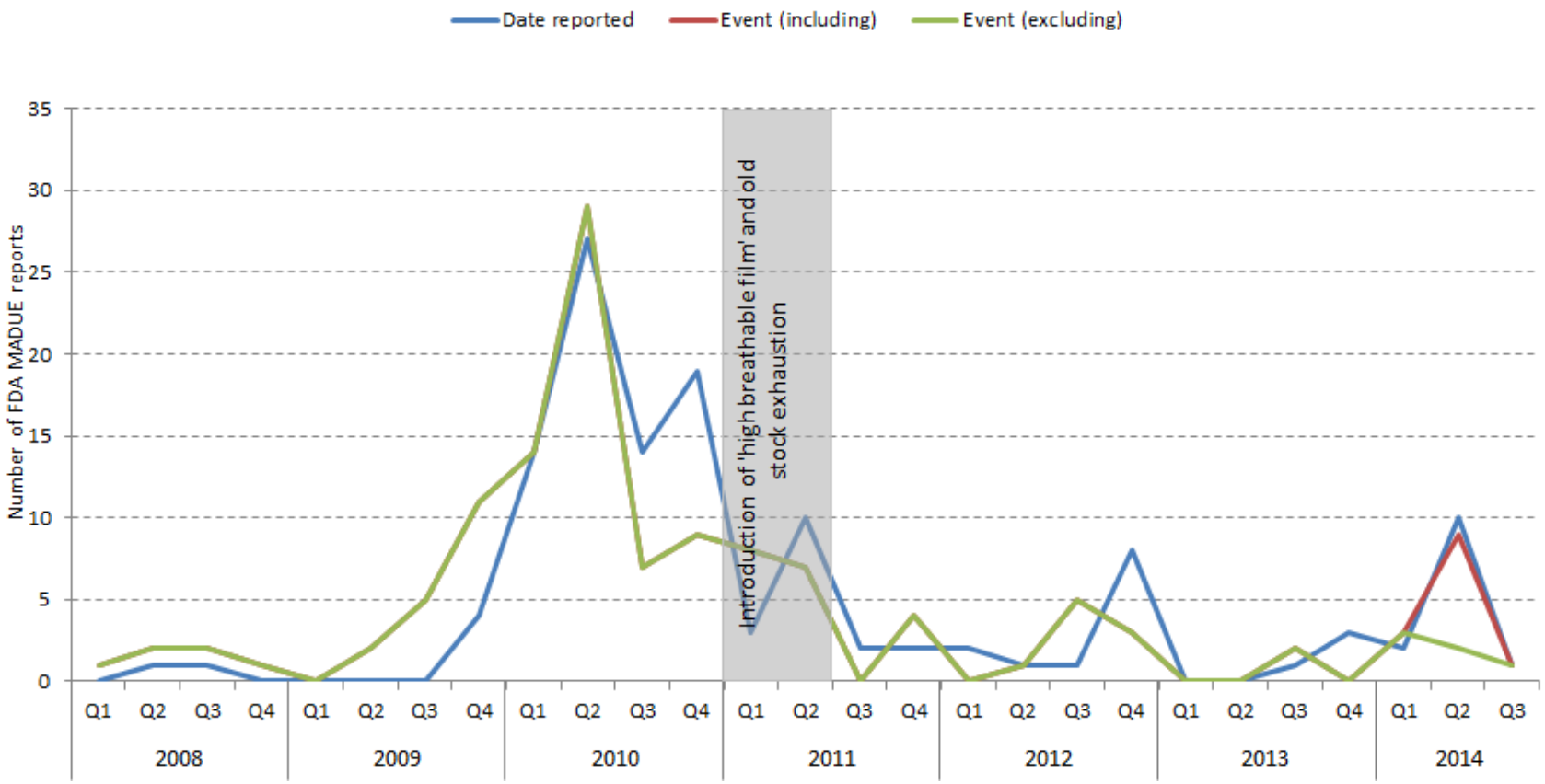
The EAC undertook an analysis of the FDA MAUDE reports pre and post the introduction of the highly breathable Tegaderm CHG dressing in the US. The analysis aimed to show whether, or not, the frequency of adverse reactions had changed following the introduction of the highly permeable dressing. Given the data available relating to incident date on FDA MAUDE this analysis was somewhat limited. First, a delay often occurred between an incident occurring and it being reported to FDA MAUDE and second, several records appear to have been identified from a published article and, therefore, have no event date, only a reporting date. In order to cover all potential bases, results have been reported in Figure 3.4 for:

- FDA MAUDE adverse reaction by date reported (report date);
- FDA MAUDE adverse reaction by incident date excluding those reports which did not include an incident date (event exclude);
- FDA MAUDE adverse reaction by incident date using report date as a substitute for incident date where required (event include).

Figure 3.4 shows that following the introduction of the highly breathable Tegaderm CHG, the number of adverse reactions reduced. It is important to note, however, that the number of dressings sold have not been included within this assessment and are thus a confounding factor on the analysis.

Two of 3 clinical experts advised that they had no experience or concerns of any adverse reactions resulting from the use of Tegaderm CHG. The remaining expert stated that there had been some concerns around increased exposure to CHG resulting in potential increase in sensitivity. Tegaderm CHG is contraindicated for patients with an allergy to CHG as described in Section 2.3.

Figure 3.4: FDA MAUDE reports over time



3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor did not attempt to synthesise data using meta-analysis stating that this was not applicable given the inclusion of only 1 study.

Data from the 4 studies included by the EAC were not synthesised in the form of a meta-analysis. Variation existed in the study methodology, patients recruited, overall treatment pathway and method of reporting outcomes. Therefore, the studies were judged too heterogeneous to allow for a meaningful combination of results. An indirect treatment comparison could have been conducted based upon the 2 studies by Timsit and colleagues alone; however, given that no other studies could be incorporated into this analysis the added value of doing so would have been minimal. A comparison of the results in the 2 studies can be made directly without a meta-analysis.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

No *de novo* work relating to the clinical evidence was undertaken by the EAC.

3.10 Conclusions on the clinical evidence

Tegaderm CHG is a transparent securement dressing used to cover and protect catheter sites and to secure devices to the skin. Although the dressing is suitable for use in any patient requiring intravascular access, its antiseptic and antibacterial properties mean it is most beneficial for use on critically ill patients, in whom infection rates are highest. In the clinical care pathway defined in NICE CG139, Tegaderm CHG would be an option of "a sterile, transparent semipermeable membrane dressing to cover the vascular access device insertion site" (2). Other dressings currently widely used within the NHS include a standard dressing (such as Opsite IV 3000, Smith and Nephew and Tegaderm IV, 3M) and a CHG sponge (Biopatch, Ethicon which is used with a standard dressing). NICE were advised by experts during the scoping stage that the Biopatch is standard care in some NHS hospitals.

The sponsor undertook reasonably robust searches using appropriate PICO criteria to identify studies relevant to the decision question. Following review of the records returned, the sponsor identified 1 study which met its selection criteria (1). The included study, by Timsit *et al.* 2012, was a multicentre RCT undertaken in French ICUs, which compared Tegaderm CHG to a standard dressing (Tegaderm transparent film dressing) and a highly adhesive dressing (Tegaderm HP transparent film dressing). The EAC replicated the sponsor's searches as far as possible and also replicated the sponsor's record review.

Application of the sponsor's selection criteria by the EAC resulted in inclusion of the same study included by the sponsor.

The key weakness of the sponsor's clinical evidence submission was the use of restrictive selection criteria. Only those studies comparing Tegaderm CHG to IV dressings used in routine care were included. Therefore, only evidence relating to 1 of the 2 comparators specified by NICE in the decision problem was included. The EAC undertook its own search and applied broader selection criteria to include any study comparing at least 2 of the 3 dressings specified in the decision problem (i.e. unlike the sponsor's review, Tegaderm CHG did not have to be included within the study). Four studies met the EAC's inclusion criteria (1, 4-6), including the study identified by the sponsor (1). An additional study comparing Tegaderm CHG to a standard dressing was included by the EAC; this study had been published as a conference poster after the sponsor's search (6). The remaining 2 included studies compared the CHG sponge to a standard dressing (4, 5).

All 4 studies included by the EAC were undertaken in critically ill patients situated in an ICU or CCU (the patient group stipulated in the decision problem). Three of the 4 studies were RCTs (1, 4, 5), with the remaining study being a prospective comparative observational study (6). As stated previously, no studies directly compared Tegaderm CHG with CHG sponge. None of the included studies reported on all of the outcomes defined in the decision problem. The results, where available, for each outcome included in the decision problem are provided.

Three papers reported the number of CRBSI. The poor quality and small sample size in Roberts *et al.* limit the usability of these results (5). The 2 studies by Timsit *et al.* provided robust and comparable rates that were homogenous in terms of definition of CRBSI and care package (1, 4). Timsit *et al.* (2012) reported a CRBSI rate of 0.5 per 1,000 catheter days for Tegaderm CHG and 1.3 per 1,000 catheter days for standard dressing (1). Timsit *et al.* (2009) reported a CRBSI rate of 0.4 per 1,000 catheter days for CHG sponge and, 1.3 per 1,000 catheter days for standard dressing (4). The rate of CRBSI was statistically significantly lower with a CHG impregnated dressing (either Tegaderm CHG or CHG sponge) than a standard dressing ($p<0.05$). Applying a Z-test enabled the EAC to test whether the results from 2 studies (1, 4) indicated that the 2 products had statistically significant differences in infection rates. The results from these tests showed no statistically significant difference between the effectiveness of Tegaderm CHG and the CHG sponge.

Given that the latest available estimate of CRBSI rates in the UK NHS is 1.48 per 1,000 catheter days, which is similar to the rate of 1.3 per 1,000 catheter days for standard dressings (8), the results from the 2 studies by Timsit *et al.* are likely to be generalisable to the NHS.

Either skin or catheter colonisation results were provided in all 4 studies. The available evidence showed that catheter colonisation rates were lower with Tegaderm CHG compared with standard dressings. This result was statistically significant in the large RCT ($p<0.0001$) (1) and statistically significant in 1 area of the catheter (intradermal section) in the observational study ($p=0.037$) (6). Evidence comparing CHG sponge with standard dressings was somewhat mixed, however, robust results from Timsit *et al.* (2009) showed a statistically significant reduction in catheter colonisation with the CHG sponge ($p=0.005$) (4).

The median length of stay in ICU was similar across all 3 treatment groups (between 10 and 12 days). No confidence estimates were provided within the literature and it is therefore difficult to assess if any differences are statistically significant (1, 4). However, given the low baseline incidence of infections, any improvement caused by the introduction of new dressing procedures is unlikely to significantly impact on length of stay.

Severe contact dermatitis reported in the 2 studies by Timsit and colleagues showed that both Tegaderm CHG and CHG sponges resulted in higher incidence rates than standard dressings. The higher incidence was statistically significant for Tegaderm CHG ($p=0.0005$), however significance was not reported in the CHG sponge study (1, 4). The sponsor advised that since the release of the latest Tegaderm CHG dressing, which is more permeable, the rate of severe contact dermatitis is around [redacted] Dermatitis was also reported a number of times in FDA MAUDE reports. These were often less severe cases than those in the RCTs, which often healed without treatment. An analysis of FDA MAUDE reports showed that incidents have reduced since the introduction of the highly permeable Tegaderm CHG dressing. No systemic adverse events were reported in any of the studies. Clinical experts advised that they had not had experience of any adverse events during their use of Tegaderm CHG.

Information was identified by the sponsor on 2 additional outcomes outside of the scope of the decision problem. Lower rates of major CRI were achieved with Tegaderm CHG and CHG sponge compared with standard dressings (1, 4). This result reached significance for Tegaderm CHG (1). A number of studies also considered the ease of use of each of the 3 dressings. Tegaderm CHG was reported in these studies, and by the expert advisors, to be at least as easy to use as standard dressings and likely to be easier to use than the CHG sponge. Tegaderm CHG is likely to be more easy to use, compared with a CHG sponge, due to the transparent nature of the dressing and because it is used as a single component.

Uncertainty remains around mortality from CRI, local site infections and quality of life, for which no evidence was identified. Clinical experts advised that CRBSI infections can have a devastating impact on quality of life, whilst the impact of severe dermatitis on quality of life is usually short term. It is likely that due to the lower rate of CRBSIs (a life threatening condition) with Tegaderm CHG and CHG sponges, an improvement in quality of life would be achieved with these dressings compared with standard dressings. The improvement in quality of life resulting from a reduction in CRBSI would likely outweigh the potential short-term quality of life decrement resulting from an increased incidence rate of dermatitis.

The sponsor concluded (section 7.9, submission) that the evidence shows that compared with standard dressings, Tegaderm CHG is associated with lower rates of CRBSI and catheter colonisation, but an increase in the incidence of dermatitis compared with standard dressings. The sponsor stated that the results of its included study are likely to be generalisable to other settings with similar catheter care and dressing protocols.

The EAC has not identified any further evidence to suggest that the conclusions drawn by the sponsor are invalid. Furthermore, consideration of studies comparing CHG sponges to standard dressings, supplemented by the Z-score analyses suggest that the rates of CRBSI and a surrogate measure of infection, such as catheter colonisation, are likely to be similar with CHG sponges and Tegaderm CHG.

In conclusion, both types of CHG impregnated dressings (Tegaderm CHG or CHG impregnated sponge) lead to lower rates of CRBSI and catheter colonisation, than standard dressings. There is a higher risk of dermatitis with both Tegaderm CHG and CHG sponges than with standard dressings, although this risk has declined with the modified Tegaderm CHG product. Users of the dressings reported that Tegaderm CHG is at least as easy to use a standard dressing and easier to use than the CHG sponge due to its transparency and all-in-one component.

4 Economic evidence

4.1 Published economic evidence

4.4.1: Critique of the sponsor's search strategy

Sponsor's search strategy

Insufficient information was provided in the submission to enable a full critique of the sponsor's search strategies or to enable any searches to be replicated by the EAC.

The databases searched by the sponsor for economic evidence were in line with NICE's guidance as stated on the submission template; MEDLINE, MEDLINE In-Process, EMBASE, Econlit and NHS EED. Additional searches were conducted using CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Database of Abstracts of Review of Effects, BIOSIS Previews, Science Citation Index Expanded, Conference Proceedings Index-Science, UK Clinical Research Network (CRN) Portfolio Database, National Research Register (NRR) Archive, Current Controlled Trials and ClinicalTrials.gov.

The range of databases was appropriate for identifying economic evidence, though the addition of specialist economic sources such as Health Economic Evaluation Database (HEED) and the Cost-Effectiveness Analysis (CEA) Registry would have enhanced the search.

No rationale is given for the inclusion of general databases for the economic evidence search which were not included in the clinical evidence search (e.g. CINAHL, Science Citation Index Expanded).

Although there was inconsistency in reporting of search dates (in both the main body of the submission and the appendix section 12.3) it seems the main databases searches were carried out in August 2013. The 4 research registers were searched in October 2012 but these searches were not updated in August 2013; no rationale is given for this. More recent searches would have improved the currency of the submission.

In addition to the database searches, the sponsor used additional search techniques to identify relevant studies. These included checking the reference lists of all relevant studies (including existing systematic reviews), citation searching for studies citing relevant articles, conducting systematic keyword searches of the internet using Google and contacting key experts in the field. Each of these approaches improved the sensitivity of the overall search methodology and complemented the database searches.

No search strategies were included in the submission for the economic evidence search. The sponsor provided a brief description of the overall search approach plus a diagram which illustrated the framework for the search strategy. Taken together, the description and diagram lacked clarity and gave a confusing indication of the search approach taken.

The brief description given of the overall search approach was as follows:

"The keyword strategies developed in the review of clinical effectiveness (section 7.1.1) were used with a sensitive economic evaluation (where applicable) or quality of life search filter aimed at restricting search results to economic and cost-related studies (used in the searches of MEDLINE, CINAHL and EMBASE)."

The term 'keyword strategies' is not defined but the description indicates that the search strategies used for the clinical evidence review were combined with either a sensitive economic evaluation filter or quality of life filter.

The description did not make it clear which (or which parts) of the strategies developed for the clinical effectiveness review were used as the basis for the economic evidence searches. The diagram indicates that it was just the terms used in the Tegaderm-focussed search. However, this diagram did not seem to relate to the cost search as it did not reflect the use of cost / quality of life filters, and indicated additional outcomes such as effectiveness and adverse events. If the economics search was based on the terms used for the clinical effectiveness Tegaderm search then it would have the same limitations as described previously in the critique of that search (Section 3.1). In addition, the terms in the Tegaderm search related to Tegaderm / CHG dressings only; if these terms were used for the economic evidence search it was not appropriate to find studies for the much broader inclusion criteria as described by the sponsor in section 8.1.2 of the submission: "Studies were included if they reported an economic evaluation of interventions for reducing CRIs for patients in acute setting".

The description indicated that either an economics filter or quality of life filter were applied. Use of a sensitive economic evaluation filter would be appropriate to find economic evidence, but use of a quality of life filter would not. There was also no rationale given as to why a search filter was applied to the MEDLINE, CINAHL and Embase searches, but not to other general databases such as the Science Citation Index.

In the PRISMA diagram the sponsor indicated that only 18 studies were retrieved in the cost-effectiveness search. This seemed a very low number, given the approach described, and added to the lack of clarity over the search methods used.

Overall, a confusing picture of the search was given. Based on the limited details given, the sponsor's economic evidence search did not seem appropriate either to identifying economic evidence on Tegaderm CHG or to the broader inclusion criteria described in section 8.1.2 of the submission. However, some of the apparent limitations of the search may be due to weaknesses in the reporting of methods; without the full strategies it is not possible to tell.

It is important to note that the sponsor's clinical evidence search was broad enough to identify economic evidence as well as clinical evidence. If the sponsor assessed results retrieved by the clinical evidence search for studies relevant to cost evidence, then any deficiencies in this separate economic evidence search would have less importance in relation to the retrieval or non-retrieval of relevant studies. Whether the sponsor did assess results retrieved in the clinical evidence search for studies relevant to economics evidence is not clear from the submission.

EAC's search strategy

The searches carried out by the EAC to identify clinical effectiveness evidence (reported in Section 3.1 and Appendix 2) were not restricted by study design and were prospectively designed to retrieve both clinical effectiveness and economic evidence. The sources searched included those required as a minimum by NICE for the search on economic evidence as stated on the submission template (MEDLINE, MEDLINE In-Process, Embase, Econlit and NHS EED) and other additional databases as previously described. These additional databases included 2 further specialist economic databases, the Health Economic Evaluation Database (HEED) and the Cost-Effectiveness Analysis (CEA) Registry. All results from these searches were assessed for relevance to either the clinical or economic reviews. No additional search for economic evidence was therefore carried out by the EAC.

Full details of all the search resources and strategies used by the EAC search (including search date and the volume of results returned) are provided Section 3.1 and Appendix 2.

4.1.2: Critique of the sponsor's study selection

Sponsor's study selection

During study selection the sponsor adopted a PICO framework, which was the same approach taken to select clinical studies. However, the PICO criteria (see table C1 of the sponsor's submission) adopted for the economic selection was broader that those adopted to select clinical studies (table B1, submission) and from the scope specified by NICE.

In the clinical section the population was limited to all patients (age ≥ 18 years) admitted to an ICU or any critical care setting requiring an intravenous catheter. In the economic review this was widened to any patient cared for in an acute setting. Hence, it included population groups not contained within the scope. This is not a major limitation because patients with infections will also be managed in general wards.

Whilst the clinical review focused specifically on studies that included Tegaderm CHG as a treatment option, the sponsor's economic review adopted the following single inclusion criterion: 'Interventions for reducing of catheter related infections'. No exclusion criteria were applied in relation to intervention. Therefore, the sponsor's selected studies included a number of interventions that were outside of the scope specified by NICE.

The only inclusion criterion adopted by the sponsor, in relation to outcomes, was: 'Studies that report an economic evaluation'. This criterion is confusing, as the term 'economic evaluation' relates to study design rather than outcomes. Thus, it is unclear what outcomes were deemed relevant for inclusion by the sponsor. Studies not reporting cost-effectiveness, for example costing studies were excluded by the sponsor. Inclusion of such studies may have helped to inform the sponsor's *de novo* model inputs further.

Economic evaluations that did not extrapolate beyond the trial duration were excluded by the sponsor, and an English language restriction was applied in line with the clinical review. Both are appropriate.

EAC's study selection

The selection criteria adopted by the EAC, to select relevant economic studies, are summarised in Table 4.1. These are consistent with the scope.

Table 4.1: Selection criteria adopted by the EAC for economic study selection

Inclusion criteria	
Patients	Adult patients (18 years or older) in ICU/CCU or HDU requiring CVC or atrial catheter insertion
Intervention	Tegaderm CHG
Comparator	CHG impregnated sponge or dressing (e.g. Biopatch); Sterile semi-permeable transparent adhesive dressing (e.g. Tegaderm IV).
Outcomes	Not specified to maximise sensitivity
Study design	Heath economic studies (Tegaderm CHG v. comparator): • Cost-effectiveness; • Cost-utility; • Cost-benefit; • Cost-minimisation; • Cost-consequence.
Language restrictions	English only
Search dates?	No limit
Exclusion criteria	
Population	Animal and in vitro studies; Patients in a non-ICU, CCU or HDU setting; Paediatric populations (under 18 years old)
Interventions	Studies where the dressing used is unclear or unspecified; Studies where dressing is used as part of a multifaceted intervention aimed at reducing infection rate. E.g. change in prep, change in equipment used and education of staff etc.
Study design	Non-comparative cost analyses including cost of illness studies

The EAC applied the selection criteria listed in Table 4.1, to the literature search reported in Section 3.1. Only health economic studies that used Tegaderm CHG as an intervention were included in the economic selection criteria. This is different from the inclusion criteria adopted by the EAC for clinical effectiveness studies, which included studies comparing standard dressings with CHG sponges (with no comparison with Tegaderm CHG) (see Section 3.3). The rationale for this was to identify whether a formal indirect treatment comparison of clinical effectiveness may be possible between Tegaderm CHG and CHG sponge using the common comparator of standard dressings. This was not possible.

Standalone economic studies of CHG sponges compared with standard dressings are not informative in identifying the cost-effectiveness of Tegaderm CHG compared with either CHG sponges or standard dressings. Hence such studies were excluded by the economic selection criteria.

4.1.3: Included and excluded studies

Sponsor's selected studies

Of the 20 records retrieved, the sponsor included 5 studies all reporting on cost benefit analysis that met its selection criteria. These studies are summarised in Table 4.2.

Table 4.2: Summary of sponsor's included economic studies

Study and setting	Design	Population	Intervention	Comparator
Veenstra *et al.* 1999 (9); US	Cost-benefit analysis	Hospitalised patients at high risk of CRI.	Antiseptic-impregnated catheter	Standard catheters
Crawford *et al.* 2004 (10); US	Cost-benefit analysis	Hospitalised patients in the Philadelphia area of USA.	CHG sponge	Standard dressing
Hockenhull *et al*. 2008 (12); UK	Cost-benefit analysis	Patients receiving CVCs in England and Wales	Anti-infective CVC	Standard CVC
Ye et al. 2011 (13); US	Cost-benefit analysis	Inpatients requiring a CVC in USA hospitals	CHG sponge	Standard dressing
Schwebel *et al.* 2012 (11); France	Cost-benefit analysis	ICU patients requiring a CVC	CHG sponge	Standard dressing

The EAC deemed that these studies could not answer the research question on the cost-consequences of adopting Tegaderm CHG compared with current practice and hence excluded them. They are not discussed further within this section. The studies did however provide information which the sponsor was able to utilise in its *de novo* economic model (see Section 4.2).

EAC's selected studies

Four studies were identified by the EAC that were not included within the sponsor's submission. These studies are summarised in Table 4.3. All 4 studies were published as conference abstracts after the sponsor's search was undertaken. Although studies undertaken in patients in non-ICU, CCU or HDU settings would have been excluded, no studies were excluded based upon this criteria alone.

Table 4.3: Summary of EAC's included economic studies

Study and Setting	Design	Population	Intervention	Comparator
Maunoury *et al.* 2013 (17); France	Cost-benefit analysis	ICU patients requiring an intravenous catheter.	Tegaderm CHG	Standard dressing
Maunoury *et al.* 2014 (18); France	Cost-benefit analysis	ICU patients requiring an intravenous catheter.	Tegaderm CHG	Standard dressing
Palka-Santini *et al*. 2014 (16); France	Cost-benefit analysis	ICU patients requiring an intravenous catheter.	Tegaderm CHG	Standard dressing
Palka-Santini *et al.* 2014 (15); France	Cost-benefit analysis	ICU patients requiring an intravenous catheter.	Tegaderm CHG	Standard dressing

4.1.4: Overview of methodologies of all included economic studies

All 4 included studies were cost-benefit analyses conducted from a French healthcare system perspective. The studies themselves were all presented at conferences, so only the abstracts are available from conference proceedings. All 4 papers were written by the same set of authors, using data from the Timsit *et al.* (2012) study (1). Each study used different economic model structures and/or reported different results, in order to assess the cost-benefits of Tegaderm CHG compared with standard dressings.

Maunoury *et al.* (2013) presented a 30-day non-homogeneous Markov model (NHMM), made of 8 health states, with Monte-Carlo simulations of 1,000 patients used for probabilistic sensitivity analysis (PSA) (17).

Maunoury *et al.* (2014) compared the same NHMM with a homogeneous Markov Model (HMM), in order to assess the impact of the modelling approach on the decision problem (i.e. whether Tegaderm CHG is cost-effective compared with standard dressings) (18). In HMM, transition probabilities between difference health states remain constant over time and between patients. In a NHMM, transition probabilities vary either over time, or between patients (55).

Palka-Santini *et al.* (2014), also examined the cost-benefits of Tegaderm CHG using a NHMM approach (16) and reported the same results as Maunoury *et al.* (2013) (17) and Maunoury *et al.* (2014) (18).

Palka-Santini *et al.* (2014) compared a NHMM to a decision tree, in order to assess whether there was coherent results across the 2 model structures (15).

The studies are reported as abstracts only and, hence, it is not possible to confirm whether the same NHMM was used in all of the studies. Given that both reported the same number of infections prevented by Tegaderm CHG, however, it would seem they are at least very similar.

Table 4.4 presents an overview of the results from the 4 studies included by the EAC. The full results from all 4 studies are provided in Appendix 4. In the results shown in Table 4.4, the currency has been converted from French euros into British pounds using the the Organisation for Economic Co-operation and Development (OECD) 2013 purchasing power parity (56). The original values in euros are shown in Appendix 4.

All 4 studies report results from the NHMM (15-18). These show that with Tegaderm CHG 11.8 infections were avoided/1,000 patients (95% CI: 3.85 to 19.64), at a cost of £115 per patient (95% CI: -£797 to £1,029) compared with standard dressings (15, 16, 18). The results from the HMM were reported in 1 study which showed Tegaderm CHG resulted in 6.45 infections avoided per 1,000 patients (95% CI: 0.15 to 12.75), with a mean extra cost of £206 per patient (95% CI: -£756 to £1,168) (18). Finally, the results of the decision tree were reported in 1 study which showed Tegaderm CHG was the dominant strategy, preventing 13.5 infections/1,000 patients, whilst saving £128 per patient (15). Within all 4 included studies either the confidence intervals cross for the 2 interventions assessed, or the confidence interval crosses zero. Therefore, there are no statistically significant results (15-18).

Table 4.4: Summary of results from EAC included studies

Study	Costs	Patient outcomes	Results
Maunoury *et al.* 2013 (17)	Unit costs incorporated into the analysis not reported.	Only outcome reported is the number of infections per treatment group.	Tegaderm CHG prevented 11.75 infections/1,000 patients Cost per patient: Tegaderm CHG = £17,496 [95% CI: £16,685 to £18,356]. Comparator = £17,031 [95% CI: £16,281 to £17,879].
Maunoury *et al.* 2014 (18)	Unit costs incorporated into the analysis not reported.	Only outcome reported is the number of infections per treatment group.	In NHMM, Tegaderm CHG resulted in 11.8 infections avoided per 1,000 patients [95% CI: 3.85 to 19.64], with a mean extra cost of £115 per patient [95%CI: -£797 to £1,029]. In HMM Tegaderm CHG resulted in 6.45 infections avoided per 1,000 patients [95% CI: 0.15 to 12.75], with a mean extra cost of £206 per patient [95%CI: -£756 to £1,168].
Palka-Santini *et al*. 2014 (16)	Unit costs incorporated into the analysis not reported.	Outcome measures: number of infections per treatment group, cost per CRBSI avoided and incremental net monetary benefit.	Tegaderm cost an extra £115 per patient [95%CI: -£797 to £1,029]. The cost per CRSBI avoided was £9,853.
Palka-Santini *et al*. 2014 (15)	Unit costs incorporated into the analysis not reported.	Only outcome reported is the number of infections per treatment group.	Based on the decision tree, Tegaderm CHG was the dominant strategy, preventing 13.5 infections/1,000 patients, whilst saving £128 per patient. For the NHMM, 11.8 infections were avoided/1,000 patients, at a cost of £115 per patient [95%CI: -£797 to £1,029].

4.1.5: Overview and critique of the sponsor's critical appraisal for each study

The sponsor reviewed each of its 5 studies individually using the quality assessment checklist adapted from Drummond and Jefferson (1996), a suitable checklist for assessing economic evaluation studies. The results of the checklist were presented in tabular form within the submission and not discussed further. As such, the results of the review were not put into context within the narrative of the submission.

It was not possible for the EAC to formally critique each study it included (15-18) because all are reported as abstracts only and, therefore, insufficient information was available. The information provided within the abstracts did not include details on the cost of infections or the resource use associated with these infections. It is, therefore, impossible to determine whether or not the results are generalisable to the UK NHS. Likewise, although all analyses were built around the clinical evidence from Timsit *et al.* (2012) (1), this was likely to be supplemented from data from other sources, about which nothing is known. Again, this precludes the ability to draw conclusions around the generalisability to the NHS of the included studies.

4.1.6: Does the sponsor's review of economic evidence draw conclusions from the data available?

Sponsor's conclusions

The sponsor drew no conclusions from the economic evidence, other than that no UK-based cost-effectiveness studies comparing Tegaderm CHG to standard dressing, were available. This is an accurate conclusion. A small number of model inputs in the sponsor's *de novo* cost analysis did use data from 3 of the studies identified during the sponsor's search; Hockenhull *et al.* (2008), Ye *et al.* (2011) and Schwebel *et al.* (2012) (11-13).

EAC's conclusions

It is difficult to draw conclusions regarding the cost-effectiveness of Tegaderm CHG compared with standard dressings based upon the results presented from the 4 abstracts (15-18). Within all papers either the confidence intervals cross for the 2 interventions assessed, or the confidence interval crosses zero. Therefore, there are no statistically significant results.

Further, as each of the 4 studies identified by the EAC were available only as abstracts, it was not possible to formally critically appraise the studies. Therefore, it is unclear whether the studies were of an acceptable quality.

Similarly, as full information is not available on each study, it is not possible to assess whether the results are generalisable to the UK NHS setting.

4.2 De novo cost analysis

The sponsor created its own *de novo* cost model which was appropriate given the lack of UK based economic evidence available on Tegaderm CHG. The EAC critically appraised this model using the methodology of Drummond and Jefferson (1996) (57). The appraisal checklist is reported in Appendix 5. The structure of the model is now described.

4.2.1 PICO analysis

In this section, the population, or patients, technology, comparator and outcomes used in the model are described.

Patients

The sponsor described the patients within the model as adult patients admitted to ICU or other critical care setting who were expected to require intravascular access for at least 48 hours. Intravascular access catheters included CVC and arterial catheters. This patient population reflects the patients included in Timsit *et al.* (2012) which was used to populate effectiveness parameters within the economic model and is consistent with the scope.

Technology

The intervention considered in the model, although not explicitly stated within the submission, was Tegaderm CHG. It is assumed that all patients within the model are suitable for dressing with Tegaderm CHG. Critically ill adult patients were modelled to require an average of 3 dressings. This assumed a mean length of stay for a patient with an intravascular catheter in situ on ICU of 10 days and a prescribed time for changing standard dressings of between 3 and 7 days.

Comparator(s)

The comparator used in the model was standard dressing, or specifically Tegaderm IV 1635. Costs were also provided for a second commonly used standard dressing, Opsite IV 3000; however, to be conservative, the sponsor used the cheaper standard dressing within its model.

The second comparator defined in the scope, CHG sponge, was not included within the model due to a lack of direct comparative clinical evidence.

Outcome

The primary outcome is a comparison of the total costs of the 2 arms. No secondary outcomes, such CRBSI avoided, are used.

4.2.2 Model structure

Software

The sponsor submitted a fully executable *de novo* model built in Microsoft Excel. The model comprised 5 worksheets. An overview of the content of each worksheet is now provided:

- 'Index'. This sheet shows the title of the model and allows the user to change the number of patients and number of probabilistic sensitivity analyses (PSA) runs within the model. Macro buttons have been provided to allow the user to view the other sheets within the model and also to run the model. Some introductory text around the number of critical care beds and their occupancy is provided.

- 'Parameters'. The input parameters for all inputs within the model were inserted on this sheet. Inputs taken from the literature were labelled as 'deterministic' inputs. The distribution around each parameter was provided and sampling of each input parameter run to inform the probabilistic results. Rows labelled 'source' existed within the sheet; however, these were not populated with any information. All inputs could be updated, as required, by the user, which, in turn, updated the row labelled 'active scenario' through visual basic coding once the 'model run' button was pressed.

- 'Calculations'. This worksheet calculated and reported the probabilistic results of the base case model analysis for all patients within the model. A breakdown of costs and the total costs were provided for both standard dressings and Tegaderm CHG.

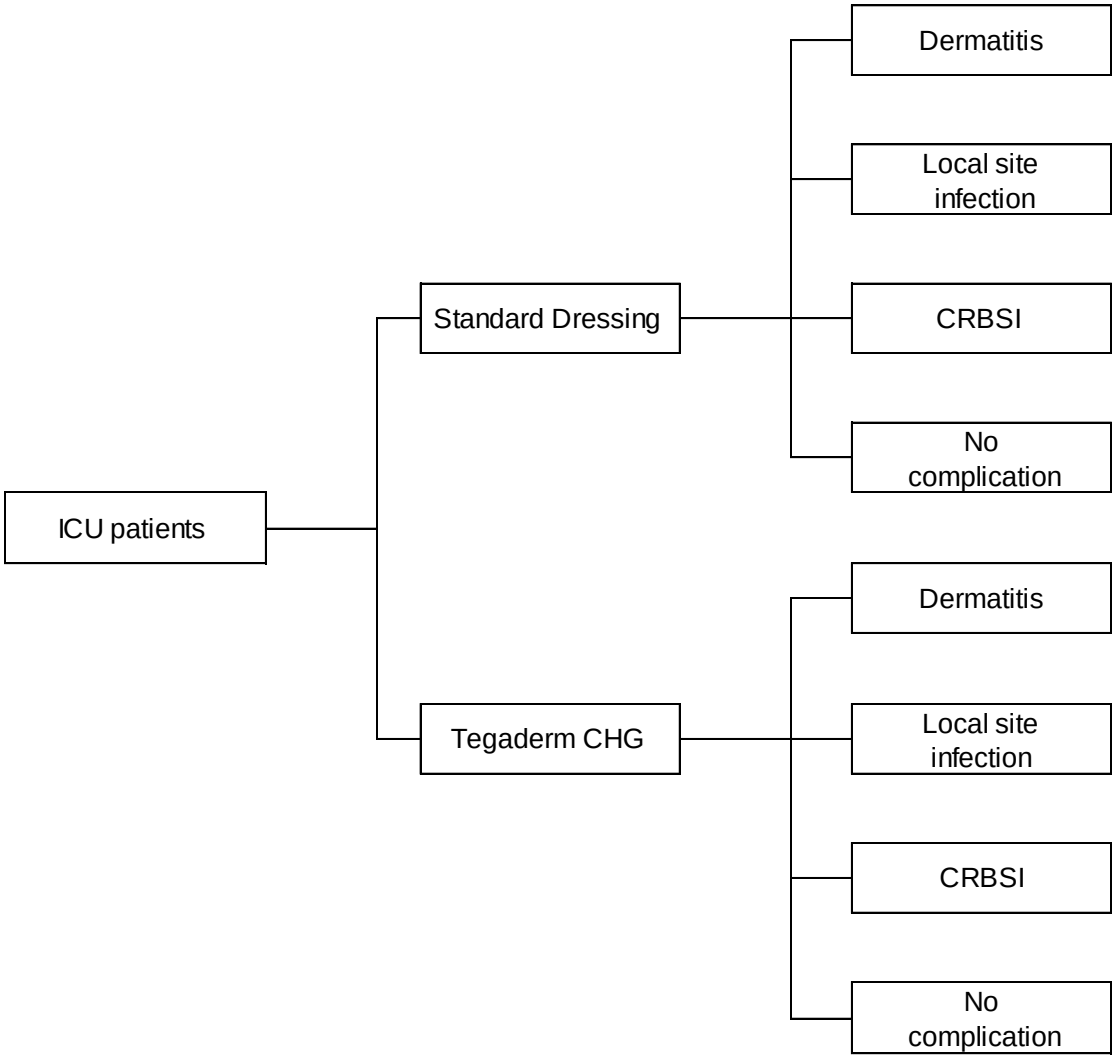
- 'Results'. The results sheet shows the probabilistic analysis, that is, the 1,000 iterations of the model. The cost savings with Tegaderm CHG are calculated for each iteration and the probability that Tegaderm CHG is cost saving is also estimated.

- 'Summary'. On the summary sheet the model results are shown per 1,000 patients (or the number of patients included within the model). These are broken down to show the costs of dressing, costs of CRBSI, costs of local site infection and costs of dermatitis. The results are also presented graphically in a bar chart.

Structure

The *de novo* economic model produced by the sponsor was a decision tree with a short time horizon of the catheterisation period plus additional length of stay associated with CRBSI. The sponsor provided a largely accurate diagram of the model in Figure 2 of its submission. Patients within the model had catheter insertion sites dressed with either standard dressings or Tegaderm CHG. Patients in both groups were at risk of developing dermatitis, a local site infection or a CRBSI. Implicitly, patients not experiencing any of the 3 complications remained in the model, but incurred no costs other than the cost of the dressings. An NHS perspective was adopted. The EAC has provided an amended version of the model structure in Figure 4.1. This includes patients who did not experience any infection or dermatitis.

Figure 4.1: Model structure



The sponsor justified its choice of model structure by referencing evidence that using Tegaderm CHG impacted upon each model endpoint. During its model development phase, the sponsor contacted Professor Tom Elliot and Dr Tony Whitehouse, University Hospital Birmingham who commented on design of the model and the parameters that were relevant to clinical practice. This was used to inform and justify the sponsor's model structure.

The impact of Tegaderm CHG on CRBSI and dermatitis was reported by Timsit *et al.* (2012) based on the results of their RCT. Local site infections, however, were not reported in the study (1). The sponsor included these, noting local infection of the intra-cutaneous tract of intravascular catheters is a complication associated with their use.

The sponsor noted training costs were excluded, explaining this service is provided by the supplier using drop in sessions that are fitted around patient care.

The model structure was identical for both Tegaderm CHG and standard dressings, as Tegaderm CHG is a direct replacement of standard dressings. This is explained in more detail in Section 2.1.5.

The sponsor applied hazard ratios to baseline rates of CRBSI and local site infection and a relative risk to the baseline rate to dermatitis to determine the rate of each complication with Tegaderm CHG. Relative risks can be applied to baseline rates simply by multiplying the baseline rate by the relative risk. The sponsor applied hazard ratios using the following formula:

> *Risk of event with Tegaderm = 1 - ((1 – baseline risk) ^ Hazard ratio)*

An alternative method of applying hazard ratios is:

> *Risk of event with Tegaderm = baseline risk * hazard ratio*

Costs were accrued through costs of intervention (i.e. Tegaderm CHG or standard dressing) and hospital treatment costs depended on whether the patients had dermatitis, local infection or CRBSI.

The model was run stochastically, meaning that distributions were specified for each input parameter, except the unit cost of the dressings, to represent uncertainty in their estimation. Monte Carlo simulation was then employed to select values at random from pre-specified distributions each time the model was run. This allows for the effects of the joint uncertainty across all the parameters of the model to be considered (14). The sponsor's base case results were probabilistic, based upon 1,000 iterations of the model.

Critique of model and structure

Expert advice was sought by the EAC around the model structure. This suggested that Tegaderm CHG is likely to reduce incidence of local site infections, defined as redness and local inflammation with possible discharge, but no systemic symptoms (see correspondence log). The EAC judged that the sponsor had, therefore, correctly included this outcome. Catheter and skin colonisation were commonly reported in the clinical evidence included in Section 3. These are surrogate outcomes with a limited impact upon patients. Expert advice stated that in NHS hospitals, swabs are not routinely taken to test for skin or catheter colonisation, therefore unless a local or systemic infection is suspected, colonisation would not be diagnosed. Therefore, exclusion of this outcome from the economic model is valid.

The EAC replicated the sponsor's calculations employed in the model in order to confirm their accuracy. An error was identified in the calculations of the cost of dermatitis. When calculating the cost of dermatitis, the sponsor multiplied the cost by the number of dressings required per patient. As the input used for the rate of dermatitis taken from the literature was per catheter (rather than per dressing) and each patient in the model had 1 catheter, there was no need to multiply the value by the number of dressings. This error was in both the standard dressing and Tegaderm CHG arms of the model so had limited impact on the overall results of the model (see Table 4.19).

The EAC also generated deterministic results, that is, results based on the fixed input (or mean) for each model input parameter. The EAC found no further mistakes in the sponsor's calculations and generated deterministic results similar to those probabilistic results that the sponsor reported. Some variation in final results would be expected given that they vary each time input parameters are randomly sampled from their distribution.

The sponsor did not report that any structural assumptions had been made in developing the model (section 9.1.6, submission). The EAC has identified the following structural assumptions:

- There is assumed to be no difference between the impact of Tegaderm CHG and standard dressings on patient outcomes following the short time horizon (10 days catheterisation time plus additional length of stay resulting from CRBSI) of the model. The clinical evidence identified in Section 3 did not report on patients for any longer than 48 hours after they had left the ICU, therefore any long term differences (not captured by the complications included within the model) between Tegaderm CHG and standard dressings are unknown. Only patients with CRBSI are judged to be at risk of adverse consequences of the event after this period.

- The length of time with a catheter is not influenced by whether a patient has an infection (either CRBSI or local). In practice, catheter dwell time may be influenced by infection; however the EAC notes that data informing the length of catheter dwell time with and without infection is not available.

- The risk of CRBSI, local infection and dermatitis are assumed to be independent. One expert advised that local infection can increase the risk of CRBSI (see correspondence log). The clinical evidence relating to Tegaderm CHG did not report local infection rates, which is a limitation of the analysis.

- Using Tegaderm CHG is assumed to only affect CRBSI, local site infection and dermatitis outcomes and not other outcomes such as numbers of patients with suspected CRBSI.

- Infection rates are assumed to be linear regardless of catheter dwell time. Evidence shows that where catheters are left *in situ* for a longer time period, the risk of infection increases (58, 59). No data were available to inform the difference in infection rate with Tegaderm CHG dependent on catheter dwell time. This is a limitation of the analysis.

- There are no organisational differences between using Tegaderm CHG compared with standard dressings, in that they are similar in terms of application, removal, adhesion, average duration before change is necessary, wastage, ordering, storage and training.

The EAC judged that these simplifying assumptions are valid and not likely to introduce significant bias.

Whilst the structure of the *de novo* model submitted by the sponsor was relatively simplistic, the structure captured the key differences measured in clinical studies between Tegaderm CHG and standard dressings. Ideally, the model would have included the third dressing type, the CHG sponge. However, the lack of comparative evidence between Tegaderm CHG and CHG sponge precludes this. In order to help inform the Medical Technologies Advisory Committee decisions, the EAC has conducted some exploratory analysis comparing Tegaderm CHG and CHG sponge in Section 4.5.

Modelling a longer timeframe to capture wider consequences for the NHS and patients of contracting a CRBSI, in addition to length of stay in ICUs and general wards would be useful. This, together with a patient perspective on the impact of CRBSI on mortality and quality of life would capture the effects of CRBSI more fully.

The EAC judged that the exclusion of training costs by the sponsor is valid. As training is provided by the supplier using short drop in sessions that are fitted around patient care, the cost per dressing of this service is likely to be negligible.

Analyses were conducted by the EAC to assess the impact of the application of hazard ratios on the results of the model. This is reported in Section 4.5.

4.2.3: Model inputs

The EAC validated the input parameters used by the sponsor via 2 methods. First, advice was sought from the clinical experts assigned by NICE (see correspondence log). Second, a targeted literature review was undertaken to identify any relevant published literature. The pragmatic literature search was developed to identify papers which reported on the following outcomes in the context of NHS / UK ICUs, CCUs or HDUs:

- Absolute rate / absolute risk of CRBSIs;
- Length of stay following CRBSIs;
- Mortality rate following CRBSIs.

The strategy comprised 3 concepts:

ICU / CCU / HDU AND CRBSIs AND UK.

The outcomes of interest (absolute rate / absolute risk / length of stay / mortality rate) were not included as a fourth concept, increasing the sensitivity of the search. The search was restricted by date from 2011 to December 2014 in order to identify any relevant literature published since the Matching Michigan study, such that any up to date estimates of CRBSI would be captured (8). The search retrieved 456 unique records which were assessed for relevance to the *de novo* model. Full details of the search and full search strategies are provided in Appendix 6.

In this section the mean value, or point estimate, used for each input parameter is described. Both ranges and distributions were assigned around each input parameter except unit dressing costs. These are discussed in Section 4.2.4.

Clinical parameters and variables

The sponsor included data from its included clinical study within its economic model (1). This was used to provide information for the model on the impact of Tegaderm CHG on CRBSI, local site infections and dermatitis. The time horizon of the model is the mean length of catheterisation for critically ill patients (10 days) taken from a study by Ye *et al.* (2011) plus any additional length of stay resulting from a CRBSI (13). This is broadly in line with the time horizon considered by Timsit *et al.* (2012) of 48 hours after ICU discharge, meaning no extrapolation of data from this study was required (1). Given the short time frame of the model, the sponsor correctly considered that discounting was not necessary.

The sponsor provided a full description of the inputs received from clinical experts during the production of its model (section 9.2.5, submission). Its experts, Professor Tom Elliott and Dr Tony Whitehouse, critiqued all model inputs and provided suggestions for the values to be used. Each clinical input has been described and critiqued by the EAC and an overview provided in Table 4.5.

Table 4.5: Clinical parameters used to populate sponsor's model

Variable	Value	Source	EAC comment
Baseline CRBSI rate	1.48 per 1,000 catheter days	Bion *et al.* (2012) (8)	The base case value used by the sponsor is appropriate.
Hazard ratio for CRBSI with Tegaderm CHG	0.402	Timsit *et al.* (2012) (1)	The base case value used by the sponsor is appropriate.
Baseline local site infection rate	0.1 per patient	Ye *et al.* (2011) (13) based on Pemberton *et al.* (1996) (60)	The EAC judges it is more appropriate to use the local site infection rate reported by NHS Wales for 2013 of 0.14 per 1,000 critical care catheter days (61).
Hazard ratio for local site infection with Tegaderm CHG	0.402	Assumed to be equal to hazard ratio for CRBSI from Timsit *et al.* (2012) (1)	The base case value used by the sponsor is appropriate.
Baseline dermatitis risk	0.0026 per catheter	Schwebel *et al.* (2012) (11) based on Timsit *et al.* (2009) (4)	The EAC judges it is more appropriate to use probability of 1 case of dermatitis in 476 patients (0.0021) from Timsit *et al.* (2012) (1).
Relative risk for dermatitis with Tegaderm CHG	4.4	Timsit *et al.* (2012) (1)	The EAC judges that given the rate of dermatitis with the new design of Tegaderm CHG is low, at [redacted], a relative risk of 1 is appropriate in the base case.

Baseline CRBSI risk

In its model the sponsor used the rate of CRBSI reported by Bion *et al.* for the final quarter of 2010 (8). To recap, this study reported on a NPSA initiative known as 'Matching Michigan' which was introduced into the NHS in April 2009 and ran for 2 years. The initiative comprised 3 interventions:

- Technical interventions - to ensure consistent use of evidence-based measures for reducing risks of CRBSI's;
- Non-technical interventions to address culture and systems within trusts and departments;
- Establishment of a standardised national reporting system.

Ninety-seven per cent of acute trusts in England participated in Matching Michigan and data were collected until March 2011. The CRBSI rate in adult ICUs fell from 3.7 CRBSIs per 1,000 catheter days in the first quarter of the study to 1.48 CRBSIs per 1,000 catheter days in the final quarter ($p<0.0001$), which is very similar to the rate of 1.3 CRBSIs per 1000 recorded by Timset *et al.* (2012) (1). The authors reported that infections rates were already trending down before the Matching Michigan programme. Further, the observed reduction in infection rates could be attributable as much to improvement efforts outside of the programme and to the awareness-raising effect of a nationwide programme as to any specific component of the programme itself.

The baseline rate of CRBSI utilised by the sponsor (for the standard dressing arm of the model) included only CRBSIs and included trusts using CHG impregnated dressings (17%) (8).

The EAC considered the results of its pragmatic literature review and also reviewed all published studies referencing Bion *et al.*, 2012 to identify any more recent studies reporting on CRBSI rates in critically ill adults within the NHS. The review of studies referencing Bion *et al.* 2012 yielded no useful studies (8).

The targeted literature review identified 2 conference abstracts from 2 NHS trusts reporting on CRBSI in the ICU more recently than Bion *et al.* (2012). Given that these abstracts were based on a single trust, their generalisability is limited. Hermon *et al.* (2013) reported the number of CRBSI every year from 2008 to 2013 (first 6 months only) for 10 ICU/HDU beds within the Royal Glamorgan hospital. The CRBSI rate has varied between 0 and 0.93 per 1,000 catheter days between 2010 and 2013, with no trend in the change of

rate over this time. These rates were based on around 2,000 catheter days per year (62).

Wong *et al.* (2014) reported on CRBSI from ICUs within Portsmouth Hospital Trust. The CRBSI rate per 1,000 CVC days was 0.29 between December 2009 and December 2013, with 1 CRBSI occurring in 2013. The annual CRBSI rate was not provided, nor any indication around the trend in CRBSI rates between 2009 and 2013 (63).

The pragmatic literature review undertaken by the EAC was supplemented with targeted searches of Google to identify if CRBSI rates were reported for any UK countries outside of England. Nationwide CRBSI rates were identified for both Scotland and Wales in critically ill adults treated within the NHS in 2013 (61, 64). Welsh health boards reported 0.19 CRBSI per 1,000 critical care catheter days in 2013 (61). No confidence intervals were provided. This included CVC inserted in any hospital location, provided the patient was critically ill. The majority (over 60%) were inserted within CCUs (61). It should be noted that CRBSI rates in Wales are consistently reported to be lower than those reported in the Matching Michigan. In 2010, there were 0.29 CRBSI per 1,000 critical care catheter days in Wales compared with 1.48 per 1,000 catheter days in England (8, 61). These differences may result may be partially attributable to heterogeneity in CRBSI definition, reporting or measurement.

The confirmed CRBSI rate in Scottish ICU's in 2013 was 0.3 per 1,000 catheter days (95% CI: 0.2-0.6) (64). The study authors noted that this rate may underestimate the true CRBSI rate in Scotland because of the lack of routine catheter tip culturing and hence the potential under classification of blood stream infections as being catheter related. In 2010, the CRBSI rate in Scottish ICU's was 0.8 per 1,000 catheter days (95% CI: 0.5 – 1.2), showing a fall in this rate over time (65). A rate of 2.4 CRBSI per 1,000 catheter days (95% CI: 1.9 to 3.0) (64) was provided for 'probable and confirmed CRBSI' in patients with a CVC in Scottish ICUs in 2013.

The CRBSI rates reported within the UK refer to CVCs only, with arterial catheters excluded from the data collection. This is inconsistent with the scope of the decision problem stipulated by NICE which includes patients requiring intravascular access with either a CVC or arterial catheter.

NHS England, Wales and Scotland have all produced similar 'bundles', or sets of practices, for preventing infection when inserting and maintaining CVCs. The insertion bundles include hand hygiene, barrier precautions, skin sterilisation with 2% CHG and avoidance of the femoral site for catheter insertion (66-68). The Scottish bundle also specifies that the insertion site

should be covered with a semi-permeable transparent dressing (standard dressing) (68). In England, measurement of compliance to the bundle and improvement in infection prevention is determined locally and it is recommended that trusts report compliance to the bundle (66). In Scotland, bundles are implemented through completion of a checklist for each patient (68) and compliance with bundles reported for all ICUs and HDUs (64). In all Welsh ICUs, monthly compliance with the care bundle is measured and collected by the Welsh Assembly Government as one of the Welsh Critical Care Quality Indicators (67). Variation in regulation of bundle compliance between the 3 countries may somewhat account for the apparent difference in 2010 CRBSI rates.

Finally, the EAC attempted to plot a line of best fit based upon the data provided in Matching Michigan in order to extrapolate the results to 2014 (8). All extrapolations resulted in negative CRBSI rates and as such this extrapolation was not utilised.

The CRBSI rate used by sponsor from Bion *et al.* is the most generalisable and robust estimate available for English ICUs and the use of this value in its base case is justified. The sponsor also conducted both deterministic sensitivity analysis (DSA) and PSA around this estimate. The CRBSI rates reported for 2013 in both Scotland (0.3 per 1,000 catheter days) and Wales (0.19 per 1,000 catheter days) are much lower than those reported for England and those used within the sponsor's sensitivity analysis (which adopted 0.5 per 1,000 catheter days as its low rate). The EAC has conducted additional DSA and PSA around this parameter, as well as scenario analyses using the Scottish 2013 CRBSI rate, as reported in Section 4.5. The scenario analyses using data from Scotland in 2013 adopts the confirmed rate of CRBSI to represent ICUs and HDUs with low baseline CRBSI rates.

Hazard ratio for CRBSI with Tegaderm CHG

The sponsor applied the hazard ratio of 0.402 reported by Timsit *et al.* (2012) to determine the rate of CRBSI with Tegaderm CHG (1). As reported in Section 3, the clinical evidence review showed that this study reports the best estimate of effectiveness of Tegaderm CHG available.

Baseline local site infection risk

The sponsor used a baseline local site infection probability of 10% per CVC, taken from 1 of its included economic studies (13). Ye *et al.* utilised a probability of local site infection from a US RCT of 72 patients, which compared standard catheters with antiseptic catheters. The probability used was that of the standard catheter group. The RCT was published in 1996,

meaning results may not be generalisable to the current NHS. Further, the small study sample size generates uncertainty in its results. The definition of local site infection from the RCT was catheter insertion sites with pus and inflammation with a culture site positive for organisms in a patient with no clinical systemic sepsis or sepsis proven by culture to be caused by another organism (60). This definition is consistent with definitions provided by the sponsor and expert advisors (see correspondence log) except that culture swabs would not always be taken in patients with suspected local site infection within the NHS.

The pragmatic literature review undertaken by the EAC identified no studies reporting local site infection rates for critically ill patients with standard dressings. Supplementary targeted web searching identified NHS data from Wales. No nationwide English data were identified.

In 2013 in Wales, there was an incidence of 0.14 local site infections per 1,000 critical care catheter days (61). Local site infections were defined where there was no positive blood culture, line tip positive culture and local signs of line infection. This value, whilst not directly comparable, is materially lower than that from 1996 used by the sponsor.

Hazard ratio for local site infection

Within its cost-consequence analysis, the sponsor applied the hazard ratio for CRBSI reported by Timsit *et al.* (2012) to local site infections. An assumption was required as no data were available to inform the impact of Tegaderm CHG on local site infections. Both the clinical advice received by the sponsor and that received by the EAC (see correspondence log) concurred that Tegaderm CHG reduces the incidence of local site infection.

The sponsor provided further justification for application of the hazard ratio for CRBSI to local site infection, stating that Ye *et al.* made the same assumption within their economic evaluation (see correspondence log). In the study by Ye *et al.* the percentage decrease risk of CRBSI was 69% for standard CVCs and 44% for antiseptic CVCs, whilst the percentage decrease risk in local site infection was 47% for both types of CVC (13). Given that data used were not actually taken from this study, this factual inaccuracy will have no material impact on results.

A local technology review undertaken at Imperial College Healthcare NHS Trust reported there was no significant difference between Tegaderm CHG and standard dressings in relation to local signs of infection including redness, exudate and swelling (69). No further information was provided regarding the

number of patients included within the study, or if it was suitably powered to assess significant changes in local site infections.

Given that all experts were in agreement that Tegaderm CHG reduces local site infection, the EAC has judged that the assumption made by the sponsor is reasonable. The EAC has undertaken univariate sensitivity analysis to assess the impact on the results of this assumption (Section 4.5.2).

Baseline dermatitis risk

The baseline dermatitis risk used by the sponsor within its model was reported by Schwebel *et al.* (2012) to be 0.0026 per catheter, based on the mean of the rate of contact dermatitis for 3 and seven day dressing change strategies that were, respectively, 1.1 and 4.1 per 1,000 catheters (11). Contact dermatitis included those patients with redness and slight thickening of the skin and those with intense redness and swelling with coalesced large blisters or spreading reaction (11). These rates were reported by Schwebel and colleagues to be taken from Timsit *et al.* (2009); however, this could not be verified by the EAC (4).

In Timsit *et al.* (2012) the probability of severe contact dermatitis requiring removal of the dressing was reported by dressing type. For patients with standard dressings, 1 out of 476 patients experienced dermatitis (0.21%) (1). The EAC judged that it is appropriate to use this probability for patients with standard dressings, in the base case.

Relative Risk of dermatitis with Tegaderm CHG

The sponsor calculated the relative risk of severe contact dermatitis using data from Timsit *et al.* (2012) for CHG versus non-CHG dressings. This yielded a relative risk of 4.4, which was verified by the EAC. The EAC judged, if using the Timsit *et al.* (2012) data, that it would have been more appropriate to calculate the relative risk of Tegaderm CHG versus standard dressings, therefore excluding highly adhesive dressings which are not used within the NHS. Twenty two of 958 (2.35%) Tegaderm CHG patients had severe contact dermatitis compared with 1 of 476 (0.21%) standard dressing patients (1). The relative risk can therefore be calculated as 11.2.

The study by Timsit *et al.* (2012) was conducted using the old, less breathable version of Tegaderm CHG. The rate of severe contact dermatitis with the new iteration of the dressing is [redacted] based upon incidents reported to 3M's global database (see Section 3.7). This is lower than the baseline risk of dermatitis with standard dressings reported in the clinical evidence (1). However, the rate of dermatitis with standard dressings may also have reduced due to improvements in breathability. The EAC

judged that a relative risk of 1 in the base case was appropriate to capture these improvements. DSA and PSA were undertaken around this value to include consideration of the rate with Tegaderm CHG of [redacted]. Combining the data from Timsit *et al.* (2012) for standard dressings and the data from the 3M database for Tegaderm CHG results in a relative risk of 0.0007.

Resource identification, measurement and valuation

The EAC has provided a description and critique of the resource identification, measurement and valuation conducted by the sponsor for use in its *de novo* economic model. This is summarised in Table 4.6. All resource use apart from that reported is assumed to be equal in the Tegaderm CHG and standard dressing arms of the model.

Table 4.6: Resource usage in sponsor's model

Variable	Value	Source	EAC comment
Cost of CRBSI	£9,990	Hockenhull *et al.* (2008) (12)	This cost is appropriate in the base case.
Cost of dermatitis	£150	Schwebel *et al.* (2012) (11)	This cost assumes the catheter is replaced. Expert advice suggests this is not usually the case. The EAC have used a value of £6.
Cost of local site infection	£250	Saint *et al.* (2000) (70)	No detail from the clinical study was available for this cost. The EAC has used a cost of £100 based upon expert advice.
Number of days with catheter	10 days	Ye *et al.* (2011) (13) from Ho and Litton (2006) (42)	This value is appropriate in the base case.
Number of dressings	3	Assumption (based on change of dressing every 3 to 7 days)	This value is appropriate in the base case.

Cost of CRBSI

Within its cost-consequence analysis, the sponsor used a cost of £9,900 for CRBSI. This cost was taken from a health technology assessment (HTA) conducted by Hockenhull *et al.* and correctly inflated by the sponsor from 2008 prices to 2012/13 prices (12). It is unclear whether or not the cost had been inflated for inclusion within the HTA from its original price in the year of 2002/03. The cost from the HTA was also used within the NICE Infection clinical guideline (2). The sponsor also verified this cost using a bottom up costing approach based on resource usage advised by experts. Table 4.7 shows the resource usage and unit costs used by the sponsor, as well as those used by the EAC. The EAC contacted expert advisors provided by NICE who validated the sponsor's estimated resource usage associated with length of stay and catheter replacement (see correspondence log).

Table 4.7: CRBSI cost breakdown

Component	Sponsor's resource usage and cost (source expert advice)	EAC resource usage and cost
Additional ICU stay for typical patient	2-3 days in ICU (3 days used in calculation) £1,800 to £2,400 per day (mean used in calculation) = **£6,300**	2.5 days in ICU (range 2-3 days) £2,085 per day (ISD Scotland, 2014) (71) **= £5,213 (£4,170 - £6,255)**
Additional ward stay for typical patient	4-7 days in ward (7 days used in calculation) £480 per day **= £3,360**	5.5 days on ward (range 4-7 days) £598 per day (NHS reference costs – average of elective and non-elective bed days) (72) **= £3,289 (£2,392- £4,186)** Although only critically ill patients in ICU or HDU are within the scope of the decision problem, additional ward stay and the subsequent cost implications resulting from a CRBSI in the ICU are of relevance to decision making within the NHS. Therefore, the sponsor correctly included this cost.
Cost of consultant	£100	Excluded (included within cost per day in ICU and ward above)
Catheter replacement	Cost of catheter = £35 Cost of consumables = £15 Cost of X-ray = £50	Cost of catheter and consumable provided by sponsor are reasonable based on costs on NHS Supply Chain (£50 in total). Cost of X-ray = £56 (73) Staff costs (30 minutes of nurse time based on PSSRU cost of a hospital

Component	Sponsor's resource usage and cost (source expert advice)	EAC resource usage and cost
	Cost of nurse to insert catheter = £40 **= £140**	nurse) = £42 (74) **= £128**
Cost of diagnosis and treatment	Not included	Cost of laboratory culture = £7 (NICE, 2012) (2) 2 lab test are conservatively assumed (one to diagnose CRBSI and 1 to confirm treatment successful) = **£14**. Cost of drugs based on cheapest treatment for most common bacterium (S aureus (Methicillin-resistant)) (75): Teicoplanin = £7.32 per day plus 2 additional doses at start of treatment (76). Treatment is for at least 14 days and up to 8 weeks (75). Assumed mean for already critically ill patients = 4 weeks, with range 2-8 weeks. **= £220 (£117 - £425)** for most common bacterium leading to CRBSI (Note: treatment for other bacteria is more expensive with costs using conservative estimates of £600 to £5,000 (75, 76)).
Total	**£9,990**	**£8,868 (£6,826 - £11,188)**

The local technology review undertaken at Imperial College Healthcare NHS Trust reported that a single avoidable healthcare associated infection was estimated to cost the NHS £7,000 and that the cost of CRBSIs is likely to be much higher due to a longer length of stay (2011 prices). Although the cost calculated by the EAC was lower than that used by the sponsor, some critically ill patients will take much longer to recover than a typical patient, thus increasing the average length of stay. As each additional day in an ICU costs over £2,000, any outlier patients incurring just a few extra days in ICU will substantially impact on the cost. Given the variation in costs, however, the EAC used a wide range in both its DSA and PSA (Section 4.5).

The EAC judged that the cost used by the sponsor in the base case is appropriate.

Cost of dermatitis

The cost of dermatitis used by the sponsor was £150 based upon resource use of 4 standard dressings, removal of catheter and insertion of a new catheter. Experts advised that catheters are not usually removed due to dermatitis; rather the treatment would involve replacement of the dressing, only. Further, contact dermatitis described by Timsit *et al.*, 2012 required removal of the CHG impregnated dressing (1). By including the cost of insertion a new catheter, the sponsor has made a conservative assumption.

The cost shown on NHS Supply Chain for a standard Tegaderm IV dressing (3M) is £1.33 and for an IV 3000 dressing (Smith and Nephew) is £1.61. The EAC has used a cost of £6 for dermatitis based on 4 standard dressings. This is based on the assumption that patients with dermatitis require more frequent dressing changes than those without dermatitis. The EAC has assumed that no additional time is required to examine the area and apply dressings and hence the additional cost used in its base case to manage dermatitis is £6.

Cost of local site infection

Within the sponsor's cost-consequence analysis, a cost of £250 for a local site infection was used. This was based on the cost reported by Saint *et al.* in a US study published in 2000 of $400. The study provides no detail on how this cost was calculated (70).

The EAC verified this cost with expert advisors. The clinical experts reported that local site infections are diagnosed through clinical judgement with or without a skin swab. Catheters are not usually removed, but can be in some patients. Patients may be treated with antibiotics; however, broad spectrum antibiotics therapy is no longer standard of care. Only where infection is suspected to be a CRBSI would routine cultural swabs and systemic antibiotics be provided. One expert was able to provide an estimate of £100 for the cost of local site infections. Given no information was provided around the cost of local site infection used by the sponsor, the EAC has used £100 in its base case analysis.

Number of days with catheter

The sponsor used a mean catheterisation time of 10 days, which was reported in the economic analysis by Ye and colleagues (13). This dwell time was reported as an assumption by Ho and Litton, who conducted a meta-analysis of studies considering CHG dressing in critically and non-critically ill patients (42).

The 2 Tegaderm CHG studies included within Section 3 of this report (the clinical evidence review) both reported the median duration of catheter placement. The UK study reported this to be 5 days (range 3 - 17 days) in the standard dressing group and 6 days (range 3 - 24 days) in the Tegaderm CHG group (6). The French RCT reported this to be 6 days (IQR 4 - 11 days) (1). These studies report the catheter time in place during the study period only, which is either the time in ICU (6) or the time in ICU plus 48 hours (1). It is likely that some patients be catheterised during their stay on a general ward; therefore the number of days with catheters is likely to be higher than that reported in the clinical studies. Clinical expert advice suggested that the 10 day duration for catheterisation used by the sponsor was reasonable.

Number of dressings

In both the Tegaderm CHG and standard dressing arms of the model, the sponsor assumed that 3 dressings were used based upon a 10 day catheterisation period. Clinical experts advised that 3 dressings within a 10 day period is realistic (see correspondence log).

Technology and comparators' costs

The sponsor provided costs for each of the 3 dressing types considered in the submission. The EAC has verified each of these against NHS Supply Chain and used the NHS Supply Chain cost within its own analysis (77). This is shown in Table 4.8.

Table 4.8: Costs used in sponsor's model

Variable	Value	Source	EAC comment
Cost of Tegaderm CHG	£6.21	3M	Cost listed on NHS Supply Chain = £6.14 (77). The EAC judges is appropriate to use a weighted average based on sales of each size of Tegaderm CHG.
Cost of standard dressing	£1.34	3M	Cost listed on NHS Supply Chain = £1.33 (77). The EAC judges it appropriate to use a weighted average based on sales of each brand of standard dressing (Opsite IV 3000 and Tegaderm IV, 3M).
Cost of CHG sponge plus standard dressing	£5.16 plus £1.33 of standard dressing = £6.49	NR	Cost listed on NHS Supply Chain = £6.80 plus standard dressing (£1.33) = £8.13 (77).

Cost of Tegaderm CHG

Within its *de novo* economic model, the sponsor used cost of £6.21 per dressing for most commonly used dressing size. That is, the 8.5 cm by 11.5 cm dressing (1657R). This is listed on NHS Supply Chain at £6.14 per dressing.

A weighted average of the cost of the 4 sizes of Tegaderm CHG can be obtained based upon their proportion of sales. The costs for each size were obtained from NHS Supply Chain and the proportion of sales from the sponsor's submission. The proportions of sales from NHS Supply Chain for each size of Tegaderm CHG were also obtained through a Freedom of Information (FOI) request (see correspondence log). These proportions were similar to those reported by the sponsor. Table 4.9 shows the data used to estimate the weighted average cost of £6.26.

Table 4.9: Weighted average cost of Tegaderm CHG

	Cost	Proportion
Tegaderm CHG 1660R	£5.68	1%
Tegaderm CHG 1657R	£6.14	85%
Tegaderm CHG 1659R	£7.17	13%
Tegaderm CHG 1658R	£5.52	1%

The EAC judged that the weighted average cost of £6.26 should be used in the base case analysis.

Cost of standard dressing

The sponsor reported the cost for 2 brands of standard dressing, both of which are commonly used within the NHS. The costs provided by the sponsor (and those reported on NHS Supply Chain) are shown:

- Tegaderm IV 1635 (3M) = £1.34 per dressing (£1.33 per dressing);
- IV 3000 10 cm by 12 cm dressing (Smith and Nephew) = £1.61 per dressing (£1.61 per dressing).

Within its economic analysis, the sponsor conservatively used the cheaper standard dressing option, Tegaderm IV.

A FOI request from NHS supply chain showed that the ratio of Tegaderm IV sales to IV 3000 sales was 0.36:1 in 2012/13. The weighted standard dressing cost from NHS Supply Chain using this ratio is £1.54 per dressing. The EAC judged that this is an appropriate base case value.

Cost of CHG impregnated dressing (not used in the model)

The only comparator CHG impregnated dressing used within the NHS is Biopatch (Ethicon). This is a CHG impregnated disc that needs to be used in conjunction with a standard dressing. The sponsor reported a cost of Biopatch of £5.16, the source of which was not reported. The cost provided on NHS Supply Chain is £6.80. The sponsor used a total cost of £6.49, including £1.33 for a standard dressing. Using the same standard dressing cost, the total is £8.13 based upon the NHS Supply Chain costs.

A FOI request from NHS Supply Chain (see correspondence log) reported that no units of Biopatch were purchased from NHS Supply Chain in the past 2 financial years. Advice from clinical experts confirmed that Biopatch is used in the NHS, so trusts may buy the patch for less from another supplier (see correspondence log).

4.2.4: Sensitivity analysis

The sponsor undertook both DSA and PSA. DSA was carried out around baseline CRBSI risk and CRBSI cost, which the sponsor deemed to be the key drivers of the *de novo* model. The model was run using a both a low and high estimate of each of the 2 parameters. For CRBSI, this was 0.5 infections per 1,000 catheter days and 2.5 infections per 1,000 catheter days. For the cost of CRBSI, £5,000 and £15,000 were considered. The ranges considered were wide, which was appropriate to capture uncertainty around the point estimate values. The EAC undertook univariate sensitivity analysis around each of the model inputs. This is described in Section 4.5.2.

The sponsor undertook PSA, by running the model 1,000 times, each time sampling a different estimate for each model input (except dressing costs). The sponsor provided the probabilistic distribution that it applied to each input parameter; however, no justification or explanation of the distributions used were provided. Table 4.10 provides an overview of each input parameter and the distributions and coefficients used. The EAC have provided a critique for each input parameter distribution.

Table 4.10: Parameter distributions for sponsor's PSA

Parameter	Mean	Distribution	EAC comment
Average length of catheter dwell time	10 days	Normal Standard error = 2 days (calculated in excel sheet as mean divided by 5)	Gamma distribution should be used to avoid negative values. The EAC judged that a larger standard error of 5 days should be used to capture uncertainty. This is informed by the IQR reported in Timsit *et al.*, 2012 (median 9 days and IQR 5 to 20 days; n = 1,879) (1).
Baseline CRBSI risk (per 1,000 catheter days)	1.48/1,000 catheter days	Normal Standard error = 0.074 (calculated in excel sheet as mean divided by 20)	Gamma distribution should be used to avoid negative values. The EAC estimated the 95% CI for CRBSI for quarter 4, 2010 from Figure 1C of Bion *et al.* using ByteScout software. The lower CI = 1.28 and the upper CI = 1.75 (8). This range includes the CRBSI reported in the clinical evidence of 1.3 CRBSI per 1000 catheter days (1). This can be used to inform the range considered in the PSA.
Baseline local site infection risk (per patient)	0.1	Normal Standard error = 0.01 (calculated in excel sheet as mean divided by 10)	The sponsor should have used a beta distribution given that the input was a probability, where: Alpha = the number of catheters with a local site infection Beta = the number of catheters without a local site infection.
Baseline dermatitis risk (per patient)	0.0026	Normal Standard error = 0.00026 (calculated in excel sheet as mean	The sponsor should have used a beta distribution given that the input was a probability, where: Alpha = number of patients with an event = 1

Parameter	Mean	Distribution	EAC comment
		divided by 10)	Beta = number of patients without an event = 475 (1)
CRBSI hazard ratio	0.402	Lognormal Alpha = -0.911 (calculated in excel sheet as log mean) Beta = -0.393 (source unclear)	The use of lognormal distribution is appropriate. Alpha and Beta should be determined using the SE (calculated using the 95% CI reported by Timsit *et al.* of 0.186 to 0.868) (1). SE = 0.174 Alpha = ((1-Mean)/((St Error/Mean)^2))-Mean = 2.79 Beta = (Alpha/Mean)-Alpha = 4.15
Local site infection hazard ratio	0.402	Lognormal Alpha = -0.911 (calculated in excel sheet as log mean) Beta = -0.393 (source unclear)	The use of lognormal distribution is appropriate. Alpha and Beta should be determined using the SE (calculated using the 95% CI reported by Timsit *et al.* of 0.186 to 0.868) (1). SE = 0.174 Alpha = ((1-Mean)/((St Error/Mean)^2))-Mean = 2.79 Beta = (Alpha/Mean)-Alpha = 4.15
Dermatitis relative risk	4.4	Lognormal Alpha = 18.034 (calculated in excel sheet as log mean)	The use of Lognormal distribution is correct. The range around the mean must be assumed.

Parameter	Mean	Distribution	EAC comment
		Beta = -0.393 (source unclear)	
Unit non antimicrobial transparent film dressings cost	£1.34	Fixed	Fixing this value is correct assuming no discounting is currently or will be undertaken by distributors.
Unit Tegaderm CHG cost	£6.21	Fixed	Fixing this value is correct assuming no discounting is currently or will be undertaken by distributors.
Cost of CRBSI	£9,900	Gamma Alpha = 198 (calculated in excel sheet as mean divided by beta) Beta = 50 (assumption)	The use of Gamma distribution is correct. The rational for assuming beta is 50 is unclear. An alternative assumption would be to assume a wide SE and use this to generate alpha and beta.
Cost of local site infection	£250	Gamma Alpha = 50 (calculated in excel sheet as mean divided by beta) Beta = 5 (assumption)	The use of Gamma distribution is correct. The rational for assuming beta is 50 is unclear. An alternative assumption would be to assume a wide SE and use this to generate alpha and beta.
Cost of dermatitis	£150	Gamma Alpha = 30 (calculated in excel sheet as mean divided by beta)	The use of Gamma distribution is correct. The rational for assuming beta is 5 is unclear. An alternative assumption would be to assume a wide SE and use this to generate alpha and beta.

Parameter	Mean	Distribution	EAC comment
		Beta = 5 (assumption)	
Mean number of dressings per catheter	3	Normal Standard error = 0.3 (calculated in excel sheet as mean divided by 10)	Gamma distribution should be used to avoid negative values. It would be more appropriate to use a larger standard error to capture uncertainty and also more consistent with Timsit *et al.*, 2012 observed variance (for standard dressing median changes per catheter was 3 with IQR of 1 to 5) (1).

4.3 Results of de novo cost analysis

4.3.1: Base-case analysis results

Probabilistic results from the sponsor's economic model were provided in section 9.5, submission. The results reported could not be verified exactly against the economic model. Given that the reported results are probabilistic in nature, that is, each time the model is re-run they will vary slightly as the input parameters are randomly selected based upon their assigned distribution. Therefore, as the model had been re-run between the results being extracted for the report and submission, there were minor differences. The EAC re-ran the model a number of times, each time yielding similar results to those reported within the sponsor's submission. Results from the sponsor base case model are reported in Table 4.11. These show that Tegaderm CHG generates cost savings of £77.26 per patient.

Table 4.11: Sponsor's probabilistic base case results per patient

	Tegaderm CHG	Standard dressing	Increment
Dressing cost	£18.63	£4.02	£14.61
CRBSI	£64.06	£146.66	-£82.60
Local site infection	£11.12	£25.04	-£13.92
Dermatitis	£5.82	£1.18	£4.64
Total	**£99.63**	**£176.89**	**-£77.26***

* Note: variation, due to rounding, exists when summing the column.

4.3.2: Sensitivity analysis results

The sponsor undertook both PSA and DSA. Univariate deterministic analysis was undertaken by varying the baseline risk of CRBSI and the CRBSI cost. These were the parameters that the sponsor deemed to be the key drivers of the model. Again, these results could not be verified precisely; however, re-running the model generated similar results to those reported by the sponsor. The results of the sponsor's univariate sensitivity analyses are shown in Table 4.12.

4.12: Sponsor's univariate sensitivity analyses results

	Baseline CRBSI risk (cost saving per patient)	CRBSI cost (cost saving per patient)
Base case	-£77	-£77
Low estimate *CRBSI risk = 0.5 per 1,000 catheter days* *CRBSI cost = £5,000*	-£23	-£36
High estimate *CRBSI risk = 5.5 per 1,000 catheter days* *CRBSI cost = £15,000*	-£135	-£119

PSA based on 1,000 iterations of the model using the distributions and coefficients reported in Table 4.10, found Tegaderm CHG to have a 98.5% probability of being cost saving over standard dressings.

4.3.3: Subgroup analysis

In line with the scope, no subgroup analysis was carried out by the sponsor.

4.3.4: Model validation

The sponsor reported that its economic model had been internally validated through replication of the Excel model in a second software (DecisionPro$^{TM)}$. The EAC identified no structural errors within the model. An error was identified within the calculation of the cost of dermatitis, however, this was a misinterpretation of data that would not have been identified through replicating the model.

The sponsor also externally validated its results against the published literature it identified during its cost-effectiveness review. In line with the other antimicrobial devices aiming to reduce CRIs, Tegaderm CHG was found to be cost saving.

4.4 Interpretation of economic evidence

Consistency with published economic literature

In Section 9.8.1 of the sponsor's submission, the results of the *de novo* model were compared with the results of the published cost-effectiveness analyses included within the sponsor's review. To recap, these analyses did not consider Tegaderm CHG, but other interventions aiming to reduce CRI such as other CHG impregnated dressings or anti-microbial CVCs. The sponsor concluded that its findings were consistent with those published previously, in that interventions to prevent CRIs are cost saving. The EAC agrees with the sponsor's interpretation of its *de novo* model in relation to other published evidence around CRI reducing interventions. As reported in Section 4.1, the EAC identified 4 conference abstracts reporting on the cost-benefits of Tegaderm CHG versus standard dressings. The results of these studies were inconclusive and given the limited information available it is difficult to draw comparisons between these studies and the sponsor's *de novo* model.

Relevance to NHS settings

In section 9.8.2 of the submission the sponsor stated that the cost analysis is relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope. Although much of the data used within the analysis was specific to ICU/CCU patients, rather than HDU patients, the EAC agrees that the analysis meets the NHS settings specified in the scope.

Strengths and weaknesses of analysis

In section 9.8.3 of the economic submission (strengths and weakness of the analysis), the sponsor correctly identified that the analysis was limited by the lack of evidence relating to cost estimates used in the analysis. The sponsor attempted to overcome this by seeking advice from clinical experts, but deemed that the analysis would benefit from a clinical study directly measuring economic outcomes. The EAC's judgement of the strengths and weaknesses of the submission is now described.

Strengths of analysis

The EAC considered that the analysis matched the scope well. The patients included within the analysis were critically ill patients in ICU or HDU who required a CVC or arterial catheter. Tegaderm CHG was compared with 1 of the comparators listed in the scope (standard dressing) and the sponsor provided justification for why the second comparator (CHG sponge) was not considered within the analysis. The scope specified that skin should be swabbed with 2% CHG in alcohol prior to dressing application and although the analysis deviated from the scope in this respect, this was necessary given the available evidence. Three clinical outcomes were included in the model – dermatitis, local site infection and CRBSI. Skin and catheter colonisation were correctly excluded from the analysis given that these would not be routinely tested for in asymptomatic patients within the NHS.

The sponsor did not include mortality following CRBSI within its model. The EAC considered this to be an acceptable approach given that data are currently unavailable to quantify this rate in patients with Tegaderm CHG. Further, although data is available for standard dressings, no clinical evidence could be identified within the UK setting for CRBSI-related mortality specifically. In 2010, however, 5.1% of deaths in England resulted from all-cause blood infections (specifically sepsis) (78). Evidence from outside of the UK shows there is no consensus on the rate of CRBSI-related mortality in clinical practice, with a wide range of values reported (i.e. 3% to 35%) (23, 25). This precludes the ability of incorporating mortality rates for Tegaderm CHG and standard dressing into this analysis in a way that accurately reflects rates in UK clinical practice. If it is accepted that Tegaderm CHG significantly reduces CRBSI rates compared with standard dressing, then it is plausible that Tegaderm CHG will have a positive impact on CRBSI-related morality, and therefore patient quality of life, in practice.

The decision tree model, using an NHS perspective was appropriate for the decision problem. It captured the main differences in clinical outcomes and reported the cost differences between Tegaderm CHG and standard dressings. Although a short time horizon was assumed, this is judged to have captured the material cost differences between dressings and was appropriate given the disease area and perspective. The model structure and parameters were verified by 2 clinical experts and are judged to be a good representation of clinical practice.

Clinical evidence on CRBSI and dermatitis was from a well-conducted RCT (1), judged to generalise to the English NHS setting and consistent with the evidence presented in the clinical section of the sponsor's submission. The model included dermatitis as an adverse event and adopted a conservative approach to its costing by assuming removal of a catheter in all cases.

Resource use and unit costs were in general appropriate. Where published evidence was scarce, the sponsor sought verification of model inputs with clinical experts, in particular, for the cost of CRBSI. In addition, the sponsor undertook univariate sensitivity analysis around the 2 inputs it deemed to be key drivers of the model and PSA to capture uncertainty in model inputs. The PSA was also, in the main, well-conducted and although there were some issues with the distributions adopted, these had a limited impact on the PSA results.

The sponsor's description of the model, inputs, results and sensitivity analyses was clear. The accompanying model had been validated by the sponsor using a robust method; it was easy to use and replicate.

Weaknesses of analysis

The EAC considered that there were 2 main weaknesses to the otherwise robust analysis conducted by the sponsor. First, within the submission there was a lack of rationale for the choice of distributions and coefficients used in PSA conducted by the sponsor. The EAC notes that the submission template does not, however, specifically require that this information should be provided by sponsors. Providing this information would have allowed the sponsor's PSA to be verified more thoroughly by the EAC, rather than the EAC simply conducting its own PSA (see Section 4.5.3).

Second, the sponsor did not attempt to make any judgement regarding the comparative cost-effectiveness of Tegaderm CHG and CHG sponge. The sponsor noted in section 9.1.3, submission that CHG impregnated dressing (or CHG sponge) was not included as a comparator given the lack of direct evidence comparing this with Tegaderm CHG. Although the lack of direct clinical evidence comparing the 2 dressings prevents a direct analysis being made, a narrative comparison would have been welcome. The EAC has provided this in Section 4.5.4.

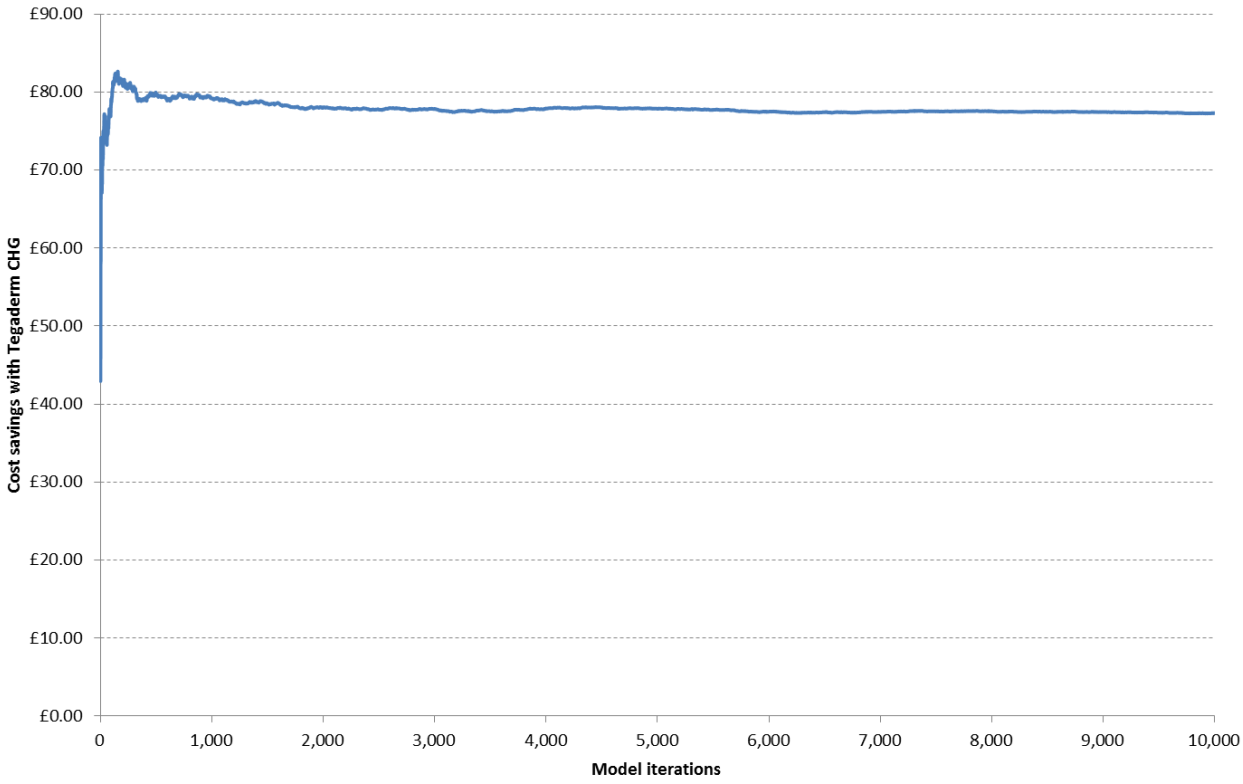
4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

4.5.1: EAC's base-case analysis

Sponsor's deterministic results

As described in Section 4.2 (specifically in Tables 4.5, 4.7, 4.8 and 4.9) the EAC disagreed with some of the input parameters and distribution ranges used by the sponsor within its *de novo* cost analysis. In order to make meaningful comparisons between the sponsor's base case results and the EAC's base case results, the EAC initially replicated the sponsor's model deterministically. That is, rather than running the model 1,000 times, each time using a different iteration for each input parameter, the calculations were carried out based on the sponsor's point estimate input values. The EAC generated a graph (Figure 4.2) to test the stability of the sponsor's probabilistic results depending upon the number of model iterations. This shows that after 1,000 iterations the models results had not fully converged and there was still some instability in the results. Therefore, each time the model is run 1,000 times, there is some variation in results; hence, more meaningful comparisons can be made using the deterministic results.

Figure 4.2: Convergence in sponsor's probabilistic results



The deterministic results of the sponsor's model, using the sponsor's inputs are shown in Table 4.13. Tegaderm CHG results in estimated cost savings of £83 per patient compared with standard dressings. When the EAC corrected the calculation relating to the cost of dermatitis the estimated cost savings with Tegaderm CHG became £86 per patient.

Table 4.13: Sponsor's deterministic base case results per patient

	Tegaderm CHG	Standard dressing	Increment
Dressing cost	£18.63	£4.02	£14.61
CRBSI	£59.16	£146.52	-£87.36
Local site infection	£10.37	£25.00	-£14.63
Dermatitis	£5.15	£1.17	£3.98
Total	**£93.31**	**£176.71**	**-£83.40**

EAC's deterministic results using English data

The EAC revised the sponsor's *de novo* model by updating a number of the input parameters to those specified in Table 4.14. The specific inputs that were changed were baseline risk of local site infection and dermatitis, relative risk of dermatitis and the costs of dermatitis, local site infection and of dressings. The CRBSI rate used in this analysis was that from quarter 4 of 2012 from Matching Michigan, which was also used by the sponsor (8). Further, the EAC updated the application of hazard ratios within the model, such that, hazard ratios were multiplied by baseline risk, as described in Section 4.2.2. Finally, the EAC corrected the calculation of the cost of dermatitis, so that the number of dressings was not included within the calculation. This was necessary as the baseline rate of dermatitis utilised was per patient or catheter, not per dressing (see Section 4.2.2).

Table 4.14: EAC input parameters, distributions and ranges

Variable	EAC point estimate	Source	EAC range and source
Baseline CRBSI rate	English data (2010): 1.48 per 1,000 catheter days Scottish data (2013): 0.3 per 1,000 catheter days	Bion *et al.* (2012) (8) Scottish ICU report (64)	DSA: Range = 0.2 to 1.75, lower CI from Scotland and upper CI from Bion *et al.* 2012 (8, 64). PSA: A Gamma distribution has been used to avoid negative values. The PSA has been run twice, first with English data and second with more recent Scottish data. Range = 1.28 to 1.75, 95% CI from Bion *et al.* 2012 (8). Range = 0.2 to 0.6, 95% CI from Scotland (64)
Hazard ratio for CRBSI with Tegaderm CHG	0.402	Timsit *et al.* (2012) (1)	DSA: Range is equal to 95% CI of 0.186 to 0.868 PSA: A Lognormal distribution has been used, with range equal to 95% CI of 0.186 to 0.868 (1)
Baseline local site infection rate	0.14 per 1,000 catheter days	NHS Wales 2013 data (61)	DSA: a range of 0 to 0.3 infections per 1,000 catheter days has been considered. PSA: A Gamma distribution has been used to avoid negative values of this rate. A large SE of 0.1 has been assumed to capture uncertainty.
Hazard ratio for local site infection with Tegaderm CHG	0.402	Assumed to be equal to hazard ratio for CRBSI from Timsit *et al.* (2012) (1)	DSA: Range is equal to 95% CI of 0.186 to 0.868 PSA: Lognormal distribution has been used, with range equal to 95% CI of 0.186 to 0.868 (1)
Baseline dermatitis probability	0.0021	Timsit *et al.* (2012) (1)	DSA: a range of 0 to 0.01 has been considered. PSA: Beta distribution has been used with alpha = 1 and beta = 475 (1).
Risk reduction for dermatitis with Tegaderm	1	Timsit *et al.* (2012) (1)	DSA: A range of +/- 100% (0 to 2). PSA: Log normal distribution used with an assumed SE of 0.5.

Variable	EAC point estimate	Source	EAC range and source
CHG			
Cost of CRBSI	£9,990	Hockenhull *et al.* (2008) (12)	DSA: A range of +/- 50% was considered (£4,950 to £14,850). PSA: Gamma distribution has been used, with a standard error of £3,000 assumed.
Cost of dermatitis	£6	Expert advice	DSA: A range of +/- 30% was considered (£4.10 to £7.80) PSA: Gamma distribution has been used, with a standard error of £3 assumed.
Cost of local site infection	£100	Expert advice	DSA: A range of +/- 30% was considered (£70 to £130). PSA: Gamma distribution has been used, with a standard error of £30 assumed.
Number of days with catheter (catheter dwell time)	10 days	Expert advice confirmation of Ho and Litton (2006) (42)	DSA: A range of +/- 50% was considered (5 to 15 days). PSA: Gamma distribution has been used, with a standard error of 5 days assumed.
Number of dressings	3	Assumption (based on change of dressing every 3 to 7 days)	DSA: A range of +/- 66% was considered (1 to 5 dressings). PSA: Gamma distribution has been used, with a standard error of 2 dressings assumed.
Cost of Tegaderm CHG	£6.26	NHS Supply Chain. Weighted average of dressing sizes (77)	This is fixed and not included in either deterministic or probabilistic analysis.
Cost of standard dressing	£1.54	NHS Supply Chain. Weighted average of brands (77)	This is fixed and not included in either deterministic or probabilistic analysis.

The results of the deterministic base case analysis conducted by the EAC show Tegaderm CHG to save an estimated £73.54 per person. The full results are shown in Table 4.15.

Table 4.15: EAC's deterministic base case results per patient using English CRBSI data

	Tegaderm CHG	Standard dressing	Increment
Dressing cost	£18.78	£4.62	£14.16
CRBSI	£58.90	£146.52	-£87.62
Local site infection	£0.06	£0.14	-£0.08
Dermatitis	£0.01	£0.01	£0.00
Total	**£77.75**	**£151.29**	**-£73.54**

EAC's deterministic results using Scottish data

The EAC also conducted scenario analyses using data on baseline CRBSI rates from Scotland in 2013 (64) (see Table 4.14). This scenario was considered given the possibility that CRBSI rates have continued to fall since the results of Matching Michigan were reported (8). The data from Scotland, rather than from Wales (both reported in Section 4.2.3) were utilised within the model as these were informed by a larger sample size and confidence estimates were provided around the mean value enabling the Scottish data to inform PSA. The authors reporting the Scottish data note that the confirmed CRBSI rate reported may underestimate the true rate in Scottish ICUs because not all sites routinely undertake catheter tip culturing. However, the EAC judged scenario analyses using this low rate to be valid in order to explore the cost-effectiveness of Tegaderm CHG in ICUs or HDUs where baseline CRBSI rates are relatively low.

Table 4.16 presents the results of the EAC's deterministic base case analysis, using the Scottish data. These show Tegaderm CHG saves an estimated £3 per person. The cost saving using the Scottish data are more modest than using the Matching Michigan data. This occurs because the baseline risk of CRBSI is lower in the Scottish data, meaning that there is less scope for improvement, or reduction in the incidence of CRBSI, by using Tegaderm CHG. Had the Scottish rate of 'probable and confirmed' CRBSI been used within this analysis (2.4 CRBSI per 1,000 catheter days), the estimated cost

savings would be greater than those generated when using the English epidemiological data.

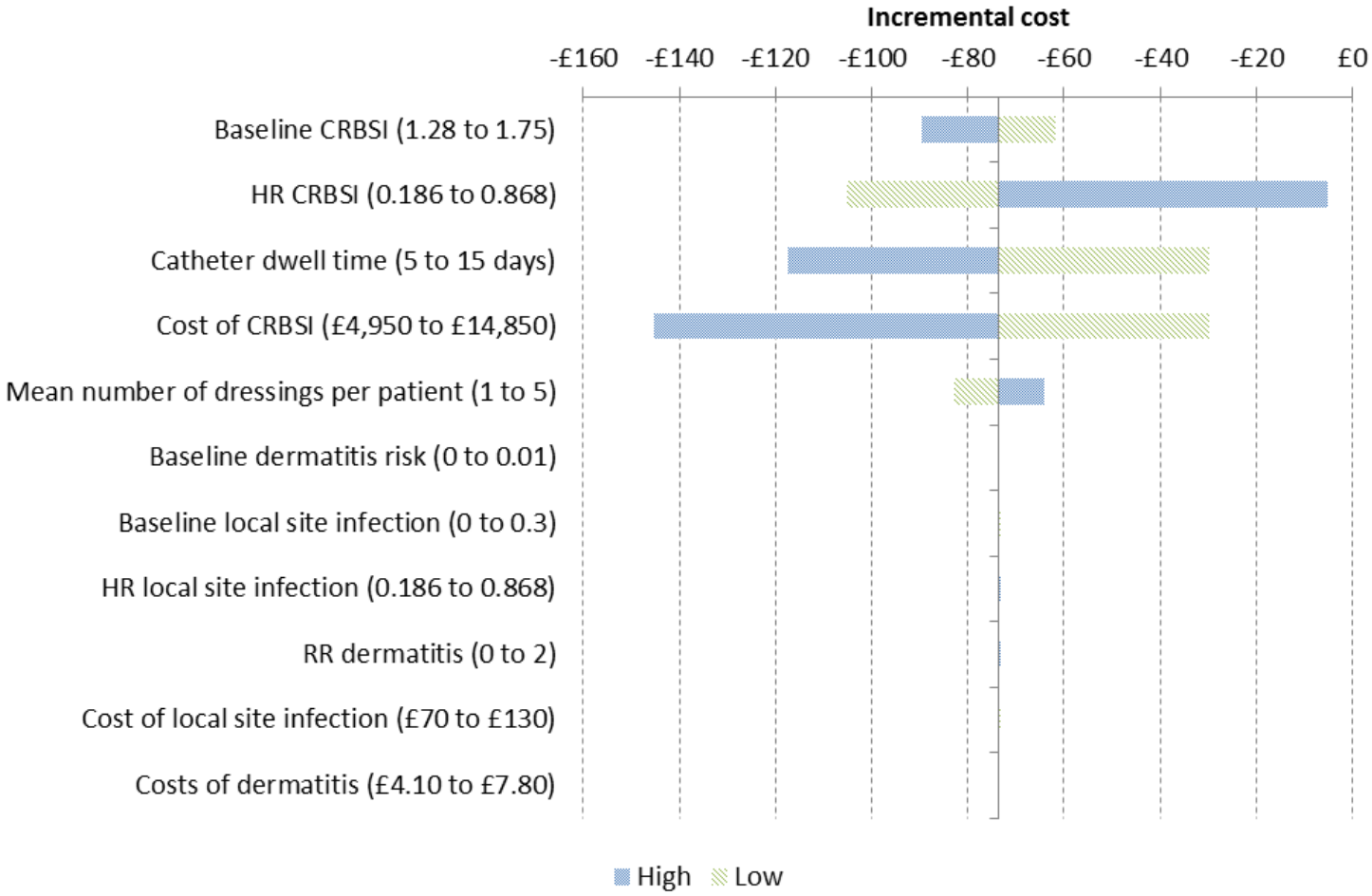
Table 4.16: EAC's deterministic base case results per patient using Scottish CRBSI data

	Tegaderm CHG	Standard dressing	Increment
Dressing cost	£18.78	£4.62	£14.16
CRBSI	£11.94	£29.70	-£17.76
Local site infection	£0.06	£0.14	-£0.08
Dermatitis	£0.01	£0.01	£0.00
Total	**£30.79**	**£34.47**	**-£3.68**

4.5.2: EAC Univariate sensitivity analysis

The EAC undertook univariate DSA around all model inputs (with the exception of the cost of Tegaderm CHG which is assumed fixed). The ranges considered by the EAC for each parameter are shown in Table 4.14. The sponsor had carried out deterministic analysis around the 2 input parameters it deemed to be the key drivers of the results: baseline risk of CRBSI and cost of CRBSI. The analysis performed by the EAC around each input is shown in the tornado diagram in Figure 4.3.

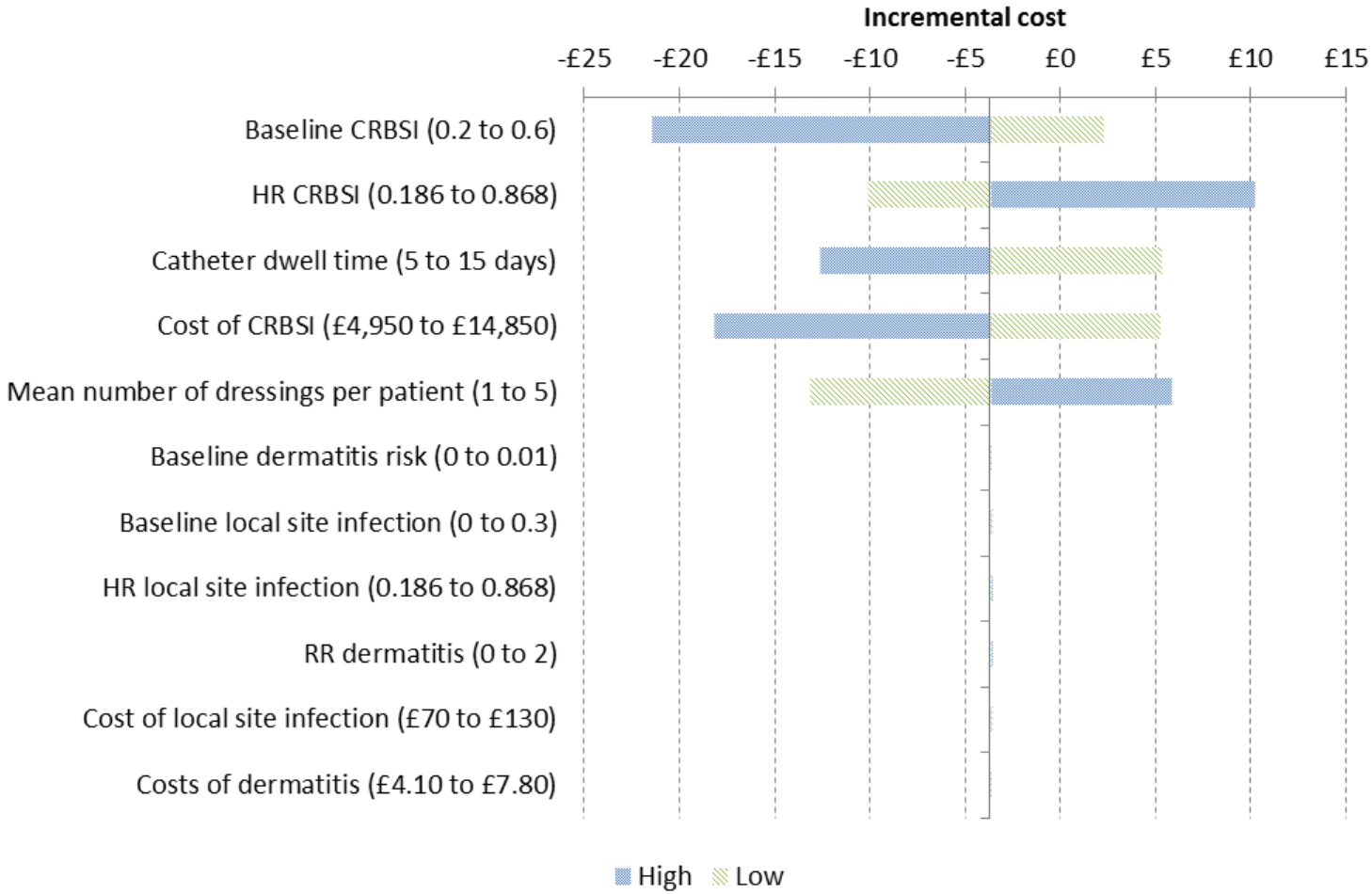
Figure 4.3: Tornado diagram of univariate sensitivity analysis using English data



This shows that the undertaking univariate sensitivity analysis around any of the model inputs does not result in Tegaderm CHG incurring costs. Although the hazard ratio of CRBSI with Tegaderm CHG, the length of stay with catheter and the cost of CRBSI all impact upon the results, they do not change the direction of the results.

In order to further explore the impact of uncertainty on the results of the model, the EAC produced a second tornado diagram, using the Scottish CRBSI rate as the base case value (0.30 CRBSI per 1,000 catheter days (64), rather than 1.48 CRBSI per 1,000 catheter days(8)). In this analysis, all remaining inputs are varied as specified in Table 4.14. This is displayed in Figure 4.4.

Figure 4.4: Tornado diagram of univariate sensitivity analysis using Scottish data



The cost savings in the scenario using the Scottish data are more modest than where the Matching Michigan data are used. In turn, the univariate sensitivity analyses show the results to be less robust. In this scenario, the direction of the results changed, i.e. Tegaderm CHG became cost incurring, with reductions in the hazard ratio of CRBSI, a reduction in the baseline CRBSI rate, an increase in the mean number of dressings per patient and a lower cost of CRBSI.

A limitation of univariate sensitivity analysis is that only 1 input is varied at a time. Figure 4.4 shows that where the catheter dwell time (or the number of days each catheter is required for) reduces, the cost savings with Tegaderm CHG are fewer. This occurs because we are still assuming that 3 dressings are required, however, the number of catheter days available to incur an infection is reduced. Likewise, where the number of dressings required increased during a 9 day catheter dwell time, Tegaderm CHG becomes cost incurring. In reality, these 2 inputs are not independent and likely to be highly correlated. Given that it is standard protocol to change dressings at least every seven days, where the number of days with a catheter increases, the number of dressings required will also increase. As such, although varying these inputs individually appears to influence the direction of the results, in reality this is unlikely to be the case.

This was explored further considering patients requiring catheterisation for 1 week, or less. In these analyses it is assumed the catheter is not swapped for a new catheter during the catheterisation period. Where 1 dressing is used, in order for Tegaderm CHG to generate cost savings, patients require a catheter for over 2 days. Where 2 dressings are used, in order for Tegaderm CHG to generate cost savings, patients require a catheter for over 5 days. Therefore, for those patients who are expected to require a catheter for a short time frame, the use of Tegaderm CHG is estimated to generate fewer cost savings.

As shown in Figure 4.4, the baseline risk of CRBSI, hazard ratio of CRBSI with Tegaderm CHG and cost of CRBSI are the main drivers of the results of the model. Using the Scottish baseline CRBSI risk, Tegaderm CHG becomes cost incurring where the hazard ratio of CRBSI is 0.526, or above, or the cost of CRBSI is £8,000 or below.

4.5.3: EAC's PSA

The EAC ran PSA using the ranges and distributions shown for each input parameter in Table 4.14. This analysis was run with 10,000 iterations for both the Matching Michigan and Scottish data. The results of the analysis are provided in Table 4.17. The results of the PSA show that using the Matching Michigan data for baseline CRBSI rate, Tegaderm CHG is cost saving in 97.8% of iterations, thus these results are robust. When the Scottish data is applied in the model, the cost savings and the probability of Tegaderm CHG being cost saving are substantially reduced, such that Tegaderm CHG is cost saving in 57.9% of iterations.

Table 4.17: EAC PSA results

	Matching Michigan data	Scottish data
Probabilistic total cost per patient with Tegaderm CHG	£78.61	£30.81
Probabilistic total cost per patient with standard dressing	£151.50	£34.37
Probabilistic incremental total cost per patient	-£72.90	-£3.56
Probability of being cost saving	97.8%	57.9%

4.5.4: Cost-effectiveness of Tegaderm CHG versus CHG sponge

The sponsor judged that the lack of comparative data between Tegaderm CHG and CHG sponge meant that the second comparator specified in the scope could not be included within the cost-effectiveness analysis. The EAC agreed that the lack of comparative evidence available makes an analysis difficult; however, the some exploratory analysis can be conducted based on the evidence available.

In order to compare Tegaderm CHG and CHG sponge, information is required to the relative clinical efficacy of the dressings, the cost of the 2 dressings and any other differences in resource use between the 2 dressings.

In Section 3.10 of this report, the EAC concluded that, on the currently available evidence, there appears to be no significant difference in the ability of Tegaderm CHG or CHG sponge to reduce CRBSI. We have no information relating to local site infections for either Tegaderm CHG or CHG sponge. In Section 4.5.1, the EAC assumed, based on advice from clinical experts, that the hazard ratio of local site infections with Tegaderm CHG is the same of CRBSI. Applying that same assumption, it would be expected that the Tegaderm CHG and CHG sponge do not significantly differ in their ability to reduce local site infections. The EAC's analysis of adverse events in Section 3.7, suggests that both Tegaderm CHG and CHG sponge cause dermatitis more regularly than standard dressings. Whether Tegaderm CHG results in a higher incidence of dermatitis that CHG sponge, or vice versa, cannot be determined based upon the available evidence. Therefore in terms of clinical efficacy, it is plausible to assume for the purposes of an exploratory cost analysis that the 2 dressings have similar efficacy and safety.

The EAC questioned expert advisors around any differences in usage of Tegaderm CHG and CHG sponge, which may have resource implications (see correspondence log). The experts advised that the 2 dressings are similar. One expert suggested that the CHG sponge takes longer to apply, likely due to having to put an additional standard dressing over the top of the CHG sponge. Another expert advised that some nurses have placed the CHG sponge upside down; meaning a replacement dressing has to be used. The advice received from experts around the greater ease of use of Tegaderm CHG compared with CHG sponge is consistent with that reported in Section 3.6.2, under ease of use and performance. No other material differences in resource usage between Tegaderm CHG and the CHG sponge were identified. Therefore, it was assumed resource usage is similar between Tegaderm CHG and CHG sponge, enabling a cost minimisation exercise to be conducted.

CHG sponge, Biopatch, is listed on NHS Supply Chain at £6.80 per dressing. The sponge must be secured with a standard dressing, the cheapest of which (Tegaderm IV) costs £1.33. This gives a total cost of £8.13, almost £2 per dressing more expensive than Tegaderm CHG. The sponsor provided a cost for Biopatch of £5.16. Given that no sales of Biopatch were made through the NHS Supply Chain in either of the previous 2 financial years, but clinicians advised they use the dressing (see correspondence log), it is likely that trusts purchase the dressing via other sources at a cheaper price than the NHS Supply Chain listed price. Using the £5.16 cost for Biopatch, results in a total cost with the standard dressing of £6.49 per dressing, slightly more expensive than Tegaderm CHG (costing £6.26).

4.6 Conclusions on the economic evidence

The sponsor included 5 economic evaluations within its cost-effectiveness review. The EAC deemed all 5 to be outside the scope of the decision problem because Tegaderm CHG was not an intervention considered within any of the evaluations (9-13). Four economic evaluations, building on clinical data from the Tegaderm CHG RCT by Timsit and colleagues (1), published as abstracts within conference proceedings, were included by the EAC (15-18). All abstracts were written by the same combination of authors and discussed a number of economic models carried out from a French healthcare system perspective. Given that these were abstracts, the limited information available precluded the ability of the EAC to make judgements around the generalisability of the studies to the current UK NHS. In all 4 studies, Tegaderm CHG was neither statistically significantly cost saving, nor statistically significantly cost incurring.

The *de novo* model submitted by the sponsor was fully executable and captured the differences in treatment with Tegaderm CHG and treatment with standard dressings, thus providing an answer to the decision problem set out in the scope. A decision tree structure was used within the model, which simulated patient pathways of critically ill adult patients requiring cardiovascular access via a CVC or arterial catheter. Outcomes within the model were: CRBSI, local site infection, dermatitis or no infection/complication. Baseline risk of infection and dermatitis were used for the standard dressing arm of the model, and hazard ratio or relative risk applied to these as appropriate for the Tegaderm CHG arm of the model. The costs were associated with dressing type, management of infection (local and systemic) and management of dermatitis.

In the sponsor's probabilistic base case they found Tegaderm CHG to save an average of £77 per patient when compared with standard dressings. PSA conducted over 1,000 iterations of the model by the sponsor found Tegaderm CHG to be cost saving in 98.5% of iterations. DSA was undertaken around the baseline rate of CRBSI and the cost of CRBSI and the result of this was Tegaderm CHG remained cost saving within the range of inputs analysed.

The EAC critically appraised the model and the accompanying narrative in the sponsor's economic submission. As the analysis compared Tegaderm CHG to standard dressings only, the key limitation of the sponsor's submission was the exclusion of any comparison with CHG sponges. Exploratory analysis undertaken by the EAC suggests that Tegaderm CHG and CHG sponges have similar clinical efficacy, a similar safety profile and similar costs. A comparative clinical study between the 2 dressings would be required to draw firm conclusions on this, however.

Regarding the *de novo* model submitted by the sponsor, the EAC judged that this was largely accurate and captured the key aspects of the disease area. However, the EAC deemed that the economic evidence provided by the sponsor was subject to several limitations which included:

- The length of time with a catheter is not influenced by whether a patient has an infection (either CRBSI or local). In practice, catheter dwell time may be influenced by infection; however, the EAC notes that data informing the length of catheter dwell time with and without infection is not available.

- Using Tegaderm CHG is assumed not to result in any differences in outcomes aside from the short-term impact of CRBSI being to increase length of stay, local site infection and dermatitis.

- Infection rates are assumed to be linear regardless of catheter dwell time. Evidence shows that where catheters are left *in situ* for a longer time period, the risk of infection increases (58, 59). No data were available to inform the difference in infection rate with Tegaderm CHG dependent on catheter dwell time.

Given the evidence available, the EAC judged that it is not possible to overcome these limitations.

The EAC corrected the dermatitis cost calculation in both arms of the model and used an alternative application of hazard ratios for Tegaderm CHG. Both had a limited impact of the results of the model. Each input used by the sponsor was considered and validated by the EAC where possible using expert advice and pragmatic literature searching. Following amendments to some model inputs (as reported in Tables 4.5, 4.7 and 4.8) and the amendments to the calculations (specified above), the EAC's base case result was very similar to that reported by the sponsor. The EAC found Tegaderm CHG generates cost savings of around £73 per patient compared with standard dressings (in both the deterministic and probabilistic base cases). Tegaderm CHG was cost saving in 98% of model iterations. The impact of

each change that was made by the EAC are shown in Table 4.19. The EAC conducted univariate sensitivity analysis which identified the hazard ratio for CRBSI as the key driver of the analysis (see Figure 4.3).

The EAC considered a second scenario for all results based upon alternate baseline CRBSI risk data. The rationale for this being that the data used in both the sponsor and the EAC's base cases reported in the Matching Michigan study was from 2010 (8). Throughout the 2 year duration of this study CRBSI rate had fallen from 3.7 CRBSI per 1,000 CVC days to 1.48 CRBSI per 1,000 catheter days; a trend that may have continued. The authors reported that infections rates were already trending down before the Matching Michigan programme and also that the observed reduction in infection rates could be attributable as much to improvement efforts outside of the programme and to the awareness-raising effect of a nationwide programme as to any specific component of the programme itself (8). The baseline rate of CRBSI since 2010 in England is unknown, hence more recent data from Scotland in 2013 has been considered in a scenario analysis, although it is noted that potential underreporting of CRBSI in Scottish ICUs may exist. The Scottish infection rates have fallen to 0.3 per 1,000 catheter days (95% CI: 0.2-0.6) in 2013 (64) from 0.8 per 1,000 catheter days (95% CI: 0.5 – 1.2) in 2010 (65). It is important to note that the Scottish infection rate in 2010 was substantially lower than the rate from Matching Michigan, also from 2010, of 1.48 CRBSI per 1,000 catheter days.

In this second scenario, Tegaderm CHG remained cost saving compared with standard dressings. However, the savings were minimal and more uncertainty existed. Tegaderm CHG resulted in cost savings of £3 per patient compared with standard dressings and was cost saving in 58% of model iterations. Under this scenario Tegaderm CHG became cost incurring where the hazard ratio of CRBSI is 0.525, or above, or the cost of CRBSI is £8,000 or below. These threshold hazard ratio and cost values are both within the ranges considered by the EAC as plausible. This scenario is likely to be representative of ICUs or HDUs with particularly low CRBSI baseline rates, rather than the average unit within England.

The use of both the Scottish and Matching Michigan data on baseline CRBSI was limited in two ways and further discussion around this is warranted given this input is a key driver of the economic analysis. First, both sets of data refer to CRBSI specifically in CVC, i.e. arterial catheters are excluded. Two studies, set in Australia and France respectively, found no significant difference in catheter colonisation between CVC and arterial catheters (79). Thus, the impact of this limitation on the results is likely to be minimal and any differences that exist in practice would be captured within the ranges of values considered in sensitivity analysis by both the sponsor and the EAC. Second,

as CHG impregnated dressings are used as standard of care in some patients (17% of ICUs in Matching Michigan), the EAC would anticipate that the baseline CRBSI for standard dressings alone is likely to be higher than the base case values used within this analysis. This, in turn, would result in greater potential cost savings with Tegaderm CHG compared with standard dressings.

The EAC considers that the sponsor put forward a well-considered economic case for Tegaderm CHG versus standard dressings, showing potential cost savings. Confidence in these results resides upon the baseline CRBSI rate and as such, in trusts or departments where baseline CRBSI infection rates are low, using of Tegaderm CHG is likely to deliver fewer cost savings compared with sites with higher CRBSI rates. However, Tegaderm CHG could still be adopted in order to maintain low CRBSI rates, whilst being more convenient than other CHG impregnated dressings. Where patients are expected to have a short term catheter dwell time of less than 2 days, the use of Tegaderm CHG may not be warranted.

The sponsor did not estimate the cost-effectiveness of Tegaderm CHG against CHG sponge. Based upon the exploratory analysis conducted by the EAC, the EAC considers that Tegaderm CHG offers small cost savings compared with the CHG sponge.

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

The additional work undertaken by the EAC around both the calculations and parameters of the model did not substantially alter the outcome of the results. In the probabilistic base case the EAC found the Tegaderm CHG to generate cost savings of £73 per patient compared with standard dressing and to be cost saving in 97.8% of model iterations. In comparison, the sponsor reported savings of £77 per patient and found Tegaderm CHG to be cost saving, compared with standard dressings, 98.5% of the time. Table 4.18 shows the base case results found by the sponsor and the EAC.

Table 4.18: Base case results; Sponsor and EAC

	Sponsor probabilistic base case	EAC probabilistic base case
Probabilistic total cost per patient with Tegaderm CHG	£99.63	£78.61
Probabilistic total cost per patient with standard dressing	£176.89	£151.50
Probabilistic incremental total cost per patient	-£77.26	-£72.90
Probability of being cost saving	98.5%	97.8%

Table 4.19 shows the cost impact of each action the EAC undertook to change the sponsor's *de novo* model. This includes both structural and parameter changes. The effect of each change is compared against the sponsor's deterministic base case saving of £83 per patient. The deterministic results, rather than probabilistic results, have been shown in Table 4.19 for clarity. Using the deterministic results means that any costs differences are due to the changes made by the EAC and not due to random effects of sampling input parameters from the range available.

Most of the changes made by the EAC had a limited impact upon the result of the model. With exception of application of hazard ratios and relative risk of dermatitis with Tegaderm CHG, all changes affected both the standard dressing and Tegaderm CHG arms of the model. The single action that had the greatest impact on the final results was the change in the baseline CRBSI rate, when the 2013 Scottish data (64), rather than the 2010 Matching Michigan data (8) were used within the model.

Table 4.19: Impact of structural and parameter changes to the *de novo* model

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£83 per patient)
Correcting mistake in cost of dermatitis calculation for Tegaderm CHG and standard dressing	-£86	-£3	103%	Amending the model for dermatitis cost causes the cost savings with Tegaderm CHG to increase. As the cost of dermatitis is greater with Tegaderm, removing multiplication by 3 dressings (amendment made) has a larger impact on the total cost for Tegaderm CHG.
Alternative method of hazard ratio application used	-£84	-£1	101%	Changing the method of application of the hazard ratio has a negligible impact on results. The number of CRBSI per 1,000 patients goes from 5.98 to 5.95. The number of local site infections goes from 41 to 40.
Baseline risk of local site infection changed from 10% of catheters to 0.14 per 1,000 catheter days	-£69	£14	82%	Inputting a more recent baseline local site infection rate into the model results in lower incremental cost savings with Tegaderm CHG. This occurs as the lower baseline rate of infection provides less scope for improvement with Tegaderm CHG.
Baseline probability of dermatitis changed from 0.0026 per patient to a probability of 0.0021	-£84	-£1	101%	Using a lower baseline probability of dermatitis with standard dressings (not including highly adhesive dressings) causes an increase in the cost savings with Tegaderm CHG as the risk increase of dermatitis is applied to fewer patients.

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£83 per patient)
Relative risk of dermatitis with Tegaderm CHG changed from 4.4 to 1	-£87	£4	105%	Inputting a lower relative risk of dermatitis to the model results in an increase of incremental savings with Tegaderm CHG. This occurs as fewer patients experience dermatitis with Tegaderm CHG and thus incur costs of treatment.
Cost of dermatitis changed from £150 to £6	-£87	-£4	105%	Reducing the cost of dermatitis results in greater cost savings with Tegaderm CHG as more of these patients have dermatitis.
Cost of local site infection changed from £250 to £100	-£75	£8	89%	Reducing the cost of local site infection results in reduced cost savings with Tegaderm CHG as fewer of these patients have local site infections.
Cost of Tegaderm CHG changed from £6.21 to £6.26	-£83	-£0	100%	The slight reduction in the cost of Tegaderm CHG has no impact on the cost savings with Tegaderm CHG.
Cost of standard dressing changed from £1.34 to £1.54	-£84	-£1	101%	The slight change increase in cost of standard dressing has results in a marginal increase in cost savings with Tegaderm CHG.
All above changes made simultaneously (EAC base case with Matching Michigan data)	-£73	£10	88%	Making all of the changes from the sponsor's base case to the EAC's base case simultaneously results in a reduction in the cost savings with Tegaderm CHG, but does not change the direction of results.

Action	Incremental cost per patient	Change from sponsor's base case	Percentage of base case incremental cost	Impact of action (compared with the sponsor's deterministic base case incremental cost of -£83 per patient)
Change of CRBSI from 1.48 per 1,000 catheter days to 0.3 per 1,000 catheter days	-£14	£69	16%	Inserting the Scottish baseline rate of CRBSI substantially reduces cost savings with Tegaderm CHG. This is because the hazard ratio for reduction in CRBSI is applied to a lower baseline rate.
All above changes made simultaneously (EAC base case with Scottish data)	-£3	£80	4%	Making all of the changes from the sponsor's base case to the EAC's base case with Scottish data simultaneously results in a reduction in the cost savings with Tegaderm CHG. This is larger than with the English data as the baseline CRBSI rate has also been changed.

5 Conclusions

The current NICE guidelines on preventing and controlling infection recommend that a sterile, transparent, semipermeable membrane dressing (standard dressing) should be used to cover vascular access device insertion sites (2). Standard practice within the NHS is to use standard dressings; some sites may also apply a CHG patch (i.e. CHG sponge) but no usage data are available because although listed on the NHS Supply Chain, there are currently no recorded sales. Tegaderm CHG is a single dressing which incorporates the transparent, semipermeable dressing properties of a standard dressing and also includes a CHG patch to provide continuous antiseptic release to the catheter insertion site. Tegaderm CHG is a direct replacement or alternative to both standard dressings and CHG sponge. The sponsor, 3M, has presented the clinical evidence and economic case to support the adoption of Tegaderm CHG to cover vascular access sites in critically ill patients.

The clinical evidence for Tegaderm CHG comprises 1 published RCT comparing Tegaderm CHG with standard dressings (1) and 1 comparative study of Tegaderm CHG and CHG sponge, published as a conference poster only (6). No evidence was identified by the sponsor comparing Tegaderm CHG to CHG sponge. The EAC identified a further 2 RCTs comparing CHG sponge to standard dressing (4, 5), which it included within its clinical evidence review to facilitate an indirect comparison of Tegaderm CHG and CHG sponge.

Evidence on CRBSI rates from 2 well conducted RCTs were available (1, 4). Timsit *et al.* (2012) reported a CRBSI rate of 0.5 per 1,000 catheter days for the Tegaderm CHG and a CRBSI rate of 1.3 per 1,000 catheter days for the standard dressing group (n = 1,879 patients and n = 4,163 catheters). A p-value of 0.02 was reported for Tegaderm CHG versus non-CHG dressings (comprising standard and highly adhesive dressings) (1). Timsit *et al.* (2009) reported a CRBSI rate of 0.4 per 1,000 catheter days for the CHG sponge and a CRBSI rate of 1.3 per 1,000 catheter days for the standard dressing group (p=0.005) based upon n = 1,636 patients and n = 3,778 catheters (4). The EAC conducted a Z-test using data from the 2 studies by Timsit and colleagues and found there to be no significant difference in the CRBSI rate with Tegaderm CHG and CHG sponge.

All 4 included clinical studies provided evidence on either skin or catheter colonisation (1, 4-6). The available evidence showed that catheter colonisation rates were lower with Tegaderm CHG compared with standard dressings. This result was statistically significant in the large RCT ($p<0.0001$) (1) and statistically significant in 1 area of the catheter (intradermal section) in the observational study ($p=0.037$) (6). Evidence comparing CHG sponge with standard dressings was somewhat mixed, however, robust results from Timsit *et al.* (2009) showed a statistically significant reduction in catheter colonisation with the CHG sponge ($p=0.005$) (4).

Clinical experts and information from studies reporting on the ease of use of 3 dressing types reported that Tegaderm CHG is at least as easy to use as standard dressings and likely to be easier to use than the CHG sponge. The transparent and single component nature of Tegaderm CHG means it may be marginally quicker to apply and result in fewer misapplications than the CHG sponge.

No systemic adverse reactions to CHG were reported in any of the 4 studies. This was explicitly stated in 2 studies (1, 4). In both studies patients with known allergies to CHG were excluded from the study, which may compromise the generalisability of adverse reactions in the studies to the NHS more generally. Severe contact dermatitis requiring removal of the dressing was reported in 2 studies (1, 4). Timsit *et al.* (2012) reported the incidence of 1.1% in Tegaderm CHG dressed catheters was statistically significantly higher than the 0.1% in standard dressed catheters ($p=0.0005$) (1). Timsit *et al.* (2009) reported that severe contact dermatitis occurred in 0.53% of CHG sponge dressed catheters and 0% of standard dressed catheters. Statistical significance was not reported (4).

The sponsor advised that since the release of the latest Tegaderm CHG dressing, which is more permeable, the rate of severe contact dermatitis has reduced to around [redacted]
Dermatitis was also reported a number of times in FDA MAUDE reports. These were often less severe cases than those in the RCTs, which usually healed without treatment. An analysis of FDA MAUDE reports showed that incidents have reduced since the introduction of the highly permeable Tegaderm CHG dressing. Clinical experts advised that they had not had experience of any adverse events during their use of Tegaderm CHG.

No information on other outcomes defined in the scope, including mortality caused by CRBSI and local site infection, was provided in any of the included clinical studies. There is also no evidence on the key patient-orientated outcome of quality of life.

The published economic evidence around Tegaderm CHG consisted of 4 conference abstracts of economic models (15-18) built around data from the RCT comparing Tegaderm CHG with standard dressings (1). In all abstracts economic modelling was carried out from a French healthcare system perspective. From the information provided within these abstracts, it was not possible to assess generalisability to the current NHS. None reported statistically significant cost differences (15-18).

The sponsor provided the EAC with a *de novo* economic model, which was based on a decision tree that mapped patient pathways over a 10 day time horizon. The model was probabilistic in nature, meaning it was run for 1,000 iterations, each time sampling a random value for each input based upon the predefined range and distribution. No extrapolation beyond the follow-up of the clinical trial data was carried out. The cost-consequence analysis utilised clinical efficacy data relating to CRBSI, local site infections and dermatitis for Tegaderm CHG and standard dressings. The second comparator defined in the scope, CHG sponge, was excluded from the sponsor's economic submission on the grounds of the lack of comparative clinical evidence.

The sponsor's *de novo* model followed an appropriate clinical pathway given the data available. In its probabilistic base case, Tegaderm CHG was found to save £77.26 per patient versus standard dressings and be cost saving in 98.5% of model iterations. The sponsor correctly identified baseline CRBSI rate and cost of CRBSI as key drivers of its economic analysis.

The EAC validated the sponsor's model inputs using advice from clinical experts and pragmatic literature searching of databases and grey literature. Seven model inputs were changed to values the EAC judged more plausible. Two changes in calculation methods, including the application of hazard ratios and the calculation of the cost of dermatitis, were also made. In the EAC's probabilistic base case, Tegaderm CHG generated cost savings of £73.54 per patient compared with standard dressings and had a 97.8% chance of being cost saving. These results were robust throughout univariate sensitivity analysis.

A second scenario was considered by the EAC, using alternative baseline CRBSI data. Here, the CRBSI of 0.3 per 1,000 catheter days from Scottish ICUs in 2013 (64), rather than 1.48 CRBSI per 1,000 catheter days from English ICUs in 2010 was utilised (8). This substantially reduced cost savings to £3.68 per patient with Tegaderm CHG versus standard dressings. The results were also more uncertain, with Tegaderm CHG generating cost savings in 57.9% of iterations. Under this scenario, a hazard ratio of CRBSI with Tegaderm CHG of 0.525 or above or a cost of CRBSI of £8,000 or below resulted in Tegaderm CHG no longer generating cost savings. Further, where the length of catheterisation was 2 days or less, using Tegaderm CHG rather than standard dressing was cost incurring. The EAC notes that the confirmed CRBSI rate reported for Scottish ICUs may be an underestimate of the true CRBSI rate and should the true CRBSI be higher, greater cost savings would be generated with Tegaderm CHG. This scenario is likely to represent those units with particularly low CRBSI rates, rather than the average ICU or HDU within England.

The EAC considered the relative cost-effectiveness of Tegaderm CHG and CHG sponge based on the data currently available. Clinical and resource use equivalence were judged to be appropriate assumptions and, thus, the problem became one of cost minimisation. Tegaderm CHG costs £6.26 per dressing; there is uncertainty on the cost of CHG sponges, with estimates ranging from £6.49 to £8.13 per dressing.

The base case results showed that adopting Tegaderm CHG in place of standard dressings is clinically effective in reducing CRBSI and local site infections, has a similar safety profile and may generate significant savings for the NHS compared with standard dressings in critically ill patients where the baseline CRBSI infection rate is around 1.48 per 1,000 catheter days. Where baseline CRBSI rates are low or patients require catheterisation for a short time frame, these potential cost savings reduce and may become negligible. Based on the limited available evidence, Tegaderm CHG offers small cost savings compared with the CHG sponge.

6 Implications for research

A source of uncertainty that the EAC encountered during the evaluation of Tegaderm CHG was the baseline CRBSI rate within ICU and HDU in the English NHS. Although good quality and applicable data were available from Matching Michigan, the data were up to 2010 and subsequent CRBSI rates have not been reported. Within the NHS in both Scotland and Wales, ICUs are required to submit data relating to CRI. Such a programme would be beneficial in England, particularly if data were broken down by CHG or non-CHG dressings.

Further information regarding the consequences of CRBSI is welcome to fully inform the benefits of Tegaderm CHG reducing CRBSI rates. Data collection may comprise, first, any change in mortality or other long term morbidity consequences resulting from CRBSI contracted in an NHS setting and second, the impact of CRBSI on patient reported outcomes. Such data collection may be undertaken as a standalone exercise.

Two comparators to Tegaderm CHG were stipulated in the decision problem defined by NICE; standard dressings and CHG impregnated dressings (referred to as CHG sponge in this report). RCT evidence comparing Tegaderm CHG to standard dressings was available to inform guidance around Tegaderm CHG (1). Comparative research of Tegaderm CHG and CHG sponge is currently lacking. If there are reasons to support the hypothesis that CHG sponges have a better clinical and safety outcomes than Tegaderm CHG then it may be appropriate to conduct further primary research. Such a study should ideally have the following design:

- Randomised control trial of critically ill patients requiring intravascular access via a CVC or arterial catheter;
- Blinding of microbiologists processing the skin and catheter cultures to dressing group;
- Adequately powered with predefined outcomes and estimates of significant clinical effect;
- Outcomes including CRBSI, local site infection, dermatitis and resource usage measurement to inform economic analysis;
- Measurement of CRBSI in line with standard UK definitions, such as those used in the Matching Michigan study (8).

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Appendix 1: Updated sponsor clinical evidence and adverse effects searches

Appendix 1 contains search result numbers and full search strategies for the EAC-updated sponsor clinical evidence and adverse effects searches. Table A1.1 gives details of the returned record numbers for each literature search source. Table A1.2 gives details of the returned record numbers for the MAUDE and MHRA searches on adverse effects.

Literature Search Results

The literature searches identified 9966 records (Table A1.1). Following deduplication 6831 records were assessed for relevance. These numbers do not include MAUDE and MHRA results (see Section 3.7).

Table A1.1: Literature search results

Resource	Records identified		
	Tegaderm search	**Comparators and CVCs search**	**Comparators and ACs search**
MEDLINE and MEDLINE in Process	391	2006	616
Embase	905	3437	951
Cochrane Database of Systematic Reviews (CDSR)	1	8	22
Cochrane Central Register of Controlled Trials (CENTRAL)	104	325	377
Health Technology Assessment Database (HTA)	0	1	0
Database of Abstracts of Reviews of Effects (DARE)	3	6	0
NHS Economic Evaluation Database (NHS EED)	4	10	0
Econlit	0	0	0
Science Citation Index Expanded (SCI-EXPANDED) --1900-present / Conference Proceedings Citation Index- Science (CPCI-S) -1990-present*	172	273	304
Clinicaltrials.gov**	50	0	0
EuroScan**	0	0	0
European Medicines Agency **	0	0	0
TOTAL	**1630**	**6066**	**2270**

* For the 2 comparator searches, only CPCI-S was searched. For the Tegaderm search both CPCI-S and SCI were searched. Search result numbers in sponsor submission indicate this is how the search was carried out.

** ClinicalTrials.gov, EuroScan, and European Medicines Agency were not searched for the 2 comparator searches as details of the strategies were not found in the submission.

MAUDE and MHRA searches

MAUDE and MHRA were searched for adverse events of Tegaderm. No search was carried out of these resources for comparators as details of the strategies were not found in the submission. The number of records identified in MAUDE and MHRA is not included in the completed PRISMA diagram.

Table A1.2: MAUDE and MHRA results

Resource	Records identified
Manufacturer and User Facility Device (MAUDE)	126
Medicines and Healthcare products Regulatory Agency (MHRA)	3
TOTAL	**129**

Search strategies: sponsor search 1 - Tegaderm

1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 391
Search strategy:

1 tegaderm.mp. (144)
2 (chlorhexidine gluconate or chg).mp. (2408)
3 Chlorhexidine/ (6428)
4 3M.mp. (4782)
5 or/2-4 (11827)
6 dressing$.mp. (19114)
7 5 and 6 (274)
8 1 or 7 (391)

2: Source: Embase 1974 to 2014 November 18

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 905
Search strategy:

1 tegaderm.mp. (521)
2 (chlorhexidine gluconate or chg).mp. (4911)
3 chlorhexidine gluconate/ (4132)
4 3M.mp. (9844)
5 or/2-4 (14699)
6 dressing$.mp. (25764)
7 5 and 6 (560)
8 1 or 7 (905)

Note: In the reported search in the sponsor submission, line 8 is not included. Through assessment of the reported results numbers in the submission, the EAC have made the assumption that this omission was a reporting error.

3: Source: Cochrane Database of Systematic Reviews (CDSR) - Issue 11 of 12, November 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 19/11/14
Retrieved records: 1
Search strategy:

#1	tegaderm:ti,ab,kw	45
#2	(chlorhexidine gluconate or chg):ti,ab,kw	413
#3	[mh ^Chlorhexidine]	1376
#4	3M:ti,ab,kw	503
#5	#2 or #3 or #4	2040
#6	dressing*:ti,ab,kw	2928
#7	#5 and #6	76
#8	#1 or #7	112
#9	#8 in Cochrane Reviews (Reviews and Protocols)	1

4: Source: Cochrane Central Register of Controlled Trials (CENTRAL) - Issue 10 of 12, October 2014

Interface / URL: Cochrane Library / Wiley Interscience

Search date: 19/11/14
Retrieved records: 104
Search strategy:

#1	tegaderm:ti,ab,kw	45
#2	(chlorhexidine gluconate or chg):ti,ab,kw	413
#3	[mh ^Chlorhexidine]	1376
#4	3M:ti,ab,kw	503
#5	#2 or #3 or #4	2040
#6	dressing*:ti,ab,kw	2928
#7	#5 and #6	76
#8	#1 or #7	112
#9	#8 in Cochrane Reviews (Reviews and Protocols)	1
#10	#8 in Other Reviews	3
#11	#8 in Trials	104

5: Source: Health Technology Assessment Database (HTA) - Issue 4 of 4 Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 19/11/14
Retrieved records: 0
Search strategy:

#1 tegaderm:ti,ab,kw 45
#2 (chlorhexidine gluconate or chg):ti,ab,kw 413
#3 [mh ^Chlorhexidine] 1376
#4 3M:ti,ab,kw 503
#5 #2 or #3 or #4 2040
#6 dressing*:ti,ab,kw 2928
#7 #5 and #6 76
#8 #1 or #7 112
#9 #8 in Cochrane Reviews (Reviews and Protocols) 1
#10 #8 in Other Reviews 3
#11 #8 in Trials 104
#12 #8 in Technology Assessments 0

6: Source: Database of Abstracts of Reviews of Effects (DARE) - Issue 4 of 4 Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 19/11/14
Retrieved records: 3
Search strategy:

#1 tegaderm:ti,ab,kw 45
#2 (chlorhexidine gluconate or chg):ti,ab,kw 413
#3 [mh ^Chlorhexidine] 1376
#4 3M:ti,ab,kw 503
#5 #2 or #3 or #4 2040
#6 dressing*:ti,ab,kw 2928
#7 #5 and #6 76
#8 #1 or #7 112
#9 #8 in Cochrane Reviews (Reviews and Protocols) 1
#10 #8 in Other Reviews 3

7: Source: NHS Economic Evaluation Database (NHS EED) - Issue 4 of 4 Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 19/11/14
Retrieved records: 4
Search strategy:

#1	tegaderm:ti,ab,kw	45
#2	(chlorhexidine gluconate or chg):ti,ab,kw	413
#3	[mh ^Chlorhexidine]	1376
#4	3M:ti,ab,kw	503
#5	#2 or #3 or #4	2040
#6	dressing*:ti,ab,kw	2928
#7	#5 and #6	76
#8	#1 or #7	112
#9	#8 in Cochrane Reviews (Reviews and Protocols)	1
#10	#8 in Other Reviews	3
#11	#8 in Trials	104
#12	#8 in Technology Assessments	0
#13	#8 in Economic Evaluations	4

8: Source: Econlit 1886 to October 2014

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 0
Search strategy:

1	tegaderm.mp.	0
2	(chlorhexidine gluconate or chg).mp.	1
3	3M.mp.	25
4	2 or 3	26
5	dressing$.mp.	138
6	4 and 5	0
7	1 or 6	0

9: Source: Science Citation Index Expanded (SCI-EXPANDED) -- 1900-present / Conference Proceedings Citation Index- Science (CPCI-S) -1990-present

Interface / URL: Web of Science
Search date: 19/11/14
Retrieved records: 172
Search strategy:

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

7 172 #6 OR #1
6 89 #5 AND #4
5 18,903 TS=(dressing*)
4 10,811 #3 OR #2
3 9,135 TS=(3M)
2 1,678 TS=((chlorhexidine gluconate or chg))
1 99 TS=(tegaderm)

Note: The submission indicates that only Conference Proceedings Citation Index- Science (CPCI-S) was searched. It reports that 145 results were retrieved. When the EAC replicated the search in CPCI-S however, only 20 results were returned. When the search was conducted across both SCI and CPCI-S, 172 results were returned. The EAC have assumed therefore that there was a reporting error, and that both SCI and CPCI-S were searched.

10: Source: ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/ct2/home
Search date: 19/11/14
Retrieved records: 50
Search strategy:

50 studies found for: tegaderm

11: Source: EuroScan

Interface / URL: http://euroscan.org.uk/
Search date: 19/11/14
Retrieved records:
Search strategy:

Homepage search box used; 'Search Euroscan' selected. Following term searched on:

Tegaderm

1 result retrieved. Assessed online and excluded by Information Specialist as not relevant: http://www.hsc.nihr.ac.uk/topics/cellutometm-epidermal-harvesting-system-for-autolo/

12: Source: European Medicines Agency

Interface / URL: http://www.ema.europa.eu
Search date: 19/11/14
Retrieved records:
Search strategy:

Homepage search box used; Following term searched on:

Tegaderm

0 results

13: Source: Manufacturer and User Facility Device (MAUDE)

Interface/URL:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Search date: 28/11/14
Retrieved records: 126
Search strategy:

'Search database' interface used. Following searches carried out using the Manufacturer, Brand Name and Date Report Received by FDA fields.

Search 1:
Manufacturer: 3m
Brand Name: tegaderm chg
Report Date From: 07/01/2000 Report Date To: 07/29/2013

109 results retrieved

Search 2:
Manufacturer: 3m
Brand Name: tegaderm chg
Report Date From: 30/07/2013 Report Date To: 28/11/2014

17 results retrieved

14: Source: Medicines and Healthcare products Regulatory Agency (MHRA)

Interface / URL: http://www.mhra.gov.uk/#page=DynamicListMedicines
Search date: 28/11/14
Retrieved records: 3
Search strategy:

Site search used at the above url. Search carried out on the following term:

tegaderm

3 results

Search strategies: sponsor search 2 - comparators and CVCs

1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 2006
Search strategy:

1 Catheterization, Central Venous/ (12205)
2 (central adj3 (venous$ or line or pressure)).tw. (23423)
3 ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw. (24277)
4 exp catheterization, peripheral/ (8817)
5 Catheters, Indwelling/ (16350)
6 ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw. (23078)
7 ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw. (926)
8 exp Vascular Access Devices/ (1264)
9 ((cva or cvad or vad or access) adj3 device$).tw. (2745)
10 (cvc$ or picc).tw. (3702)
11 or/1-10 (74071)
12 dressing$.mp. (19114)
13 exp Bandages/ (20303)
14 bandage$.mp. (17540)
15 adhesive$.mp. (63931)
16 gel$.mp. (464940)
17 gauze$.mp. (3209)
18 tape.mp. (16533)
19 film.mp. (74478)
20 (permeable or impermeable or non-permeable).mp. (25625)
21 ethicon.tw. (898)

22 (smith adj2 nephew).tw. (527)
23 or/12-22 (665830)
24 11 and 23 (1896)
25 opsite$.tw. (114)
26 biopatch$.tw. (16)
27 or/24-26 (2006)

2: Source: Embase 1974 to 2014 November 18

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 3437
Search strategy:

1 central venous catheterization/ (7085)
2 central venous catheter/ (11562)
3 (central adj3 (venous$ or line or pressure)).tw. (31155)
4 ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw. (31830)
5 catheterization/ (36713)
6 indwelling catheter/ (8791)
7 ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw. (30935)
8 ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw. (1152)
9 ((cva or cvad or vad or access) adj3 device$).tw. (4079)
10 (cvc$ or picc).tw. (5685)
11 or/1-10 (113469)
12 dressing$.mp. (25764)
13 exp silver dressing/ or exp foam dressing/ or exp hydrogel dressing/ or exp biological dressing/ or exp hydrocolloid dressing/ or exp wound dressing/ or exp gauze dressing/ or exp occlusive dressing/ (11341)
14 exp bandage/ (12287)
15 bandage$.mp. (14193)
16 adhesive$.mp. (55834)
17 gel$.mp. (512884)
18 gauze$.mp. (4588)
19 tape.mp. (18778)
20 film.mp. (91080)
21 (permeable or impermeable or non-permeable).mp. (28082)
22 ethicon.tw. (1576)
23 (smith adj2 nephew).tw. (856)
24 or/12-23 (731760)
25 11 and 24 (3210)
26 opsite$.tw. (214)
27 biopatch$.tw. (48)
28 or/25-27 (3437)

3: Source: Cochrane Database of Systematic Reviews (CDSR) - Issue 11 of 12, November 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 8
Search strategy:

#1	[mh ^"Catheterization, Central Venous"]	782
#2	(central next/3 (venous* or line or pressure)):ti,ab,kw	2564
#3	((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw	2112
#4	[mh "Catheterization, Peripheral"]	722
#5	[mh ^"Catheters, Indwelling"]	962
#6	((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw	1981
#7	((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw	18
#8	((cva or cvad or vad or access) next/3 device*):ti,ab,kw	144
#9	(cvc* or picc):ti,ab,kw	367
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	5020
#11	dressing*:ti,ab,kw	2928
#12	[mh Bandages]	2231
#13	bandage*:ti,ab,kw	2220
#14	adhesive*:ti,ab,kw	3156
#15	gel*:ti,ab,kw	7649
#16	gauze*:ti,ab,kw	571
#17	tape:ti,ab,kw	2271
#18	film:ti,ab,kw	2304
#19	(permeable or impermeable or non-permeable):ti,ab,kw	395
#20	ethicon:ti,ab,kw	119
#21	(smith next/2 nephew):ti,ab,kw	82
#22	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	19360
#23	#10 and #22	317
#24	opsite*:ti,ab,kw	36
#25	biopatch*:ti,ab,kw	9
#26	#23 or #24 or #25	350
#27	#26 in Cochrane Reviews (Reviews and Protocols)	8

Note: In the reported Cochrane Library search in the submission, line #26 is: #24 or #25. Through assessment of the reported results numbers in the submission, the EAC have made the assumption that the omission of #23 in this line was a reporting error. This note also applies to search numbers 4, 5, 6 and 7 below.

4: Source: Cochrane Central Register of Controlled Trials (CENTRAL) - Issue 10 of 12, October 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 325
Search strategy:

#1	[mh ^"Catheterization, Central Venous"]	782
#2	(central next/3 (venous* or line or pressure)):ti,ab,kw	2564
#3	((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw	2112
#4	[mh "Catheterization, Peripheral"]	722
#5	[mh ^"Catheters, Indwelling"]	962
#6	((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw	1981
#7	((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw	18
#8	((cva or cvad or vad or access) next/3 device*):ti,ab,kw	144
#9	(cvc* or picc):ti,ab,kw	367
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	5020
#11	dressing*:ti,ab,kw	2928
#12	[mh Bandages]	2231
#13	bandage*:ti,ab,kw	2220
#14	adhesive*:ti,ab,kw	3156
#15	gel*:ti,ab,kw	7649
#16	gauze*:ti,ab,kw	571
#17	tape:ti,ab,kw	2271
#18	film:ti,ab,kw	2304
#19	(permeable or impermeable or non-permeable):ti,ab,kw	395
#20	ethicon:ti,ab,kw	119
#21	(smith next/2 nephew):ti,ab,kw	82
#22	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	19360
#23	#10 and #22	317
#24	opsite*:ti,ab,kw	36
#25	biopatch*:ti,ab,kw	9
#26	#23 or #24 or #25	350
#27	#26 in Cochrane Reviews (Reviews and Protocols)	8
#28	#26 in Other Reviews	6
#29	#26 in Trials	325

5: Source: Health Technology Assessment Database (HTA) - Issue 4 of 4, Oct 2012

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 1
Search strategy:

#1 [mh ^"Catheterization, Central Venous"] 782
#2 (central next/3 (venous* or line or pressure)):ti,ab,kw 2564
#3 ((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw 2112
#4 [mh "Catheterization, Peripheral"] 722
#5 [mh ^"Catheters, Indwelling"] 962
#6 ((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw 1981
#7 ((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw 18
#8 ((cva or cvad or vad or access) next/3 device*):ti,ab,kw 144
#9 (cvc* or picc):ti,ab,kw 367
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 5020
#11 dressing*:ti,ab,kw 2928
#12 [mh Bandages] 2231
#13 bandage*:ti,ab,kw 2220
#14 adhesive*:ti,ab,kw 3156
#15 gel*:ti,ab,kw 7649
#16 gauze*:ti,ab,kw 571
#17 tape:ti,ab,kw 2271
#18 film:ti,ab,kw 2304
#19 (permeable or impermeable or non-permeable):ti,ab,kw 395
#20 ethicon:ti,ab,kw 119
#21 (smith next/2 nephew):ti,ab,kw 82
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 19360
#23 #10 and #22 317
#24 opsite*:ti,ab,kw 36
#25 biopatch*:ti,ab,kw 9
#26 #23 or #24 or #25 350
#27 #26 in Cochrane Reviews (Reviews and Protocols) 8
#28 #26 in Other Reviews 6
#29 #26 in Trials325
#30 #26 in Technology Assessments1

6: Source: Database of Abstracts of Reviews of Effects (DARE) - Issue 4 of 4, Oct 2012

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 6
Search strategy:

#1	[mh ^"Catheterization, Central Venous"]	782
#2	(central next/3 (venous* or line or pressure)):ti,ab,kw	2564
#3	((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw	2112
#4	[mh "Catheterization, Peripheral"]	722
#5	[mh ^"Catheters, Indwelling"]	962
#6	((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw	1981
#7	((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw	18
#8	((cva or cvad or vad or access) next/3 device*):ti,ab,kw	144
#9	(cvc* or picc):ti,ab,kw	367
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	5020
#11	dressing*:ti,ab,kw	2928
#12	[mh Bandages]	2231
#13	bandage*:ti,ab,kw	2220
#14	adhesive*:ti,ab,kw	3156
#15	gel*:ti,ab,kw	7649
#16	gauze*:ti,ab,kw	571
#17	tape:ti,ab,kw	2271
#18	film:ti,ab,kw	2304
#19	(permeable or impermeable or non-permeable):ti,ab,kw	395
#20	ethicon:ti,ab,kw	119
#21	(smith next/2 nephew):ti,ab,kw	82
#22	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	19360
#23	#10 and #22	317
#24	opsite*:ti,ab,kw	36
#25	biopatch*:ti,ab,kw	9
#26	#23 or #24 or #25	350
#27	#26 in Cochrane Reviews (Reviews and Protocols)	8
#28	#26 in Other Reviews	6

7: Source: NHS Economic Evaluation Database (NHS EED) - Issue 4 of 4, Oct 2012

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 10
Search strategy:

#1	[mh ^"Catheterization, Central Venous"]	782
#2	(central next/3 (venous* or line or pressure)):ti,ab,kw	2564
#3	((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw	2112
#4	[mh "Catheterization, Peripheral"]	722
#5	[mh ^"Catheters, Indwelling"]	962
#6	((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw	1981
#7	((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw	18
#8	((cva or cvad or vad or access) next/3 device*):ti,ab,kw	144
#9	(cvc* or picc):ti,ab,kw	367
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	5020
#11	dressing*:ti,ab,kw	2928
#12	[mh Bandages]	2231
#13	bandage*:ti,ab,kw	2220
#14	adhesive*:ti,ab,kw	3156
#15	gel*:ti,ab,kw	7649
#16	gauze*:ti,ab,kw	571
#17	tape:ti,ab,kw	2271
#18	film:ti,ab,kw	2304
#19	(permeable or impermeable or non-permeable):ti,ab,kw	395
#20	ethicon:ti,ab,kw	119
#21	(smith next/2 nephew):ti,ab,kw	82
#22	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	19360
#23	#10 and #22	317
#24	opsite*:ti,ab,kw	36
#25	biopatch*:ti,ab,kw	9
#26	#23 or #24 or #25	350
#27	#26 in Cochrane Reviews (Reviews and Protocols)	8
#28	#26 in Other Reviews	6
#29	#26 in Trials	325
#30	#26 in Technology Assessments	1
#31	#26 in Economic Evaluations	10

8: Source: Econlit 1886 to October 2014

Interface / URL: OvidSP
Search date: 20/11/14
Retrieved records: 0
Search strategy:

1	(central adj3 (venous$ or line or pressure)).tw.	60
2	((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw.	0
3	((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw.	23
4	((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw.	0
5	((cva or cvad or vad or access) adj3 device$).tw.	15
6	(cvc$ or picc).tw.	26
7	or/1-6	124
8	dressing$.mp.	138
9	bandage$.mp.	3
10	adhesive$.mp.	13
11	gel$.mp.	830
12	gauze$.mp.	3
13	tape.mp.	224
14	film.mp.	498
15	(permeable or impermeable or non-permeable).mp.	55
16	ethicon.tw.	0
17	(smith adj2 nephew).tw.	1
18	or/8-17	1758
19	7 and 18	0
20	opsite$.tw.	0
21	biopatch$.tw.	0
22	or/19-21	0

9: Source: Conference Proceedings Citation Index- Science (CPCI-S) - 1990-present

Interface / URL: Web of Science
Search date: 20/11/14
Retrieved records: 273
Search strategy:

Indexes=CPCI-S Timespan=All years

22 273 #21 OR #20 OR #19
21 1 TS=(biopatch*)
20 11 TS=(opsite*)
19 264 #18 AND #7
18 300,317 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
17 34 TS=((smith NEAR/2 nephew))
16 95 TS=(ethicon)
15 4,673 TS=((permeable or impermeable or non-permeable))
14 235,705 TS=(film)
13 10,592 TS=(tape)
12 296 TS=(gauze*)
11 47,775 TS=(gel*)
10 13,203 TS=(adhesive*)
9 282 TS=(bandage*)
8 2,101 TS=(dressing*)
7 7,754 #6 OR #5 OR #4 OR #3 OR #2 OR #1
6 762 TS=((cvc* or picc))
5 2,066 TS=(((cva or cvad or vad or access) NEAR/3 device*))
4 71 TS=(((catheter* or cannulat* or access*) NEAR/5 (hickman or broviac or cook)))
3 1,698 TS=(((catheter* or cannulat* or access*) NEAR/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)))
2 2,084 TS=(((venous or vein* or intravenous) NEAR/3 (catheter* or cannulat* or access*)))
1 2,926 TS=((central NEAR/3 (venous* or line or pressure)))

Search strategies: sponsor search 2 - comparators and ACs

1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 616
Search strategy:

1 Catheterization, Central Venous/ (12205)
2 (central adj3 (venous$ or line or pressure)).tw. (23423)
3 ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw. (24277)
4 exp catheterization, peripheral/ (8817)
5 Catheters, Indwelling/ (16350)
6 ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw. (23078)
7 ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw. (926)
8 exp Vascular Access Devices/ (1264)
9 ((cva or cvad or vad or access) adj3 device$).tw. (2745)
10 (cvc$ or picc).tw. (3702)
11 or/1-10 (74071)
12 dressing$.mp. (19114)
13 exp Bandages/ (20303)
14 bandage$.mp. (17540)
15 adhesive$.mp. (63931)
16 gel$.mp. (464940)
17 gauze$.mp. (3209)
18 tape.mp. (16533)
19 film.mp. (74478)
20 (permeable or impermeable or non-permeable).mp. (25625)
21 ethicon.tw. (898)
22 (smith adj2 nephew).tw. (527)
23 or/12-22 (665830)
24 11 and 23 (1896)
25 opsite$.tw. (114)
26 biopatch$.tw. (16)
27 or/24-26 (2006)
28 ((arterial or artery or arteries or intra arterial) adj3 line).tw. (1257)
29 (art line or a line).tw. (7652)
30 ((arterial or artery or arteries or intra arterial) adj3 (catheter$ or cannulat$ or access$)).tw. (14735)
31 ((catheter$ or cannulat$ or access$) adj5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)).tw. (2692)
32 ((catheter$ or cannulat$ or access$) adj5 (seldinger or punktion)).tw. (245)

33 ((arterial or artery or arteries or intra arterial) adj3 device$).tw. (813)
34 IAC.tw. (1287)
35 28 or 29 or 30 or 31 or 32 or 33 or 34 (27018)
36 23 and 35 (735)
37 36 not 27 (616)

2: Source: Embase 1974 to 2014 November 18

Interface / URL: OvidSP
Search date: 19/11/14
Retrieved records: 951
Search strategy:

1 central venous catheterization/ (7085)
2 central venous catheter/ (11562)
3 (central adj3 (venous$ or line or pressure)).tw. (31155)
4 ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw. (31830)
5 catheterization/ (36713)
6 indwelling catheter/ (8791)
7 ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw. (30935)
8 ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw. (1152)
9 ((cva or cvad or vad or access) adj3 device$).tw. (4079)
10 (cvc$ or picc).tw. (5685)
11 or/1-10 (113469)
12 dressing$.mp. (25764)
13 exp silver dressing/ or exp foam dressing/ or exp hydrogel dressing/ or exp biological dressing/ or exp hydrocolloid dressing/ or exp wound dressing/ or exp gauze dressing/ or exp occlusive dressing/ (11341)
14 exp bandage/ (12287)
15 bandage$.mp. (14193)
16 adhesive$.mp. (55834)
17 gel$.mp. (512884)
18 gauze$.mp. (4588)
19 tape.mp. (18778)
20 film.mp. (91080)
21 (permeable or impermeable or non-permeable).mp. (28082)
22 ethicon.tw. (1576)
23 (smith adj2 nephew).tw. (856)
24 or/12-23 (731760)
25 11 and 24 (3210)
26 opsite$.tw. (214)
27 biopatch$.tw. (48)
28 or/25-27 (3437)
29 artery catheterization/ (6855)
30 artery catheter/ (3835)

31 ((arterial or artery or arteries or intra arterial) adj3 line).tw. (1891)
32 (art line or a line).tw. (8064)
33 ((arterial or artery or arteries or intra arterial) adj3 (catheter$ or cannulat$ or access$)).tw. (19001)
34 ((catheter$ or cannulat$ or access$) adj5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)).tw. (4025)
35 ((catheter$ or cannulat$ or access$) adj5 (seldinger or punktion)).tw. (378)
36 IAC.tw. (1519)
37 or/29-36 (38396)
38 24 and 37 (1179)
39 38 not 28 (951)

3: Source: Cochrane Database of Systematic Reviews (CDSR) - Issue 11 of 12, November 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 22
Search strategy:

#1 [mh ^"Catheterization, Central Venous"] 782
#2 (central next/3 (venous* or line or pressure)):ti,ab,kw 2564
#3 ((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw 2112
#4 [mh "Catheterization, Peripheral"] 722
#5 [mh ^"Catheters, Indwelling"] 962
#6 ((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw 1981
#7 ((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw 18
#8 ((cva or cvad or vad or access) next/3 device*):ti,ab,kw 144
#9 (cvc* or picc):ti,ab,kw 367
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 5020
#11 dressing*:ti,ab,kw 2928
#12 [mh Bandages] 2231
#13 bandage*:ti,ab,kw 2220
#14 adhesive*:ti,ab,kw 3156
#15 gel*:ti,ab,kw 7649
#16 gauze*:ti,ab,kw 571
#17 tape:ti,ab,kw 2271
#18 film:ti,ab,kw 2304
#19 (permeable or impermeable or non-permeable):ti,ab,kw 395
#20 ethicon:ti,ab,kw 119
#21 (smith next/2 nephew):ti,ab,kw 82
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 19360
#23 #10 and #22 317

#24 opsite*:ti,ab,kw 36
#25 biopatch*:ti,ab,kw 9
#26 #23 or #24 or #25 350
#27 ((arterial or artery or arteries or intra arterial) next/3 line):ti,ab,kw 204
#28 (art line or a line):ti,ab,kw 14208
#29 ((arterial or artery or arteries or intra arterial) next/3 (catheter* or cannulat* or access*)):ti,ab,kw 1062
#30 ((catheter* or cannulat* or access*) next/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)):ti,ab,kw 156
#31 ((catheter* or cannulat* or access*) next/5 (seldinger or punktion)):ti,ab,kw 13
#32 IAC:ti,ab,kw 35
#33 #27 or #28 or #29 or #30 or #31 or #32 15332
#34 #22 and #33 437
#35 #34 not #26 399
#36 #35 in Cochrane Reviews (Reviews and Protocols) 22

Note: In the reported Cochrane Library search in the submission, line #34 is: #23 and #33. Through assessment of the reported results numbers in the submission, the EAC have made the assumption this is a reporting error. This note also applies to search numbers 4, 5, 6 and 7 below.

4: Source: Cochrane Central Register of Controlled Trials (CENTRAL) - Issue 10 of 12, October 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 377
Search strategy:

#1 [mh ^"Catheterization, Central Venous"] 782
#2 (central next/3 (venous* or line or pressure)):ti,ab,kw 2564
#3 ((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw 2112
#4 [mh "Catheterization, Peripheral"] 722
#5 [mh ^"Catheters, Indwelling"] 962
#6 ((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw 1981
#7 ((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw 18
#8 ((cva or cvad or vad or access) next/3 device*):ti,ab,kw 144
#9 (cvc* or picc):ti,ab,kw 367
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 5020
#11 dressing*:ti,ab,kw 2928
#12 [mh Bandages] 2231
#13 bandage*:ti,ab,kw 2220

#14 adhesive*:ti,ab,kw 3156
#15 gel*:ti,ab,kw 7649
#16 gauze*:ti,ab,kw 571
#17 tape:ti,ab,kw 2271
#18 film:ti,ab,kw 2304
#19 (permeable or impermeable or non-permeable):ti,ab,kw 395
#20 ethicon:ti,ab,kw 119
#21 (smith next/2 nephew):ti,ab,kw 82
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 19360
#23 #10 and #22 317
#24 opsite*:ti,ab,kw 36
#25 biopatch*:ti,ab,kw 9
#26 #23 or #24 or #25 350
#27 ((arterial or artery or arteries or intra arterial) next/3 line):ti,ab,kw 204
#28 (art line or a line):ti,ab,kw 14208
#29 ((arterial or artery or arteries or intra arterial) next/3 (catheter* or cannulat* or access*)):ti,ab,kw 1062
#30 ((catheter* or cannulat* or access*) next/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)):ti,ab,kw 156
#31 ((catheter* or cannulat* or access*) next/5 (seldinger or punktion)):ti,ab,kw 13
#32 IAC:ti,ab,kw 35
#33 #27 or #28 or #29 or #30 or #31 or #32 15332
#34 #22 and #33 437
#35 #34 not #26 399
#36 #35 in Cochrane Reviews (Reviews and Protocols) 22
#37 #35 in Other Reviews 0
#38 #35 in Trials377

5: Source: Health Technology Assessment Database (HTA) - Issue 4 of 4, Oct 2012

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 0
Search strategy:

#1 [mh ^"Catheterization, Central Venous"] 782
#2 (central next/3 (venous* or line or pressure)):ti,ab,kw 2564
#3 ((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw 2112
#4 [mh "Catheterization, Peripheral"] 722
#5 [mh ^"Catheters, Indwelling"] 962
#6 ((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw 1981

#7 ((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw 18
#8 ((cva or cvad or vad or access) next/3 device*):ti,ab,kw 144
#9 (cvc* or picc):ti,ab,kw 367
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 5020
#11 dressing*:ti,ab,kw 2928
#12 [mh Bandages] 2231
#13 bandage*:ti,ab,kw 2220
#14 adhesive*:ti,ab,kw 3156
#15 gel*:ti,ab,kw 7649
#16 gauze*:ti,ab,kw 571
#17 tape:ti,ab,kw 2271
#18 film:ti,ab,kw 2304
#19 (permeable or impermeable or non-permeable):ti,ab,kw 395
#20 ethicon:ti,ab,kw 119
#21 (smith next/2 nephew):ti,ab,kw 82
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 19360
#23 #10 and #22 317
#24 opsite*:ti,ab,kw 36
#25 biopatch*:ti,ab,kw 9
#26 #23 or #24 or #25 350
#27 ((arterial or artery or arteries or intra arterial) next/3 line):ti,ab,kw 204
#28 (art line or a line):ti,ab,kw 14208
#29 ((arterial or artery or arteries or intra arterial) next/3 (catheter* or cannulat* or access*)):ti,ab,kw 1062
#30 ((catheter* or cannulat* or access*) next/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)):ti,ab,kw 156
#31 ((catheter* or cannulat* or access*) next/5 (seldinger or punktion)):ti,ab,kw 13
#32 IAC:ti,ab,kw 35
#33 #27 or #28 or #29 or #30 or #31 or #32 15332
#34 #22 and #33 437
#35 #34 not #26 399
#36 #35 in Cochrane Reviews (Reviews and Protocols) 22
#37 #35 in Other Reviews 0
#38 #35 in Trials377
#39 #35 in Technology Assessments0

6: Source: Database of Abstracts of Reviews of Effects (DARE) - Issue 4 of 4, Oct 2012

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 0
Search strategy:

#1 [mh ^"Catheterization, Central Venous"] 782
#2 (central next/3 (venous* or line or pressure)):ti,ab,kw 2564
#3 ((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw 2112
#4 [mh "Catheterization, Peripheral"] 722
#5 [mh ^"Catheters, Indwelling"] 962
#6 ((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw 1981
#7 ((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw 18
#8 ((cva or cvad or vad or access) next/3 device*):ti,ab,kw 144
#9 (cvc* or picc):ti,ab,kw 367
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 5020
#11 dressing*:ti,ab,kw 2928
#12 [mh Bandages] 2231
#13 bandage*:ti,ab,kw 2220
#14 adhesive*:ti,ab,kw 3156
#15 gel*:ti,ab,kw 7649
#16 gauze*:ti,ab,kw 571
#17 tape:ti,ab,kw 2271
#18 film:ti,ab,kw 2304
#19 (permeable or impermeable or non-permeable):ti,ab,kw 395
#20 ethicon:ti,ab,kw 119
#21 (smith next/2 nephew):ti,ab,kw 82
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 19360
#23 #10 and #22 317
#24 opsite*:ti,ab,kw 36
#25 biopatch*:ti,ab,kw 9
#26 #23 or #24 or #25 350
#27 ((arterial or artery or arteries or intra arterial) next/3 line):ti,ab,kw 204
#28 (art line or a line):ti,ab,kw 14208
#29 ((arterial or artery or arteries or intra arterial) next/3 (catheter* or cannulat* or access*)):ti,ab,kw 1062
#30 ((catheter* or cannulat* or access*) next/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)):ti,ab,kw 156
#31 ((catheter* or cannulat* or access*) next/5 (seldinger or punktion)):ti,ab,kw 13
#32 IAC:ti,ab,kw 35

#33 #27 or #28 or #29 or #30 or #31 or #32 15332
#34 #22 and #33 437
#35 #34 not #26 399
#36 #35 in Cochrane Reviews (Reviews and Protocols) 22
#37 #35 in Other Reviews 0

7: Source: NHS Economic Evaluation Database (NHS EED) - Issue 4 of 4, Oct 2012

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 20/11/14
Retrieved records: 0
Search strategy:

#1 [mh ^"Catheterization, Central Venous"] 782
#2 (central next/3 (venous* or line or pressure)):ti,ab,kw 2564
#3 ((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw 2112
#4 [mh "Catheterization, Peripheral"] 722
#5 [mh ^"Catheters, Indwelling"] 962
#6 ((catheter* or cannulation or access*) next/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)):ti,ab,kw 1981
#7 ((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw 18
#8 ((cva or cvad or vad or access) next/3 device*):ti,ab,kw 144
#9 (cvc* or picc):ti,ab,kw 367
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 5020
#11 dressing*:ti,ab,kw 2928
#12 [mh Bandages] 2231
#13 bandage*:ti,ab,kw 2220
#14 adhesive*:ti,ab,kw 3156
#15 gel*:ti,ab,kw 7649
#16 gauze*:ti,ab,kw 571
#17 tape:ti,ab,kw 2271
#18 film:ti,ab,kw 2304
#19 (permeable or impermeable or non-permeable):ti,ab,kw 395
#20 ethicon:ti,ab,kw 119
#21 (smith next/2 nephew):ti,ab,kw 82
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 19360
#23 #10 and #22 317
#24 opsite*:ti,ab,kw 36
#25 biopatch*:ti,ab,kw 9
#26 #23 or #24 or #25 350
#27 ((arterial or artery or arteries or intra arterial) next/3 line):ti,ab,kw 204
#28 (art line or a line):ti,ab,kw 14208

#29 ((arterial or artery or arteries or intra arterial) next/3 (catheter* or cannulat* or access*)):ti,ab,kw 1062
#30 ((catheter* or cannulat* or access*) next/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)):ti,ab,kw 156
#31 ((catheter* or cannulat* or access*) next/5 (seldinger or punktion)):ti,ab,kw 13
#32 IAC:ti,ab,kw 35
#33 #27 or #28 or #29 or #30 or #31 or #32 15332
#34 #22 and #33 437
#35 #34 not #26 399
#36 #35 in Cochrane Reviews (Reviews and Protocols) 22
#37 #35 in Other Reviews 0
#38 #35 in Trials377
#39 #35 in Technology Assessments0
#40 #35 in Economic Evaluations 0

8: Source: Econlit 1886 to October 2014

Interface / URL: OvidSP
Search date: 20/11/14
Retrieved records: 0
Search strategy:

1 (central adj3 (venous$ or line or pressure)).tw.60
2 ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw. 0
3 ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw. 23
4 ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw. 0
5 ((cva or cvad or vad or access) adj3 device$).tw. 15
6 (cvc$ or picc).tw. 26
7 or/1-6 124
8 dressing$.mp. 138
9 bandage$.mp. 3
10 adhesive$.mp. 13
11 gel$.mp. 830
12 gauze$.mp. 3
13 tape.mp. 224
14 film.mp. 498
15 (permeable or impermeable or non-permeable).mp. 55
16 ethicon.tw. 0
17 (smith adj2 nephew).tw. 1
18 or/8-17 1758
19 7 and 18 0
20 opsite$.tw. 0
21 biopatch$.tw. 0
22 or/19-21 0

23 ((arterial or artery or arteries or intra arterial) adj3 line).tw. 0
24 (art line or a line).tw. 231
25 ((arterial or artery or arteries or intra arterial) adj3 (catheter$ or cannulat$ or access$)).tw. 3
26 ((catheter$ or cannulat$ or access$) adj5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)).tw.4
27 ((catheter$ or cannulat$ or access$) adj5 (seldinger or punktion)).tw. 0
28 ((arterial or artery or arteries or intra arterial) adj3 device$).tw. 0
29 IAC.tw. 27
30 or/23-29 265
31 30 and 18 0
32 31 not 22 0

9: Source: Conference Proceedings Citation Index- Science (CPCI-S) --1990-present

Interface / URL: Web of Science
Search date: 20/11/14
Retrieved records: 304
Search strategy:

Indexes=CPCI-S Timespan=All years

31 304 #30 not #22
30 315 #29 AND #18
29 7,702 #28 OR #27 OR #26 OR #25 OR #24 OR #23
28 405 TS=(IAC)
27 19 TS=(((catheter* or cannulat* or access*) NEAR/5 (seldinger or punktion)))
26 291 TS=(((catheter* or cannulat* or access*) NEAR/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)))
25 1,286 TS=(((arterial or artery or arteries or "intra arterial") NEAR/3 (catheter* or cannulat* or access*)))
24 5,638 TS=((art-line or a-line))
23 180 TS=((arterial or artery or arteries or "intra arterial") NEAR/3 line)
22 273 #21 OR #20 OR #19
21 1 TS=(biopatch*)
20 11 TS=(opsite*)
19 264 #18 AND #7
18 300,317 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
17 34 TS=((smith NEAR/2 nephew))
16 95 TS=(ethicon)
15 4,673 TS=((permeable or impermeable or non-permeable))
14 235,705 TS=(film)
13 10,592 TS=(tape)
12 296 TS=(gauze*)
11 47,775 TS=(gel*)

# 10	13,203 TS=(adhesive*)
# 9	282 TS=(bandage*)
# 8	2,101 TS=(dressing*)
# 7	7,754 #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 6	762 TS=((cvc* or picc))
# 5	2,066 TS=(((cva or cvad or vad or access) NEAR/3 device*))
# 4	71 TS=(((catheter* or cannulat* or access*) NEAR/5 (hickman or broviac or cook)))
# 3	1,698 TS=(((catheter* or cannulat* or access*) NEAR/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)))
# 2	2,084 TS=(((venous or vein* or intravenous) NEAR/3 (catheter* or cannulat* or access*)))
# 1	2,926 TS=((central NEAR/3 (venous* or line or pressure)))

Appendix 2: EAC additional clinical evidence and adverse effects searches

Appendix 2 contains search result numbers and full search strategies details for the EAC additional clinical evidence and adverse effects searches. Table A2.1 gives details of the returned record numbers for each literature search source. Table A2.2 gives details of the returned record numbers for the MAUDE and MHRA searches on adverse effects

Literature Search Results

The literature searches identified 1755 records (Table A2.1). Following deduplication 1214 records were assessed for relevance. These numbers do not include MAUDE and MHRA results (see Section 3.7).

Table A2.1: Literature search results

Resource	Records identified
MEDLINE and MEDLINE in Process	230
Embase	873
Cochrane Database of Systematic Reviews (CDSR)	1
Cochrane Central Register of Controlled Trials (CENTRAL)	92
Health Technology Assessment Database (HTA)	2
Database of Abstracts of Reviews of Effects (DARE)	7
NHS Economic Evaluation Database (NHS EED)	11
HEED	52
Econlit	2
Science Citation Index Expanded (SCI-EXPANDED) --1900-present / Conference Proceedings Citation Index- Science (CPCI-S) -1990-present	257
Clinicaltrials.gov	104
WHO International Clinical Trials Registry Platform	110
ISRCTN registry	1
CEA Registry	0
EuroScan	0
European Medicines Agency	0
Association for Vascular Access (AVA) Annual Meeting	10
World Congress of Vascular Access (WoCoVA)	0
Healthcare Infection Society Conference	1
SHEA (Society of Hospital Epidemiologists of America) Conference	0
Association of Surgeons in Primary Care website	0
British Association of Critical Care Nurses website	0
British Cardiovascular Intervention Society website	0
British Cardiovascular Society website	0
Intensive Care Society website	0
National Infusion and Vascular Access Society website	1
Royal College of Nursing website	0
Royal College of Physicians website	0
The Royal College of Anaesthetists website	0
Association of Anaesthetists of Great Britain and Ireland website	0
British Association of Parenteral and Enteral Nutrition website	0
Royal College of Surgeons of England website	0
Critical Care Patient Liaison Committee website	1
Fiona Elizabeth Agnew Trust website	0

Resource	Records identified
ICU Steps website	0
MRSA Action UK website	0
The Patients Association website	0
United Kingdom Sepsis Trust website	0
TOTAL	**1755**
TOTAL after deduplication	**1214**

MAUDE and MHRA searches

MAUDE and MHRA were searched for adverse events. No search was carried out of these resources for comparators as details of the strategies were not found in the submission. The number of records identified in MAUDE and MHRA is not included in the completed PRISMA diagram.

Table A2.2: MAUDE and MHRA results

Resource	Records identified
Manufacturer and User Facility Device (MAUDE)	199
Medicines and Healthcare products Regulatory Agency (MHRA)	3

Search strategies: EAC additional clinical evidence and adverse effects searches

1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 25/11/14
Retrieved records: 230
Search strategy:

1 Catheterization/ (47106)
2 Catheterization, Central Venous/ (12212)
3 exp Catheterization, Peripheral/ (8822)
4 Cardiac Catheterization/ (40962)
5 exp Catheters/ (19630)
6 Catheter-Related Infections/ (2264)
7 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kf. (195245)
8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs).ti,ab,kf. (5442)
9 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (103)
10 (central adj3 (venous or pressure)).ti,ab,kf. (21893)
11 (central adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (10248)
12 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (5819)
13 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (22893)

14 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kf. (6890)
15 (art line$1 or a line$1 or IAC or IACs).ti,ab,kf. (9422)
16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (831)
17 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kf. (9310)
18 ((invasive or percutaneous) adj3 device$).ti,ab,kf. (2294)
19 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kf. (8146)
20 (IVD or IVDs).ti,ab,kf. (1454)
21 (hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1).ti,ab,kf. (6679)
22 or/1-21 (319106)
23 Bandages/ (14372)
24 Occlusive Dressings/ (3632)
25 exp Gels/ (36117)
26 exp Surgical Sponges/ (2955)
27 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag$ or gel or gels or film or films or secur$).ti,ab,kf. (579803)
28 (transparen$ or see-through or permeable or semipermeable).ti,ab,kf. (51475)
29 or/23-28 (650615)
30 Chlorhexidine/ (6430)
31 (chlorhexidine$ or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1).ti,ab,kf,rn. (9288)
32 (3M or 3MTM).ti,ab,kf. (4684)
33 ("johnson & johnson$" or "johnson and johnson$").ti,ab,kf. (798)
34 ethicon$.ti,ab,kf. (904)
35 or/30-34 (15568)
36 22 and 29 and 35 (180)
37 (tegaderm$ or biopatch$).ti,ab,kf. (161)
38 36 or 37 (328)
39 exp animals/ not humans/ (4094649)
40 (editorial or comment or case reports).pt. (2605322)
41 case report.ti. (166720)
42 38 not (39 or 40 or 41) (259)
43 limit 42 to english language (236)
44 remove duplicates from 43 (230)

2: Source: Embase 1974 to 2014 November 24

Interface / URL: OvidSP
Search date: 24/11/14
Retrieved records: 873
Search strategy:

1 catheterization/ (36764)
2 exp central venous catheterization/ (7090)
3 heart catheterization/ (48661)
4 exp artery catheterization/ (7133)
5 catheter/ or exp central venous catheter/ or indwelling catheter/ or artery catheter/ or arterial line/ or exp pulmonary artery catheter/ or umbilical artery catheter/ (65583)
6 catheter complication/ or catheter infection/ (12952)
7 (catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$).ti,ab,kw. (257525)
8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs).ti,ab,kw. (7978)
9 ((PIC or CVP) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (169)
10 (central adj3 (venous or pressure)).ti,ab,kw. (29462)
11 (central adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (13735)
12 (peripheral adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (6944)
13 ((venous or intravenous or vein$1 or vascular or intravascular or IV) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (31730)
14 ((arterial or intraarterial or artery or arteries) adj3 (line$1 or access$ or site or sites or device$)).ti,ab,kw. (9678)
15 (art line$1 or a line$1 or IAC or IACs).ti,ab,kw. (10135)
16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kw. (1534)
17 (access$ adj3 (device$ or site or sites or route$1)).ti,ab,kw. (12300)
18 ((invasive or percutaneous) adj3 device$).ti,ab,kw. (3454)
19 (CVA or CVAD or CVADs or VAD or VADs).ti,ab,kw. (12601)
20 (IVD or IVDs).ti,ab,kw. (2034)
21 (hickman$1 or broviac$1 or cook$1 or seldinger$1 or punktion$1).ti,ab,kw. (9156)
22 or/1-21 (403815)
23 exp "bandages and dressings"/ (35237)
24 exp gel/ (43635)
25 surgical sponge/ (874)
26 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag$ or gel or gels or film or films or secur$).ti,ab,kw. (643739)
27 (transparen$ or see-through or permeable or semipermeable).ti,ab,kw. (54778)

28 or/23-27 (735159)
29 chlorhexidine gluconate/ or alcohol plus chlorhexidine gluconate/ or 2 propanol plus chlorhexidine gluconate/ (4164)
30 chlorhexidine/ (12261)
31 (chlorhexidine$ or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1).ti,ab,kw,rn. (16338)
32 (3M or 3MTM).ti,ab,kw,dm. (8291)
33 ("johnson & johnson$" or "johnson and johnson$").ti,ab,kw,dm. (4478)
34 ethicon$.ti,ab,kw,dm. (5102)
35 or/29-34 (33643)
36 22 and 28 and 35 (547)
37 (tegaderm$ or biopatch$).ti,ab,kw,dv,tn. (591)
38 36 or 37 (1063)
39 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5018756)
40 editorial.pt. (458252)
41 case report.ti. (206069)
42 38 not (39 or 40 or 41) (955)
43 limit 42 to english language (875)
44 remove duplicates from 43 (873)

3: Source: Cochrane Database of Systematic Reviews (CDSR) - Issue 11 of 12, November 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 24/11/14
Retrieved records: 1
Search strategy:

#1 [mh ^Catheterization] 1481
#2 [mh ^"Catheterization, Central Venous"] 782
#3 [mh "Catheterization, Peripheral"] 722
#4 [mh ^"Cardiac Catheterization"] 994
#5 [mh Catheters] 1153
#6 [mh ^"Catheter-Related Infections"] 187
#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*):ti,ab,kw 15005
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs):ti,ab,kw 408
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 6
#10 (central near/3 (venous or pressure)):ti,ab,kw 2684
#11 (central near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 472
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 250
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device*)):ti,ab,kw 1624

#14 ((arterial or intraarterial or artery or arteries) near/3 (line* or lines or access* or site or sites or device*)):ti,ab,kw 595
#15 ("art line" or "art lines" or "a line" or "a lines" or IAC or IACs):ti,ab,kw 201
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs):ti,ab,kw 77
#17 (access* near/3 (device* or site or sites or route or routes)):ti,ab,kw 477
#18 ((invasive or percutaneous) near/3 device*):ti,ab,kw 165
#19 (CVA or CVAD or CVADs or VAD or VADs):ti,ab,kw 365
#20 (IVD or IVDs):ti,ab,kw 22
#21 (hickman* or broviac* or cook* or seldinger* or punktion*):ti,ab,kw 975
#22 19465
#23 [mh ^Bandages] 1490
#24 [mh ^"Occlusive Dressings"] 451
#25 [mh Gels] 2081
#26 [mh "Surgical Sponges"] 143
#27 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag* or gel or gels or film or films or secur*):ti,ab,kw 20484
#28 (transparen* or see-through or permeable or semipermeable):ti,ab,kw 983
#29 {or #23-#28} 26052
#30 [mh ^Chlorhexidine] 1376
#31 (chlorhexidine* or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1):ti,ab,kw 2362
#32 (3M or 3MTM):ti,ab,kw 504
#33 ("johnson & johnson" or "johnson and johnson"):ti,ab,kw 182
#34 ethicon*:ti,ab,kw 120
#35 3146
#36 #22 and #29 and #35 56
#37 (tegaderm* or biopatch*):ti,ab,kw 54
#38 #36 or #37 99
#39 #38 in Cochrane Reviews (Reviews and Protocols) 1

4: Source: Cochrane Central Register of Controlled Trials (CENTRAL) - Issue 10 of 12, October 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 24/11/14
Retrieved records: 92
Search strategy:

#1 [mh ^Catheterization] 1481
#2 [mh ^"Catheterization, Central Venous"] 782
#3 [mh "Catheterization, Peripheral"] 722
#4 [mh ^"Cardiac Catheterization"] 994

#5 [mh Catheters] 1153
#6 [mh ^"Catheter-Related Infections"] 187
#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) 16748
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) 510
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)) 13
#10 (central near/3 (venous or pressure)) 2936
#11 (central near/3 (line or lines or access* or site or sites or device*)) 695
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)) 310
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device*)) 2084
#14 ((arterial or intraarterial or artery or arteries) near/3 (line* or lines or access* or site or sites or device*)) 689
#15 ("art line" or "art lines" or "a line" or "a lines" or IAC or IACs) 328
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#17 (access* near/3 (device* or site or sites or route or routes)) 646
#18 ((invasive or percutaneous) near/3 device*) 204
#19 (CVA or CVAD or CVADs or VAD or VADs) 697
#20 (IVD or IVDs) 37
#21 (hickman* or broviac* or cook* or seldinger* or punktion*) 4771
#22 25617
#23 [mh ^Bandages] 1490
#24 [mh ^"Occlusive Dressings"] 451
#25 [mh Gels] 2081
#26 [mh "Surgical Sponges"] 143
#27 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag* or gel or gels or film or films or secur*) 23735
#28 (transparen* or see-through or permeable or semipermeable) 2720
#29 {or #23-#28} 26052
#30 [mh ^Chlorhexidine] 1376
#31 (chlorhexidine* or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1) 2560
#32 (3M or 3MTM) 718
#33 ("johnson & johnson" or "johnson and johnson") 541
#34 ethicon* 190
#35 {or #30-#34} 3921
#36 #22 and #29 and #35 161
#37 (tegaderm* or biopatch*) 88
#38 #36 or #37 227

#39 #38 in Other Reviews 7
#40 #38 in Trials92

5: Source: Health Technology Assessment Database (HTA) - Issue 4 of 4, Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 24/11/14
Retrieved records: 2
Search strategy:

#1 [mh ^Catheterization] 1481
#2 [mh ^"Catheterization, Central Venous"] 782
#3 [mh "Catheterization, Peripheral"] 722
#4 [mh ^"Cardiac Catheterization"] 994
#5 [mh Catheters] 1153
#6 [mh ^"Catheter-Related Infections"] 187
#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) 16748
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) 510
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)) 13
#10 (central near/3 (venous or pressure)) 2936
#11 (central near/3 (line or lines or access* or site or sites or device*)) 695
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)) 310
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device*)) 2084
#14 ((arterial or intraarterial or artery or arteries) near/3 (line* or lines or access* or site or sites or device*)) 689
#15 ("art line" or "art lines" or "a line" or "a lines" or IAC or IACs) 328
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#17 (access* near/3 (device* or site or sites or route or routes)) 646
#18 ((invasive or percutaneous) near/3 device*) 204
#19 (CVA or CVAD or CVADs or VAD or VADs) 697
#20 (IVD or IVDs) 37
#21 (hickman* or broviac* or cook* or seldinger* or punktion*) 4771
#22 25617
#23 [mh ^Bandages] 1490
#24 [mh ^"Occlusive Dressings"] 451
#25 [mh Gels] 2081
#26 [mh "Surgical Sponges"] 143

#27 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag* or gel or gels or film or films or secur*) 23735
#28 (transparen* or see-through or permeable or semipermeable) 2720
#29 {or #23-#28} 26052
#30 [mh ^Chlorhexidine] 1376
#31 (chlorhexidine* or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1) 2560
#32 (3M or 3MTM) 718
#33 ("johnson & johnson" or "johnson and johnson") 541
#34 ethicon* 190
#35 3921
#36 #22 and #29 and #35 161
#37 (tegaderm* or biopatch*) 88
#38 #36 or #37 227
#39 #38 in Other Reviews 7
#40 #38 in Trials92
#41 #38 in Technology Assessments2

6: Source: Database of Abstracts of Reviews of Effects (DARE) - Issue 4 of 4, Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 24/11/14
Retrieved records: 7
Search strategy:

#1 [mh ^Catheterization] 1481
#2 [mh ^"Catheterization, Central Venous"] 782
#3 [mh "Catheterization, Peripheral"] 722
#4 [mh ^"Cardiac Catheterization"] 994
#5 [mh Catheters] 1153
#6 [mh ^"Catheter-Related Infections"] 187
#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) 16748
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) 510
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)) 13
#10 (central near/3 (venous or pressure)) 2936
#11 (central near/3 (line or lines or access* or site or sites or device*)) 695
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)) 310
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device*)) 2084

#14 ((arterial or intraarterial or artery or arteries) near/3 (line* or lines or access* or site or sites or device*)) 689
#15 ("art line" or "art lines" or "a line" or "a lines" or IAC or IACs) 328
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#17 (access* near/3 (device* or site or sites or route or routes)) 646
#18 ((invasive or percutaneous) near/3 device*) 204
#19 (CVA or CVAD or CVADs or VAD or VADs) 697
#20 (IVD or IVDs) 37
#21 (hickman* or broviac* or cook* or seldinger* or punktion*) 4771
#22 {Health and Social Care Information Centre, #1-`#21} 25617
#23 [mh ^Bandages] 1490
#24 [mh ^"Occlusive Dressings"] 451
#25 [mh Gels] 2081
#26 [mh "Surgical Sponges"] 143
#27 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag* or gel or gels or film or films or secur*) 23735
#28 (transparen* or see-through or permeable or semipermeable) 2720
#29 {or #23-#28} 26052
#30 [mh ^Chlorhexidine] 1376
#31 (chlorhexidine* or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1) 2560
#32 (3M or 3MTM) 718
#33 ("johnson & johnson" or "johnson and johnson") 541
#34 ethicon* 190
#35 {or #30-#34} 3921
#36 #22 and #29 and #35 161
#37 (tegaderm* or biopatch*) 88
#38 #36 or #37 227
#39 #38 in Other Reviews 7

7: Source: NHS Economic Evaluation Database (NHS EED) - Issue 4 of 4, Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 24/11/14
Retrieved records: 11
Search strategy:

#1 [mh ^Catheterization] 1481
#2 [mh ^"Catheterization, Central Venous"] 782
#3 [mh "Catheterization, Peripheral"] 722
#4 [mh ^"Cardiac Catheterization"] 994
#5 [mh Catheters] 1153
#6 [mh ^"Catheter-Related Infections"] 187

#7 (catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) 16748
#8 (CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) 510
#9 ((PIC or CVP) near/3 (line or lines or access* or site or sites or device*)) 13
#10 (central near/3 (venous or pressure)) 2936
#11 (central near/3 (line or lines or access* or site or sites or device*)) 695
#12 (peripheral near/3 (line or lines or access* or site or sites or device*)) 310
#13 ((venous or intravenous or vein or veins or vascular or intravascular or IV) near/3 (line or lines or access* or site or sites or device*)) 2084
#14 ((arterial or intraarterial or artery or arteries) near/3 (line* or lines or access* or site or sites or device*)) 689
#15 ("art line" or "art lines" or "a line" or "a lines" or IAC or IACs) 328
#16 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#17 (access* near/3 (device* or site or sites or route or routes)) 646
#18 ((invasive or percutaneous) near/3 device*) 204
#19 (CVA or CVAD or CVADs or VAD or VADs) 697
#20 (IVD or IVDs) 37
#21 (hickman* or broviac* or cook* or seldinger* or punktion*) 4771
#22 {Health and Social Care Information Centre, #1-`#21} 25617
#23 [mh ^Bandages] 1490
#24 [mh ^"Occlusive Dressings"] 451
#25 [mh Gels] 2081
#26 [mh "Surgical Sponges"] 143
#27 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag* or gel or gels or film or films or secur*) 23735
#28 (transparen* or see-through or permeable or semipermeable) 2720
#29 (or #23-#28) 26052
#30 [mh ^Chlorhexidine] 1376
#31 (chlorhexidine* or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1) 2560
#32 (3M or 3MTM) 718
#33 ("johnson & johnson" or "johnson and johnson") 541
#34 ethicon* 190
#35 {or #30-#34} 3921
#36 #22 and #29 and #35 161
#37 (tegaderm* or biopatch*) 88
#38 #36 or #37 227
#39 #38 in Other Reviews 7
#40 #38 in Trials92

#41 #38 in Technology Assessments 2
#42 #38 in Economic Evaluations 11

8: Source: Science Citation Index Expanded (SCI-EXPANDED) - 1900-present / Conference Proceedings Citation Index- Science (CPCI-S) -1990-present

Interface / URL: Web of Science
Search date: 25/11/14
Retrieved records: 257
Search strategy:

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

31 257 ((#28 not (#29 or #30))) AND LANGUAGE: (English)
30 122,457 TI="case report"
29 2,385,390 TI=("rat" or "rats" or "rodent" or "rodents" or "mouse" or "mice" or "murine" or "hamster" or "hamsters" or "gerbil" or "gerbils" or "animal" or "animals" or "dogs" or "dog" or "canine" or "pig" or "pigs" or "piglet" or "piglets" or "cats" or "bovine" or "cow" or "cows" or "cattle" or "sheep" or "ewe" or "ewes" or "horse" or "horses" or "equine" or "ovine" or "porcine" or "monkey" or "monkeys" or "primate" or "primates" or "rhesus macaque" or "rhesus macaques" or "rabbit" or "rabbits") NOT TS=human*
28 277 #26 OR #25 Refined by: [excluding] DOCUMENT TYPES: (EDITORIAL MATERIAL)
27 285 #26 OR #25
26 122 TS=(tegaderm* or biopatch*)
25 173 #24 AND #19 AND #16
24 18,287 #23 OR #22 OR #21 OR #20
23 699 TS=ethicon*
22 576 TS=("Johnson & Johnson*" or "Johnson and Johnson*")
21 9,142 TS=("3M" or "3MTM")
20 7,959 TS=(chlorhexidine* or "CHG" or "MOR84MUD8E" or "18472-51-0" or "R4KO0DY52L" or "55-56-1")
19 1,961,474 #18 OR #17
18 154,837 TS=(transparen* or "see-through" or "permeable" or "semipermeable")
17 1,847,798 TS=("dressing" or "dressings" or "pad" or "pads" or "disc" or "discs" or "disk" or "disks" or "sponge" or "sponges" or "spongy" or "foam" or "foams" or "foamy" or bandag* or "gel" or "gels" or "film" or "films" or secur*)
16 323,010 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
15 48,607 TS=(hickman* or broviac* or cook* or seldinger* or punktion*)
14 1,548 TS=("IVD" or "IVDs")
13 9,110 TS=("CVA" or "CVAD" or "CVADs" or "VAD" or "VADs")
12 3,117 TS=(("invasive" or "percutaneous") near/3 device*)

11 16,190 TS=(access* near/3 (device* or "site" or "sites" or "route" or "routes"))
10 707 TS=("CA-BSI" or "CA-BSIs" or "CABSI" or "CABSIs" or "CR-BSI" or "CR-BSIs" or "CRBSI" or "CRBSIs" or "CLA-BSI" or "CLA-BSIs" or "CLABSI" or "CLABSIs")
9 25,016 TS=("art line" or "art lines" or "a line" or "a lines" or "IAC" or "IACs")
8 7,987 TS=(("arterial" or "intraarterial" or "artery" or "arteries") near/3 ("line" or "lines" or access* or "site" or "sites" or device*))
7 25,580 TS=(("venous" or "intravenous" or "vein" or "veins" or "vascular" or "intravascular" or "IV") near/3 ("line" or "lines" or access* or "site" or "sites" or device*))
6 6,638 TS=("peripheral" near/3 ("line" or "lines" or access* or "site" or "sites" or device*))
5 16,584 TS=("central" near/3 ("line" or "lines" or access* or "site" or "sites" or device*))
4 22,054 TS=("central" near/3 ("venous" or "pressure"))
3 217 TS=(("PIC" or "CVP") near/3 ("line" or "lines" or access* or "site" or "sites" or device*))
2 13,326 TS=("CVC" or "CVCs" or "CVL" or "CVLs" or "PICC" or "PICCs" or "PIV" or "PIVs")
1 164,341 TS=(catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*)

9: Source: Econlit – 1886 to October 2014

Interface / URL: OvidSP
Search date: 25/11/14
Retrieved records: 2
Search strategy:

1 (chlorhexidine$ or CHG or MOR84MUD8E or 18472-51-0 or R4KO0DY52L or 55-56-1).af. (1)
2 (tegaderm$ or biopatch$).af. (0)
3 (dressing or dressings or pad or pads or disc or discs or disk or disks or sponge or sponges or spongy or foam or foams or foamy or bandag$ or gel or gels or film or films or secur$).af. (51590)
4 (transparen$ or see-through or permeable or semipermeable).af. (6203)
5 or/3-4 (57276)
6 (3M or 3MTM).af. (30)
7 ("johnson & johnson$" or "johnson and johnson$").af. (36)
8 ethicon$.af. (0)
9 or/6-8 (66)
10 5 and 9 (1)
11 or/1-2,10 (2)
12 limit 11 to english (2)

10: Source: HEED

Interface / URL: EBSCOHost
Search date: 25/11/14
Retrieved records: 52
Search strategy:

S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 Limiters - Language: English (52)
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 (52)
S6 TX ("johnson & johnson*" OR "johnson and johnson*") (3)
S5 TX (3M OR 3MTM) (6)
S4 TX ethicon* (4)
S3 TX (tegaderm* OR biopatch*) (1)
S2 DG chlorhexidine (21)
S1 TX (chlorhexidine* OR CHG OR MOR84MUD8E OR "18472-51-0" OR R4KO0DY52L OR "55-56-1") (30)

11: Source: Clinicaltrials.gov

Interface / URL: https://clinicaltrials.gov/
Search date: 26/11/14
Retrieved records: 104 (104 returned in total across 2 searches)
Search strategy:

Following searches carried out using the Expert search interface:

1. tegaderm OR tegadermtm OR biopatch OR biopatchtm = 57
2. (chlorhexidine OR CHG) AND (dressing OR dressings OR pad OR pads OR disc OR discs OR disk OR disks OR sponge OR sponges OR spongy OR foam OR foams OR foamy OR bandage OR bandages OR bandaged OR gel OR gels OR film OR films OR securement OR transparent OR see-through OR permeable OR semipermeable) = 47

12: Source: WHO International Clinical Trials Registry Platform

Interface / URL: http://apps.who.int/trialsearch/
Search date: 26/11/14
Retrieved records: 110
Search strategy:

Following searches carried out using the standard interface:

1. tegaderm* OR biopatch* = 35 (36 records for 35 trials found)
2. CHG = 30 (32 records for 30 trials found)
3. chlorhexidine AND dressing* OR chlorhexidine AND pad OR chlorhexidine AND pads OR chlorhexidine AND disc OR chlorhexidine AND discs OR chlorhexidine AND disk OR chlorhexidine AND disks OR chlorhexidine AND sponge OR chlorhexidine AND sponges OR chlorhexidine AND spongy OR chlorhexidine AND foam OR chlorhexidine AND foams OR chlorhexidine AND foamy OR chlorhexidine AND bandage* OR chlorhexidine AND gel OR chlorhexidine AND gels OR chlorhexidine AND film OR chlorhexidine AND films OR chlorhexidine AND secur* OR chlorhexidine AND transparen* OR chlorhexidine AND see-through OR chlorhexidine AND permeable OR chlorhexidine AND semipermeable = 45 (47 records for 45 trials found)

13: Source: ISRCTN registry

Interface / URL: http://www.isrctn.com/
Search date: 26/11/14
Retrieved records: 1
Search strategy:

Following searches carried out using the standard search interface:

1. tegaderm OR tegadermtm OR biopatch OR biopatchtm = 0 (3 results returned. All assessed online by information specialist and excluded as irrelevant)
2. CHG = 1
3. chlorhexidine AND (dressing OR dressings OR pad OR pads OR disc OR discs OR disk OR disks OR sponge OR sponges OR spongy OR foam OR foams OR foamy OR bandage OR bandages OR bandaged OR gel OR gels OR film OR films OR securement OR transparent OR see-through OR permeable OR semipermeable) = 0 (10 results returned. All assessed online by information specialist – 9 excluded as irrelevant, 1 excluded as a duplicate of result retrieved previously)

14: Source: CEA Registry

Interface / URL: https://research.tuft
s-nemc.org/cear4/
Search date: 26/11/14
Retrieved records: 0
Search strategy:

Following searches conducted using the basic interface:

1. tegaderm = 0
2. tegadermtm = 0
3. biopatch = 0
4. biopatchtm = 0
5. CHG = 0 (1 results returned, assessed and excluded online by information specialist as irrelevant)
6. Chlorhexidine = 0 (2 results returned, assessed online – 1 excluded as a duplicate of a record identified via another source, 1 excluded as wrong intervention)

15: Source: EuroScan

Interface / URL: http://euroscan.org.uk/
Search date: 26/11/14
Retrieved records: 0
Search strategy:

Technology search used, with 'Search EuroScan sites' selected. Following searches run:

1. tegaderm = 0 (1 result returned, assessed and excluded online by information specialist as irrelevant)
2. tegadermtm = 0
3. biopatch = 0
4. biopatchtm = 0
5. CHG = 0
6. Chlorhexidine = 0

16: Source: European Medicines Agency

Interface / URL: http://euroscan.org.uk/
Search date: 26/11/14
Retrieved records: 0
Search strategy:

Homepage site-wide search used. Following searches run:

1. tegaderm = 0
2. tegadermtm = 0
3. biopatch = 0
4. biopatchtm = 0
5. CHG = 0 (16 results returned. Assessed online by information specialist, all excluded as irrelevant)
6. chlorhexidine AND (dressing OR dressings OR pad OR pads OR disc OR discs OR disk OR disks OR sponge OR sponges OR spongy OR foam OR foams OR foamy OR bandage OR bandages OR bandaged OR gel OR gels OR film OR films OR securement OR transparent OR see-through OR permeable OR semipermeable) = 0 (54 results returned. Assessed online by information specialist, all excluded as irrelevant)

Document Library search used at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/document_library_search.jsp

Following terms searched in the title field:

Chlorhexidine = 0 (2 results returned; assessed online by information specialist and excluded as irrelevant)

17: Source: Manufacturer and User Facility Device (MAUDE)

Interface/URL:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Search date: 21/11/14 and 28/11/14
Retrieved records: 199
Search strategy:

'Search database' interface used. Following searches carried out using the Manufacturer, Brand Name and Date Report Received by FDA fields as indicated below.

Search 1:
Manufacturer: 3m
Brand Name: tegaderm chg
Report Date From: 07/01/2000 Report Date To: 07/29/2013
109 results retrieved

Search 2:
Manufacturer: 3m
Brand Name: tegaderm chg
Report Date From: 30/07/2013 Report Date To: 28/11/2014

17 results retrieved

Search 3:

Brand: Biopatch
Report Date From: 01/01/2012 Report Date To: 21/11/2014

73 results retrieved

18: Source: Medicines and Healthcare products Regulatory Agency (MHRA)

Interface / URL: http://www.mhra.gov.uk/#page=DynamicListMedicines
Search date: 28/11/14
Retrieved records: 3
Search strategy:

Site search used at the above URL. Search carried out on the following terms:

tegaderm = 3 results
biopatch = 0 results

Conference searches

Note: for all conference searches, returned results were assessed against review inclusion criteria for relevance by searcher. Only those judged to be relevant or potentially relevant were selected for further consideration.

19: Source: Association for Vascular Access (AVA) Annual Meeting

Interface/URL: see below
Search date: 25/11/14 – 26/11/14
Retrieved Records: 10
Search Strategy:

2014: Association for Vascular Access (AVA) Annual Meeting 2014

Searched the following terms using the search box on the 'Educational Presentations' page of the AVA Annual Meeting 2014 at the URL:
http://www.eventscribe.com/2014/ava/SearchByKeyword.asp

Tegaderm - 0
Biopatch - 0
CHG – 1 (1 returned, 1 selected as relevant)
Chlorhexidine –1 (7 returned, 1 selected as relevant)
3M - 0
Ethicon - 0

Searched the following terms using the search box on the 'Poster Gallery' page of the AVA Annual Meeting 2014 at the URL:
http://www.eventscribe.com/2014/posters/ava/ListView.asp

Tegaderm - 0
Biopatch - 0
CHG – 1 (1 returned, 1 selected as relevant)
Chlorhexidine – 2 (2 returned, 2 selected as relevant)
3M - 0
Ethicon – 0

2013: Association for Vascular Access (AVA) Annual Meeting 2013

Searched the following terms using the search box on the 'Poster Gallery' page of the AVA Annual Meeting 2013 at the URL:
http://www.eventscribe.com/2013/posters/ava/ListView.asp

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 1 (1 returned, 1 selected as relevant)
3M – 0 (1 returned, 0 selected as relevant)
Ethicon – 0

2012: Association for Vascular Access (AVA) Annual Meeting 2012

Only programme schedule available. Searched the following terms using the 'ctrl and F' search box in the PDF copy of the 2012 AVA annual meeting programme schedule, at the URL:
https://www.avainfo.org/website/download.asp?id=281442

Tegaderm - 0
Biopatch - 0
CHG – 1 relevant study selected
Chlorhexidine – 2 relevant studies selected
3M –0
Ethicon – 0

2011: Association for Vascular Access (AVA) Annual Meeting 2011

Only programme schedule available. Searched the following terms using the 'ctrl and F' search box in the PDF copy of the 2011 AVA annual meeting programme schedule, at the URL:
https://www.avainfo.org/website/download.asp?id=280450

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 1 relevant study selected
3M – 0
Ethicon – 0

20: Source: World Congress on Vascular Access (WoCoVA)

Interface/URL: see below
Search date: 26/11/14
Retrieved Records: 0
Search Strategy:

2014: 3rd World Congress on Vascular Access, WoCoVA 2014, Berlin - Germany, 18-20 June 2014
Searched the following terms in the 'Quick Search' box at the URL:
http://www.vascular-access.info/article/wocova-2014-abstracts

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0 (1 returned, 0 selected as relevant)
3M – 0
Ethicon – 0

2012: WoCoVA 2nd World Congress on Vascular Access - Amsterdam, The Netherlands - June 27-29, 2012.

Searched the following terms in the 'Quick Search' box at the URL:
http://www.vascular-access.info/article/abstracts-from-wocova-2nd-world-congress-on-vascular-access--amsterdam-the-netherlands--june-27-29-2012

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0 (1 returned, 0 selected as relevant)
3M – 0
Ethicon – 0

21: Source: Healthcare Infections Society International Conference

Interface/URL: see below
Search date: 26/11/14
Retrieved Records: 1
Search Strategy:

2014: 9th Healthcare Infections Society (HIS) International Conference, 16-18 November 2014, Lyon Convention Centre, France.

Searched the following terms using the 'ctrl and F' search box in the PDF copy of the 'Oral Abstracts', at the URL:
http://www.his.org.uk/events/his2014/abstracts/#.VHW6iIusWE7

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

Searched the following terms using the 'ctrl and F' search box in the PDF copy of the 'Poster Abstracts', at the URL:
http://www.his.org.uk/events/his2014/abstracts/#.VHW6iIusWE7

Tegaderm - 0
Biopatch - 0
CHG – 1 relevant study selected
Chlorhexidine – 0
3M – 0
Ethicon – 0

2012: 8th Healthcare Infections Society (HIS) International Conference, 2012

Abstracts are available to members only. E-mail sent to conference organisers requesting a copy of abstracts 26/11/14. No reply received. Follow-up e-mail sent 10/12/14. No reply received as of 15/12/14.

22: Source: Spring Conference of the Society for Healthcare Epidemiology of America (SHEA)

Interface/URL: see below
Search date: 26/11/14
Retrieved Records: 0
Search Strategy:

Note: In 2012, SHEA joined IDSA at IDWeek as their Scientific Meeting - abstracts were submitted through IDSA and not SHEA. In 2014 SHEA accepted a limited number of abstracts total for their training conference. No abstracts at SHEA 2012. For the years 2012 and 2014 therefore, IDWeek was also searched.

2014: 2014 Spring Conference of the Society for Healthcare Epidemiology of America (SHEA), April 3-6, Denver

Abstracts are only available to attendees. Conference organisers contacted for copy of abstracts 26/11/14 and received on same date. PDF searched (using 'ctrl and F') for following terms:

Tegaderm – 0 relevant studies selected
Biopatch – 0 relevant studies selected
CHG – 0 relevant studies selected
Chlorhexidine – 0 relevant studies selected
3M – 0 relevant studies selected
Ethicon – 0 relevant studies selected

IDWeek 2014, October 8-12, Philadelphia, USA

All abstracts downloaded from URL at:
https://idsa.confex.com/idsa/2014/viewsessionpdf.cgi and saved as a combined PDF. PDF then searched (using 'ctrl and F') for keywords:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

2012: IDWeek 2012, October 16-21, San Diego, USA
All abstracts downloaded from above URL:
https://idsa.confex.com/idsa/2012/webprogram/meeting2012-10-16.html (by clicking on 'Abstracts in PDF') and saved as a combined PDF. PDF then searched (using 'ctrl and F') for keywords:

Tegaderm - 0
Biopatch – 0

CHG – 0
3M – 0
Ethicon – 0

2011: 21st Annual SHEA Scientific Meeting Conference, April 1-4

Searched the following terms in the 'Search' box at the URL:
https://shea.confex.com/shea/2011/webprogram/

Tegaderm - 0
Biopatch - 0
CHG – 0 (24 returned, 0 relevant studies selected)
Chlorhexidine – 0 (50 returned, 0 relevant studiers selected)
3M – 0
Ethicon – 0

Website searches

Note: For all website searches, returned results were assessed against review inclusion criteria for relevance by searcher. Only those judged to be relevant or potentially relevant were selected for further consideration.

23: Source: Association of Surgeons in Primary Care website

Interface/URL: http://www.aspc-uk.net/
Search Date: 26/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

24: Source: British Association of Critical Care Nurses website

Interface/URL: http://www.baccn.org.uk/
Search Date: 26/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

25: Source: British Cardiovascular Intervention Society website

Interface/URL: http://www.bcis.org.uk/pages/default.asp
Search Date: 26/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

26: Source: British Cardiovascular Society website

Interface/URL: http://www.bcs.com/pages/default.asp
Search Date: 26/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

27: Source: Intensive Care Society website

Interface/URL: http://www.ics.ac.uk/
Search Date: 26/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch – 2 (0 relevant studies)
CHG – 0
Chlorhexidine – 1 (0 relevant studies)
3M – 1 (0 relevant studies)
Ethicon – 1 (0 relevant studies)

28: Source: National Infusion and Vascular Access Society website

Interface/URL: http://www.nivas.org.uk/
Search Date: 27/11/14
Retrieved Records: 1
Search Strategy:

No search function on the website, so keywords below were used in the 'Google Advanced Search' to check the site:

Tegaderm – 1 potentially relevant study – but no copy available. NIVAS contacted 27/11/14. NIVAS replied - have contacted the organisers and asked for permission to obtain the abstract, will inform EAC once they hear back. Most recent email from NIVAS was on 05/12/14.
Biopatch - 0
CHG – 0 (3 returned, but 0 additional studies selected)
Chlorhexidine – 0 (9 returned, but 0 additional studies selected)
3M – 0 (4 returned, but 0 additional studies selected)
Ethicon – 2 (0 studies selected)

29 Source: Royal College of Nursing website

Interface/URL: http://www.rcn.org.uk/
Retrieved Records: 0
Search Date: 27/11/14
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm – 0 (1 returned, 0 relevant studies selected)
Biopatch – 0
CHG – 0 (4 returned, 0 relevant studies selected)
Chlorhexidine – 0 (24 returned, 0 relevant studies selected)

3M – 0 (120 returned, 0 relevant studies selected)
Ethicon – 0 (50 returned, 0 relevant studies selected)

30: Source: Royal College of Physicians website

Interface/URL: https://www.rcplondon.ac.uk/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

31: Source: The Royal College of Anaesthetists website

Interface/URL:
https://www.rcoa.ac.uk/content/search?cx=009352006448159467736%3Adf2oiygfg8q&cof=FORID%3A11&ie=ISO-8859-1&query=biopatch
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0 (2 returned, 0 relevant studies selected)
Chlorhexidine – 0 (2 returned, 0 relevant studies selected)
3M – 0
Ethicon – 0

32: Source: Association of Anaesthetists of Great Britain and Ireland website

Interface/URL: http://www.aagbi.org/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0

CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

33: Source: British Association of Parenteral and Enteral Nutrition website

Interface/URL: http://www.bapen.org.uk/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

34: Source: Royal College of Surgeons of England website

Interface/URL: https://www.rcseng.ac.uk/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm – 0 (2 returned, 0 relevant studies selected)
Biopatch - 0
CHG – 0 (1 returned, 0 relevant studies selected)
Chlorhexidine – 0 (5 returned, 0 relevant studies selected)
3M – 0 (13 returned, 0 relevant studies selected)
Ethicon – 0 (29 returned, 0 relevant studies selected)

35: Source: Critical Care Patient Liaison Committee website

Interface/URL: http://ccforum.com/
Search Date: 27/11/14
Retrieved Records: 1
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm – 0 (6 returned, 0 relevant studies selected)
Biopatch – 0 (3 returned, 0 relevant studies selected)

CHG – 0 (9 returned, 0 relevant studies selected)
Chlorhexidine – 1 (92 returned, 1 relevant studies selected)
3M – 0 (14 returned, 0 relevant studies selected)
Ethicon – 0 (17 returned, 0 relevant studies selected)

36: Source: Fiona Elizabeth Agnew Trust website

Interface/URL: http://www.featuk.org.uk/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

No search function on the website, so keywords below were used in the 'Google Advanced Search' to check the site:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

37: Source: ICU Steps website

Interface/URL: http://www.icusteps.org/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

38: Source: MRSA Action UK website

Interface/URL: http://mrsaactionuk.net/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

No search function on the website, so keywords below were used in the 'Google Advanced Search' to check the site:

Tegaderm - 0

Biopatch - 0
CHG – 0
Chlorhexidine – 0 (12 returned, 0 relevant studies selected)
3M – 0 (6 returned, 0 relevant studies selected)
Ethicon – 0

39: Source: The Patients Association website

Interface/URL: http://www.patients-association.com/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0
Chlorhexidine – 0
3M – 0
Ethicon – 0

40: Source: United Kingdom Sepsis Trust website

Interface/URL: http://sepsistrust.org/
Search Date: 27/11/14
Retrieved Records: 0
Search Strategy:

Searched the following terms in the 'Search' box at the above URL:

Tegaderm - 0
Biopatch - 0
CHG – 0 (1 returned, 0 relevant studies selected)
Chlorhexidine – 0 (1 returned, 0 relevant studies selected)
3M – 0
Ethicon – 0

Appendix 3: EAC clinical review excluded studies

Study	Reason for exclusion at full paper review
Arrowsmith *et al.* (2011) (80)	Full paper could not be retrieved (conference preceding only)
Arvaniti *et al.* (2012) (81)	Intervention not appropriate
Crawford *et al.* (2004) (10)	Outcomes not appropriate
Daniels (2012) (82)	Review which cannot be included in its entirety due to studies undertaken in inappropriate patient group. Included studies assessed for relevance (no new studies were identified)
Eggimann *et al.* (2011) (83)	Study design not appropriate
Eggimann *et al.* (2010) (84)	Study design not appropriate
Goldstein (2012) (85)	Outcomes not appropriate
Gould (2011) (86)	Study design not appropriate
Gould (2010) (87)	Patient population not appropriate
Hayes Inc. (2008) (88)	Paper could not be retrieved
Ho (2006) (42)	Review which cannot be included in its entirety due to studies undertaken in inappropriate patient group. Included studies assessed for relevance (no new studies were identified)
Ho (2010) (89)	Erratum of Ho (2006). Review which cannot be included in its entirety due to studies undertaken in inappropriate patient group. Included studies assessed for relevance (no new studies were identified)
Madeo *et al.* (2010) (90)	Study design not appropriate
Maki *et al.* (2000) (91)	Patient population not appropriate
Maunoury *et al.* (2014) (18)	Outcomes not appropriate (included in cost-effectiveness review)
Maunoury *et al.* (2013) (17)	Outcomes not appropriate (included in cost-effectiveness review)
NCT00548132 (2006) (92)	Comparator not appropriate (not defined)
NCT01142934 (2009) (47)	Outcomes not appropriate (no results available)
NCT01733940 (2012) (93)	Outcomes not appropriate (no results available)
O'Horo and Baum (2013) (94)	Patient population not appropriate
Palka-Santini *et al.* (2014a) (15)	Outcomes not appropriate (included in cost-effectiveness review)
Palka-Santini *et al.* (2014b) (16)	Outcomes not appropriate (included in cost-effectiveness review)
Ruschulte *et al.* (2009) (95)	Patient population not appropriate
Safdar (2005) (96)	Patient population not appropriate
Safdar and Maki (2013) (97)	Patient population not appropriate
Safdar *et al.* (2014) (43)	Review which cannot be included in its entirety due to studies undertaken in inappropriate patient group. Included studies assessed for relevance (no new studies were identified)
Sharma (2013) (98)	Comparator not appropriate (not defined)
Sucy and Curchoe (2005) (99)	Study design not appropriate
Timsit *et al.* (2012) (100)	Duplicate of included study (conference abstract of Timsit *et al.*, 2012)
Ullman *et al.* (2014) (101)	Review which cannot be included in its entirety due to studies undertaken in inappropriate intervention. Included studies cannot be assessed for relevance as conference abstract only.

Appendix 4: Summary of EAC's included economic studies

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
Maunoury *et al.,* 2013 (17)	France	A NHMM with 8 states. Includes Monte Carlo simulations for PSA. The model compared Tegaderm CHG to non-antimicrobial dressings.	ICU patients receiving a CVC. Patient characteristics not reported.	Unit costs incorporated into the analysis not reported.	Only outcome reported is the number of infections per treatment group.	Tegaderm CHG prevented 11.75 infections/1,000 patients Cost per patient: Tegaderm CHG = £17,496 [95% CI: £16,685 to £18,356][1]. Comparator = £17,031 [95% CI: £16,281 to £17,879][2].
Maunoury *et al.,* 2014 (18)	Not reported, however, appears to be based on Timsit *et al.* (2012) and therefore based in France.	HMM and NHMM Markov models were built and compared; and PSA undertaken. The models compared Tegaderm CHG to standard dressings.	ICU patients receiving a CVC. Patient characteristics not reported.	Unit costs incorporated into the analysis not reported.	Only outcome reported is the number of infections per treatment group.	In NHMM, Tegaderm CHG resulted in 11.8 infections avoided per 1,000 patients [95% CI: 3.85 to 19.64], with a mean extra cost of £115 per patient [95%CI: -£797 to £1,029][3]. In HMM Tegaderm CHG resulted in 6.45 infections avoided per 1,000 patients [95% CI: 0.15 to 12.75], with a mean extra cost of £206 per patient [95%CI: -£756 to £1,168][4].
Palka-Santini *et al.,* 2014 (16)	France	A NHMM with 8 states. Includes Monte Carlo simulations for PSA. The model compared Tegaderm CHG to non-antimicrobial dressings.	ICU patients receiving a CVC. Patient characteristics not reported.	Unit costs incorporated into the analysis not reported.	Outcome measures: number of infections per treatment group, cost per CRBSI avoided and incremental net monetary benefit.	Tegaderm cost an extra £115 per patient [95%CI: -£797 to £1,029][5]. The cost per CRSBI avoided was £9,853[6].
Palka-Santini et al., 2014 (15)	France	A previously developed NHMM and classical decision tree were compared. Both DSA and PSA were also conducted. The models compared	Not reported. However, study appears to be based on Timsit (2012) and therefore, relevant patient population	Unit costs incorporated into the analysis not reported.	Only outcome reported is the number of infections per treatment group.	Based on the decision tree, Tegaderm CHG was the dominant strategy, preventing 13.5 infections/1,000 patients, whilst saving £128 per patient[7]. For the NHMM, 11.8 infections were avoided/1,000 patients, at

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
		Tegaderm CHG to standard transparent dressings.	is ICU patients receiving CVC. Patient characteristics not reported.			a cost of £115 per patient [95%CI: -£797 to £1,029][8].

[1] Costs were reported in euros: €21,391 [95% CI: €20,399 to €22,443]. These were converted into pounds using the appropriate purchasing power parity.

[2] Costs were reported in euros: €20,822 [95% CI: €19,905 to €21,859]. These were converted into pounds using the appropriate purchasing power parity

[3] Costs were reported in euros: €141 per patient [95%CI: -€ 975 to € 1,258]. These were converted into pounds using the appropriate purchasing power parity.

[4] Costs were reported in euros: €252 per patient [95%CI: -€ 924 to €1,428]. These were converted into pounds using the appropriate purchasing power parity.

[5] Costs were reported in euros: €141 per patient [95%CI: € -975; € 1,258]. These were converted into pounds using the appropriate purchasing power parity.

[6] Costs were reported in euros: €12,046 per CRBSI avoided. This was converted into pounds using the appropriate purchasing power parity.

[7] Costs were reported in euros: savings of €157 per patient. This was converted into pounds using the appropriate purchasing power parity.

[8] Costs were reported in euros: €141 per patient [95%CI: € -975; € 1,258]. These were converted into pounds using the appropriate purchasing power parity.

Appendix 5: Quality assessment of sponsor's *de novo* economic model

Study question	Response (Yes/No/Not clear/NA)	EAC comments
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	One of the 2 comparators described in the scope were used as a comparator and justification for this was provided.
6. Was the form of economic evaluation stated?	Not clear	The analysis was described broadly as a cost-effectiveness analysis. Specifically, it was a cost-consequence model incorporating a decision tree.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Justification for use of a cost-effectiveness analysis was not provided, however, this form of analysis incorporating both costs and consequences made best used of the data identified in the clinical evidence review.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	Details were provided on Timsit *et al.* (2012), which was used to populate the effectiveness estimates. No justification was provided for the application of the effectiveness of Tegaderm CHG in reducing CRBSI to local site infections.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	

Study question	Response (Yes/No/Not clear/NA)	EAC comments
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	With the exception of the cost of local site infection.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Not clear	Currency was reported. Cost years were provided for some costs, but not for others.
19. Were details of price adjustments for inflation or currency conversion given?	Not clear	Costs reported in dollars were converted into pounds, but conversion rate source was not provided. The cost of CRBSI was inflated to 'present day costs' with the source provided.
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Costs were not discounted due to the short time horizon of the model.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared?	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	

Study question	Response (Yes/No/Not clear/NA)	EAC comments
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	The generalisability of input parameters to the current NHS was discussed and expert advice sought. The results were deemed to apply to the NHS.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ (59). Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in healthcare. York: Centre for Reviews and Dissemination		

Appendix 6: Pragmatic literature search for model input parameter critique

A pragmatic literature search was developed to identify papers which reported on the following outcomes in the context of NHS / UK ICUs, CCUs or HDUs:

- Absolute rate / absolute risk of catheter-related blood stream infections (CRBSIs);
- Length of stay following CRBSIs;
- Mortality rate following CRBSIs.

The strategy was comprised of 3 concepts:

ICU / CCU / HDU AND CRBSIs AND UK.

The outcomes of interest (absolute rate / absolute risk / length of stay / mortality rate) were not included as a fourth concept, increasing the sensitivity of the search.

The bibliographic database strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title and abstract fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The search was not designed to be exhaustive, but to target papers which were most likely to be relevant to the research question, and to retrieve result numbers which were manageable within the context of project timelines and resources. The strategy was therefore focused and pragmatic. The strategy required that retrieved studies were indexed with the most relevant subject headings and / or explicitly included relatively specific terms for each of the 3 concepts in the record. There is no robust way to limit results to a specific geographic setting; including 'UK' as a third concept is in itself highly pragmatic and the included location terms were selective. The strategy used a number of additional pragmatic focusing techniques, including an emphasis on title searches, with search terms in the abstracts being linked by relatively narrow adjacency operators and enhanced by use of frequency operators which specify how many times a search term must appear in an abstract for the record to be retrieved. MeSH headings were at times searched as major descriptors only and limited by the use of subheadings.

Reflecting the methods used for the clinical evidence review and the economic evidence review, non-English language publications were excluded from the search results. The strategy excluded animal studies using a standard algorithm and also excluded publication types unlikely to yield relevant study reports: news items, comments, editorials and letters. Results were limited to studies published from 2011 to date. The choice of date was informed by existing available data on CRBSI rates up to the start of 2011, as reported in the Matching Michigan study (8).

The MEDLINE strategy was translated appropriately for other databases. The strategy for MEDLINE is shown in Figure A6.1 and the full strategies (including search dates) are included in below.

Figure A6.1: Search strategy for Ovid MEDLINE(R) In-Process & Other Non-indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1	exp Critical Care/ (45504)
2	exp Intensive Care Units/ (59318)
3	(acute care or critical care or critically ill or critical illness$).ti,ab,kf. (61489)
4	(high dependency adj2 (care or unit$1)).ti,ab,kf. (551)
5	intensive care.ti,ab,kf. (95622)
6	intensive therapy unit$1.ti,ab,kf. (569)
7	(ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs).ti,ab,kf. (36212)
8	(level 2 care or level 3 care or level two care or level three care).ti,ab,kf. (15)
9	or/1-8 (186830)
10	Catheter-Related Infections/ (2284)
11	(CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (853)
12	((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (4169)
13	((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (8655)
14	(catheter-related or catheter associated).ti,ab,kf. (6815)
15	((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (23)
16	((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (838)
17	(CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated).ti,ab,kf. (461)
18	((central line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (387)
19	((central line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (891)
20	((line-associated or line-related) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (272)
21	((line-associated or line-related) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (569)
22	(*Catheterization/ or *Catheterization, Central Venous/ or exp *Catheterization, Peripheral/ or *Cardiac Catheterization/ or exp *Catheters/) and (*Infection/ or *Bacterial Infections/ or exp *Sepsis/) (3078)
23	Catheterization/co or Cardiac Catheterization/co (92)

24	(*Catheterization/ae or *Catheterization, Central Venous/ae or exp *Catheterization, Peripheral/ae or *Cardiac Catheterization/ae or exp *Catheters/ae) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs).ti. (2997)
25	(*Catheterization/ae or *Catheterization, Central Venous/ae or exp *Catheterization, Peripheral/ae or *Cardiac Catheterization/ae or exp *Catheters/ae) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs).ab. /freq=2 (2667)
26	or/10-25 (15022)
27	9 and 26 (2643)
28	exp Great Britain/ (312045)
29	(Britain$1 or British or GB$1 or UK$1 or United Kingdom$1 or National Health Service$1 or NHS$1 or "Department of Health$1" or DoH$1).ti,ab,in,hw,kf. (1275301)
30	(England$ or English or Birmingham$ or Bradford$ or Brighton$ or Bristol$ or Cambridge$ or Canterbury$ or Carlisle$ or Chelmsford$ or Chester$ or Chichester$ or Coventry$ or Derby$ or Durham$ or Ely$1 or Exeter$ or Gloucester$ or Hereford$ or Hull$1 or Lancaster$ or Leeds or Leicester$ or Lichfield$ or Lincoln$ or Liverpool$ or London$ or Manchester$ or Newcastle$ or Norwich$ or Nottingham$ or Oxford$ or Peterborough$ or Plymouth$ or Portsmouth$ or Preston$ or Ripon$ or Salford$ or Salisbury$ or Sheffield$ or Southampton$ or St Albans or Stoke$1 or Sunderland$ or Truro$ or Wakefield$ or Westminster$ or Winchester$ or Wolverhampton$ or York$ or Northumberland$ or Tyne$ or Cumbria$ or Lancashire$ or Blackpool$ or Blackburn$ or Darlington$ or Stockton$ or Middlesbrough$ or Hartlepool$ or Redcar$ or Humber$ or Merseyside$ or Halton$ or Warrington$ or Cheshire$ or Shropshire$ or Telford$ or Staffordshire$ or Midlands or Warwickshire$ or Rutland$ or Northamptonshire$ or Norfolk$ or Suffolk$ or Essex$ or Southend$ or Thurrock$ or Hertfordshire$ or Bedford$ or Luton$ or Milton Keynes or Buckinghamshire$ or Gloucestershire$ or Worcestershire$ or Somerset$ or Wiltshire$ or Swindon$ or Berkshire$ or Medway$ or Kent$ or Sussex$ or Surrey$ or Hampshire$ or Isle of Wight$ or Dorset$ or Poole or Bournemouth$ or Somerset$ or Devon$ or Torbay$ or Cornwall$ or Bolton$ or Oldham$ or Rochdale$ or Stockport$ or Tameside$ or Trafford$ or Wigan$ or Knowsley$ or Sefton$ or St Helens or Wirral$ or Barnsley$ or Doncaster$ or Rotherham$ or Gateshead$ or Dudley$ or Sandwell$ or Solihull$ or Walsall$ or Calderdale$ or Kirklees).ti,ab,in,hw,kf. (3512988)
31	(Scotland$ or Scottish or Scots or Aberdeen$ or Dundee$ or Edinburgh$ or Glasgow$ or Inverness$ or Perth$ or Stirling$ or Angus$ or Argyll$ or Bute$1 or Clackmannanshire$ or Dumfries or Galloway$ or Ayrshire$ or Dunbartonshire$ or Lothian$ or Renfrewshire$ or Falkirk$ or Fife$ or Highland$ or Inverclyde$ or Midlothian$ or Moray$ or Lanarkshire$ or Kinross$ or Grampian$ or Strathclyde$ or Tayside$ or Orkney$ or Shetland$ or Western Isles or Arran$1 or Forth Valley$ or Cambuslang$ or Rutherglen$ or Strathkelvin$).ti,ab,in,hw,kf. (196178)
32	(Wales or Welsh or Bangor$ or Cardiff$ or Newport$ or St Asaph$ or St David$ or Swansea$ or Blaenau Gwent$ or Bridgend$ or Caerphilly$ or Carmarthenshire$ or Ceredigion$ or Cardiganshire$ or Conwy$ or Aberconwy$ or Colwyn$ or Denbighshire$ or Flintshire$ or Gwynedd$ or Caernarfonshire$ or Merionethshire$ or Anglesey$ or Merthyr Tydfil$ or Monmouthshire$ or Port Talbot$ or Pembrokeshire$ or Powys or Rhondda$ or Torfaen$ or Wrexham$).ti,ab,in,hw,kf. (113784)
33	(Northern Ireland$ or Northern Irish or Armagh$ or Belfast$ or Derry$ or Lisburn$ or Newry$ or Antrim$ or Ballymena$ or Ballymoney$ or Banbridge$ or Carrickfergus or Castlereagh$ or Coleraine$ or Cookstown$ or Craigavon$ or Dungannon$ or South Tyrone$ or Fermanagh$ or Larne$1 or Limavady$ or Magherafelt$ or Moyle$ or Mourne$1 or Newtownabbey$ or North Down$ or Omagh$ or Strabane$).ti,ab,in,hw,kf. (22045)
34	or/28-33 (4185997)
35	27 and 34 (657)
36	exp animals/ not humans/ (4099183)
37	(news or comment or editorial or letter).pt. (1577340)
38	35 not (36 or 37) (643)
39	limit 38 to (english language and yr="2011 -Current") (166)

Key to Ovid symbols and commands	
.ti,ab,in,hw,kf.	Restricts search to title, abstract, institution, subject heading word and keyword headings fields
/	Restricts search to Medical Subject Headings (MeSH)
*	Searches the Medical Subject Headings (MeSH) as a major descriptor only
$	Truncation symbol
adjn	Words must appear with n words of each other
ab. /freq=n	Records containing the term are retrieved only if that term occurs at least n times in the abstract
.pt.	Restricts search to publication type field

The literature search was conducted using a range of relevant core bibliographic databases. The databases searched are shown in Table A6.1.

Table A6.1: Databases and information sources searched

Database / information source	Interface / URL
MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley Interscience
Health Technology Assessment Database (HTA)	Cochrane Library / Wiley Interscience
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley Interscience
NHS Economic Evaluation Database (NHS EED)	Cochrane Library / Wiley Interscience

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

Literature Search Results

The searches identified 605 records (Table A6.2). Following deduplication 456 records were assessed for relevance.

Table A6.2: Literature search results

Resource	Records identified
MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE	166
Embase	342
Cochrane Database of Systematic Reviews (CDSR)	11
Cochrane Central Register of Controlled Trials (CENTRAL)	50
Health Technology Assessment Database (HTA)	5
Database of Abstracts of Reviews of Effects (DARE)	15
NHS Economic Evaluation Database (NHS EED)	16
TOTAL	**605**
TOTAL after deduplication	**456**

Search strategies

1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 10/12/14
Retrieved records: 166
Search strategy:

1 exp Critical Care/ (45504)
2 exp Intensive Care Units/ (59318)
3 (acute care or critical care or critically ill or critical illness$).ti,ab,kf. (61489)
4 (high dependency adj2 (care or unit$1)).ti,ab,kf. (551)
5 intensive care.ti,ab,kf. (95622)
6 intensive therapy unit$1.ti,ab,kf. (569)
7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs).ti,ab,kf. (36212)
8 (level 2 care or level 3 care or level two care or level three care).ti,ab,kf. (15)
9 or/1-8 (186830)
10 Catheter-Related Infections/ (2284)
11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kf. (853)
12 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (4169)
13 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (8655)
14 (catheter-related or catheter associated).ti,ab,kf. (6815)
15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (23)

16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (838)

17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated).ti,ab,kf. (461)

18 ((central line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (387)

19 ((central line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (891)

20 ((line-associated or line-related) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (272)

21 ((line-associated or line-related) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kf. (569)

22 (*Catheterization/ or *Catheterization, Central Venous/ or exp *Catheterization, Peripheral/ or *Cardiac Catheterization/ or exp *Catheters/) and (*Infection/ or *Bacterial Infections/ or exp *Sepsis/) (3078)

23 Catheterization/co or Cardiac Catheterization/co (92)

24 (*Catheterization/ae or *Catheterization, Central Venous/ae or exp *Catheterization, Peripheral/ae or *Cardiac Catheterization/ae or exp *Catheters/ae) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs).ti. (2997)

25 (*Catheterization/ae or *Catheterization, Central Venous/ae or exp *Catheterization, Peripheral/ae or *Cardiac Catheterization/ae or exp *Catheters/ae) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs).ab. /freq=2 (2667)

26 or/10-25 (15022)

27 9 and 26 (2643)

28 exp Great Britain/ (312045)

29 (Britain$1 or British or GB$1 or UK$1 or United Kingdom$1 or National Health Service$1 or NHS$1 or "Department of Health$1" or DoH$1).ti,ab,in,hw,kf. (1275301)

30 (England$ or English or Birmingham$ or Bradford$ or Brighton$ or Bristol$ or Cambridge$ or Canterbury$ or Carlisle$ or Chelmsford$ or Chester$ or Chichester$ or Coventry$ or Derby$ or Durham$ or Ely$1 or Exeter$ or Gloucester$ or Hereford$ or Hull$1 or Lancaster$ or Leeds or Leicester$ or Lichfield$ or Lincoln$ or Liverpool$ or London$ or Manchester$ or Newcastle$ or Norwich$ or Nottingham$ or Oxford$ or Peterborough$ or Plymouth$ or Portsmouth$ or Preston$ or Ripon$ or Salford$ or Salisbury$ or Sheffield$ or Southampton$ or St Albans or Stoke$1 or Sunderland$ or Truro$ or Wakefield$ or Westminster$ or Winchester$ or Wolverhampton$ or York$ or Northumberland$ or Tyne$ or Cumbria$ or Lancashire$ or Blackpool$ or Blackburn$ or Darlington$ or Stockton$ or Middlesbrough$ or Hartlepool$ or Redcar$ or Humber$ or Merseyside$ or Halton$ or Warrington$ or Cheshire$ or Shropshire$ or Telford$ or Staffordshire$ or Midlands or Warwickshire$ or Rutland$ or Northamptonshire$ or Norfolk$ or Suffolk$ or Essex$ or Southend$ or Thurrock$ or Hertfordshire$ or Bedford$ or Luton$ or Milton Keynes or Buckinghamshire$ or Gloucestershire$ or Worcestershire$ or Somerset$ or Wiltshire$ or Swindon$ or Berkshire$ or Medway$ or Kent$ or Sussex$ or Surrey$ or Hampshire$ or Isle of Wight$ or Dorset$ or Poole or Bournemouth$ or Somerset$ or Devon$ or Torbay$ or Cornwall$ or Bolton$ or Oldham$ or Rochdale$ or Stockport$ or Tameside$ or Trafford$ or Wigan$ or Knowsley$ or Sefton$ or St Helens or Wirral$ or Barnsley$ or Doncaster$ or Rotherham$ or Gateshead$ or Dudley$ or Sandwell$ or Solihull$ or Walsall$ or Calderdale$ or Kirklees).ti,ab,in,hw,kf. (3512988)

31 (Scotland$ or Scottish or Scots or Aberdeen$ or Dundee$ or Edinburgh$ or Glasgow$ or Inverness$ or Perth$ or Stirling$ or Angus$ or Argyll$ or Bute$1 or Clackmannanshire$ or Dumfries or Galloway$ or Ayrshire$ or Dunbartonshire$ or Lothian$ or Renfrewshire$ or Falkirk$ or Fife$ or Highland$ or Inverclyde$ or Midlothian$ or Moray$ or Lanarkshire$ or Kinross$ or Grampian$ or Strathclyde$ or Tayside$ or Orkney$ or Shetland$ or Western Isles or Arran$1 or Forth Valley$ or Cambuslang$ or Rutherglen$ or Strathkelvin$).ti,ab,in,hw,kf. (196178)

32 (Wales or Welsh or Bangor$ or Cardiff$ or Newport$ or St Asaph$ or St David$ or Swansea$ or Blaenau Gwent$ or Bridgend$ or Caerphilly$ or Carmarthenshire$ or Ceredigion$ or Cardiganshire$ or Conwy$ or Aberconwy$ or Colwyn$ or Denbighshire$ or Flintshire$ or Gwynedd$ or Caernarfonshire$ or Merionethshire$ or Anglesey$ or Merthyr Tydfil$ or Monmouthshire$ or Port Talbot$ or Pembrokeshire$ or Powys or Rhondda$ or Torfaen$ or Wrexham$).ti,ab,in,hw,kf. (113784)

33 (Northern Ireland$ or Northern Irish or Armagh$ or Belfast$ or Derry$ or Lisburn$ or Newry$ or Antrim$ or Ballymena$ or Ballymoney$ or Banbridge$ or Carrickfergus or Castlereagh$ or Coleraine$ or Cookstown$ or Craigavon$ or Dungannon$ or South Tyrone$ or Fermanagh$ or Larne$1 or Limavady$ or Magherafelt$ or Moyle$ or Mourne$1 or Newtownabbey$ or North Down$ or Omagh$ or Strabane$).ti,ab,in,hw,kf. (22045)

34 or/28-33 (4185997)

35 27 and 34 (657)

36 exp animals/ not humans/ (4099183)

37 (news or comment or editorial or letter).pt. (1577340)

38 35 not (36 or 37) (643)
39 limit 38 to (english language and yr="2011 -Current") (166)

2: Source: Embase 1974 to 2014 December 10

Interface / URL: OvidSP
Search date: 11/12/14
Retrieved records: 342
Search strategy:

1 *intensive care/ or exp *intensive care nursing/ or *newborn intensive care/ (59662)
2 *intensive care unit/ (22066)
3 (acute care or critical care or critically ill or critical illness$).ti,ab,kw. (87016)
4 (high dependency adj2 (care or unit$1)).ti,ab,kw. (959)
5 intensive care.ti,ab,kw. (129191)
6 intensive therapy unit$1.ti,ab,kw. (716)
7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs).ti,ab,kw. (64421)
8 (level 2 care or level 3 care or level two care or level three care).ti,ab,kw. (70)
9 or/1-8 (238394)
10 *catheter infection/ (4412)
11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs).ti,ab,kw. (1562)
12 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (5192)
13 ((catheter$ or microcatheter$ or cannula$ or microcannula$ or canula$ or microcanula$) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (11793)
14 (catheter-related or catheter associated).ti,ab,kw. (9081)
15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (67)
16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (1331)
17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated).ti,ab,kw. (742)

18 ((central line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (585)

19 ((central line$1 or venous line$1 or intravenous line$1 or vascular line$1 or intravascular line$1 or IV line$1 or peripheral line$1 or PIC line$1 or CVP line$1 or arterial line$1 or intraarterial line$1 or artery line$1 or arteries line$1 or art line$1 or a line$1 or IAC or IACs) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (1415)

20 ((line-associated or line-related) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ti. (423)

21 ((line-associated or line-related) adj5 (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)).ab,kw. (926)

22 (*catheterization/ or exp *central venous catheterization/ or *heart catheterization/ or exp *artery catheterization/ or *catheter/ or exp *central venous catheter/ or *indwelling catheter/ or *artery catheter/ or *arterial line/ or exp *pulmonary artery catheter/ or *umbilical artery catheter/) and (*infection/ or *bloodstream infection/ or *bacterial infection/ or exp *sepsis/ or *cross infection/) (2178)

23 *catheter complication/ (879)

24 *catheterization/co or *heart catheterization/co (85)

25 (*catheterization/ or exp *central venous catheterization/ or *heart catheterization/ or exp *artery catheterization/ or *catheter/ or exp *central venous catheter/ or *indwelling catheter/ or *artery catheter/ or *arterial line/ or exp *pulmonary artery catheter/ or *umbilical artery catheter/) and (*infectious complication/ or *infection complication/ or *medical device complication/ or *complication/ or *medical device contamination/ or *device infection/) (148)

26 (*catheterization/ae or exp *central venous catheterization/ae or *heart catheterization/ae or exp *artery catheterization/ae or *catheter/ae or exp *central venous catheter/ae or *indwelling catheter/ae or *artery catheter/ae or *arterial line/ae or exp *pulmonary artery catheter/ae or *umbilical artery catheter/ae) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs).ti. (1013)

27 (*catheterization/ae or exp *central venous catheterization/ae or *heart catheterization/ae or exp *artery catheterization/ae or *catheter/ae or exp *central venous catheter/ae or *indwelling catheter/ae or *artery catheter/ae or *arterial line/ae or exp *pulmonary artery catheter/ae or *umbilical artery catheter/ae) and (infect$ or sepsis$ or septic$ or sepses or postsepsis$ or bacter?emi$ or bacill?emi$ or fung?emi$ or HAI or HAIs or HCAI or HCAIs or BSI or BSIs).ab. /freq=2 (756)

28 or/10-27 (20224)

29 9 and 28 (3806)

30 United Kingdom/ (338349)

31 (Britain$1 or British or GB$1 or UK$1 or United Kingdom$1 or National Health Service$1 or NHS$1 or "Department of Health$1" or DoH$1).ti,ab,in,ad,hw,kw. (2435975)

32 (England$ or English or Birmingham$ or Bradford$ or Brighton$ or Bristol$ or Cambridge$ or Canterbury$ or Carlisle$ or Chelmsford$ or Chester$ or Chichester$ or Coventry$ or Derby$ or Durham$ or Ely$1 or Exeter$ or Gloucester$ or Hereford$ or Hull$1 or Lancaster$ or Leeds or Leicester$ or Lichfield$ or Lincoln$ or Liverpool$ or London$ or Manchester$ or Newcastle$ or Norwich$ or Nottingham$ or Oxford$ or Peterborough$ or Plymouth$ or Portsmouth$ or Preston$ or Ripon$ or Salford$ or Salisbury$ or Sheffield$ or Southampton$ or St Albans or Stoke$1 or Sunderland$ or Truro$ or Wakefield$ or Westminster$ or Winchester$ or Wolverhampton$ or York$ or Northumberland$ or Tyne$ or Cumbria$ or Lancashire$ or Blackpool$ or Blackburn$ or Darlington$ or Stockton$ or Middlesbrough$ or Hartlepool$ or Redcar$ or Humber$ or Merseyside$ or Halton$ or Warrington$ or Cheshire$ or Shropshire$ or Telford$ or Staffordshire$ or Midlands or Warwickshire$ or Rutland$ or Northamptonshire$ or Norfolk$ or Suffolk$ or Essex$ or Southend$ or Thurrock$ or Hertfordshire$ or Bedford$ or Luton$ or Milton Keynes or Buckinghamshire$ or Gloucestershire$ or Worcestershire$ or Somerset$ or Wiltshire$ or Swindon$ or Berkshire$ or Medway$ or Kent$ or Sussex$ or Surrey$ or Hampshire$ or Isle of Wight$ or Dorset$ or Poole or Bournemouth$ or Somerset$ or Devon$ or Torbay$ or Cornwall$ or Bolton$ or Oldham$ or Rochdale$ or Stockport$ or Tameside$ or Trafford$ or Wigan$ or Knowsley$ or Sefton$ or St Helens or Wirral$ or Barnsley$ or Doncaster$ or Rotherham$ or Gateshead$ or Dudley$ or Sandwell$ or Solihull$ or Walsall$ or Calderdale$ or Kirklees).ti,ab,in,ad,hw,kw. (2903393)

33 (Scotland$ or Scottish or Scots or Aberdeen$ or Dundee$ or Edinburgh$ or Glasgow$ or Inverness$ or Perth$ or Stirling$ or Angus$ or Argyll$ or Bute$1 or Clackmannanshire$ or Dumfries or Galloway$ or Ayrshire$ or Dunbartonshire$ or Lothian$ or Renfrewshire$ or Falkirk$ or Fife$ or Highland$ or Inverclyde$ or Midlothian$ or Moray$ or Lanarkshire$ or Kinross$ or Grampian$ or Strathclyde$ or Tayside$ or Orkney$ or Shetland$ or Western Isles or Arran$1 or Forth Valley$ or Cambuslang$ or Rutherglen$ or Strathkelvin$).ti,ab,in,ad,hw,kw. (346206)

34 (Wales or Welsh or Bangor$ or Cardiff$ or Newport$ or St Asaph$ or St David$ or Swansea$ or Blaenau Gwent$ or Bridgend$ or Caerphilly$ or Carmarthenshire$ or Ceredigion$ or Cardiganshire$ or Conwy$ or Aberconwy$ or Colwyn$ or Denbighshire$ or Flintshire$ or Gwynedd$ or Caernarfonshire$ or Merionethshire$ or Anglesey$ or Merthyr Tydfil$ or Monmouthshire$ or Port Talbot$ or Pembrokeshire$ or Powys or Rhondda$ or Torfaen$ or Wrexham$).ti,ab,in,ad,hw,kw. (161519)

35 (Northern Ireland$ or Northern Irish or Armagh$ or Belfast$ or Derry$ or Lisburn$ or Newry$ or Antrim$ or Ballymena$ or Ballymoney$ or Banbridge$ or Carrickfergus or Castlereagh$ or Coleraine$ or Cookstown$ or Craigavon$ or Dungannon$ or South Tyrone$ or Fermanagh$ or Larne$1 or Limavady$ or Magherafelt$ or Moyle$ or Mourne$1 or Newtownabbey$ or North Down$ or Omagh$ or Strabane$).ti,ab,in,ad,hw,kw. (38866)

36 or/30-35 (3959739)
37 29 and 36 (681)
38 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5027588)
39 (editorial or letter).pt. (1321192)
40 37 not (38 or 39) (669)
41 limit 40 to (english language and yr="2011 -Current") (342)

3: Source: Cochrane Central Register of Controlled Trials (CENTRAL) - Issue 11 of 12, November 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 11/12/14
Retrieved records: 50
Search strategy:

#1 [mh "Critical Care"] 1856
#2 [mh "Intensive Care Units"] 2640
#3 ("acute care" or "critical care" or "critically ill" or critical next illness*) 13291
#4 ("high dependency" near/2 (care or unit*)) 100
#5 "intensive care" 16402
#6 intensive next therapy next unit* 72
#7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs) 4260
#8 ("level 2 care" or "level 3 care" or "level two care" or "level three care") 3
#9 26516
#10 [mh ^"Catheter-Related Infections"] 187
#11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#12 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 607
#13 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1552
#14 (catheter-related or catheter associated) 3007
#15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 6
#16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 115

#17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated) 75

#18 ((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 19

#19 ((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 72

#20 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 11

#21 ((line-associated or line-related) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 43

#22 ([mh ^Catheterization] or [mh ^"Catheterization, Central Venous"] or [mh "Catheterization, Peripheral"] or [mh ^"Cardiac Catheterization"] or [mh Catheters]) and ([mh ^Infection] or [mh ^"Bacterial Infections"] or [mh Sepsis] or [mh ^"Cross Infection"]) 530

#23 ([mh ^Catheterization/AE] or [mh ^"Catheterization, Central Venous"/AE] or [mh "Catheterization, Peripheral"/AE] or [mh ^"Cardiac Catheterization"/AE] or [mh Catheters/AE]) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs) 648

#24 {or #10-#23} 3787

#25 #9 and #24 911

#26 [mh "Great Britain"] 5467

#27 (Britain* or British or GB or UK or United next Kingdom* or National next Health next Service* or NHS or Department next of next Health* or DoH) 116687

#28 (England* or English or Birmingham* or Bradford* or Brighton* or Bristol* or Cambridge* or Canterbury* or Carlisle* or Chelmsford* or Chester* or Chichester* or Coventry* or Derby* or Durham* or Ely* or Exeter* or Gloucester* or Hereford* or Hull* or Lancaster* or Leeds or Leicester* or Lichfield* or Lincoln* or Liverpool* or London* or Manchester* or Newcastle* or Norwich* or Nottingham* or Oxford* or Peterborough* or Plymouth* or Portsmouth* or Preston* or Ripon* or Salford* or Salisbury* or Sheffield* or Southampton* or "St Albans" or Stoke* or Sunderland* or Truro* or Wakefield* or Westminster* or Winchester* or Wolverhampton* or York* or Northumberland* or Tyne* or Cumbria* or Lancashire* or Blackpool* or Blackburn* or Darlington* or Stockton* or Middlesbrough* or Hartlepool* or Redcar* or Humber* or Merseyside* or Halton* or Warrington* or Cheshire* or Shropshire* or Telford* or Staffordshire* or Midlands or Warwickshire* or Rutland* or Northamptonshire* or Norfolk* or Suffolk* or Essex* or Southend* or Thurrock* or Hertfordshire* or Bedford* or Luton* or "Milton Keynes" or Buckinghamshire* or Gloucestershire* or Worcestershire* or Somerset* or Wiltshire* or Swindon* or Berkshire* or Medway* or Kent* or Sussex* or Surrey* or Hampshire* or Isle next of next Wight or Dorset* or Poole or Bournemouth* or Somerset* or Devon* or Torbay* or Cornwall* or Bolton* or Oldham* or Rochdale* or Stockport* or Tameside* or Trafford* or Wigan* or Knowsley* or Sefton* or "St Helens" or Wirral* or Barnsley* or Doncaster* or Rotherham* or Gateshead* or Dudley* or Sandwell* or Solihull* or Walsall* or Calderdale* or Kirklees) 156466

#29 (Scotland* or Scottish or Scots or Aberdeen* or Dundee* or Edinburgh* or Glasgow* or Inverness* or Perth* or Stirling* or Angus* or Argyll* or Bute* or Clackmannanshire* or Dumfries or Galloway* or Ayrshire* or Dunbartonshire* or Lothian* or Renfrewshire* or Falkirk* or Fife* or Highland* or Inverclyde* or Midlothian* or Moray* or Lanarkshire* or Kinross* or Grampian* or Strathclyde* or Tayside* or Orkney* or Shetland* or "Western Isles" or Arran* or Forth next Valley* or Cambuslang* or Rutherglen* or Strathkelvin*) 16752

#30 (Wales or Welsh or Bangor* or Cardiff* or Newport* or St next Asaph* or St next David* or Swansea* or Blaenau next Gwent* or Bridgend* or Caerphilly* or Carmarthenshire* or Ceredigion* or Cardiganshire* or Conwy* or Aberconwy* or Colwyn* or Denbighshire* or Flintshire* or Gwynedd* or Caernarfonshire* or Merionethshire* or Anglesey* or Merthyr next Tydfil* or Monmouthshire* or Port next Talbot* or Pembrokeshire* or Powys or Rhondda* or Torfaen* or Wrexham*) 5592

#31 (Northern next Ireland* or Northern next Irish or Armagh* or Belfast* or Derry* or Lisburn* or Newry* or Antrim* or Ballymena* or Ballymoney* or Banbridge* or Carrickfergus or Castlereagh* or Coleraine* or Cookstown* or Craigavon* or Dungannon* or South next Tyrone* or Fermanagh* or Larne* or Limavady* or Magherafelt* or Moyle* or Mourne* or Newtownabbey* or North next Down* or Omagh* or Strabane*) 1679

#32 {or #26-#31} 224461

#33 #25 and #32 Publication Year from 2011 to 2014 268

#34 #25 Publication Year from 2011 to 2014 369

#35 #33 in Trials50

4: Source: Health Technology Assessment Database (HTA) - Issue 4 of 4, Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 11/12/14
Retrieved records: 5
Search strategy:

#1 [mh "Critical Care"] 1856
#2 [mh "Intensive Care Units"] 2640
#3 ("acute care" or "critical care" or "critically ill" or critical next illness*) 13291
#4 ("high dependency" near/2 (care or unit*)) 100
#5 "intensive care" 16402
#6 intensive next therapy next unit* 72
#7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs) 4260
#8 ("level 2 care" or "level 3 care" or "level two care" or "level three care") 3
#9 26516
#10 [mh ^"Catheter-Related Infections"] 187
#11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#12 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 607
#13 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1552
#14 (catheter-related or catheter associated) 3007
#15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 6
#16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 115
#17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated) 75

#18	((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti	19
#19	((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs))	72
#20	((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti	11
#21	((line-associated or line-related) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs))	43
#22	([mh ^Catheterization] or [mh ^"Catheterization, Central Venous"] or [mh "Catheterization, Peripheral"] or [mh ^"Cardiac Catheterization"] or [mh Catheters]) and ([mh ^Infection] or [mh ^"Bacterial Infections"] or [mh Sepsis] or [mh ^"Cross Infection"])	530
#23	([mh ^Catheterization/AE] or [mh ^"Catheterization, Central Venous"/AE] or [mh "Catheterization, Peripheral"/AE] or [mh ^"Cardiac Catheterization"/AE] or [mh Catheters/AE]) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)	648
#24	{or #10-#23}	3787
#25	#9 and #24	911
#26	[mh "Great Britain"]	5467
#27	(Britain* or British or GB or UK or United next Kingdom* or National next Health next Service* or NHS or Department next of next Health* or DoH)	116687

#28 (England* or English or Birmingham* or Bradford* or Brighton* or Bristol* or Cambridge* or Canterbury* or Carlisle* or Chelmsford* or Chester* or Chichester* or Coventry* or Derby* or Durham* or Ely* or Exeter* or Gloucester* or Hereford* or Hull* or Lancaster* or Leeds or Leicester* or Lichfield* or Lincoln* or Liverpool* or London* or Manchester* or Newcastle* or Norwich* or Nottingham* or Oxford* or Peterborough* or Plymouth* or Portsmouth* or Preston* or Ripon* or Salford* or Salisbury* or Sheffield* or Southampton* or "St Albans" or Stoke* or Sunderland* or Truro* or Wakefield* or Westminster* or Winchester* or Wolverhampton* or York* or Northumberland* or Tyne* or Cumbria* or Lancashire* or Blackpool* or Blackburn* or Darlington* or Stockton* or Middlesbrough* or Hartlepool* or Redcar* or Humber* or Merseyside* or Halton* or Warrington* or Cheshire* or Shropshire* or Telford* or Staffordshire* or Midlands or Warwickshire* or Rutland* or Northamptonshire* or Norfolk* or Suffolk* or Essex* or Southend* or Thurrock* or Hertfordshire* or Bedford* or Luton* or "Milton Keynes" or Buckinghamshire* or Gloucestershire* or Worcestershire* or Somerset* or Wiltshire* or Swindon* or Berkshire* or Medway* or Kent* or Sussex* or Surrey* or Hampshire* or Isle next of next Wight or Dorset* or Poole or Bournemouth* or Somerset* or Devon* or Torbay* or Cornwall* or Bolton* or Oldham* or Rochdale* or Stockport* or Tameside* or Trafford* or Wigan* or Knowsley* or Sefton* or "St Helens" or Wirral* or Barnsley* or Doncaster* or Rotherham* or Gateshead* or Dudley* or Sandwell* or Solihull* or Walsall* or Calderdale* or Kirklees) 156466

#29 (Scotland* or Scottish or Scots or Aberdeen* or Dundee* or Edinburgh* or Glasgow* or Inverness* or Perth* or Stirling* or Angus* or Argyll* or Bute* or Clackmannanshire* or Dumfries or Galloway* or Ayrshire* or Dunbartonshire* or Lothian* or Renfrewshire* or Falkirk* or Fife* or Highland* or Inverclyde* or Midlothian* or Moray* or Lanarkshire* or Kinross* or Grampian* or Strathclyde* or Tayside* or Orkney* or Shetland* or "Western Isles" or Arran* or Forth next Valley* or Cambuslang* or Rutherglen* or Strathkelvin*) 16752

#30 (Wales or Welsh or Bangor* or Cardiff* or Newport* or St next Asaph* or St next David* or Swansea* or Blaenau next Gwent* or Bridgend* or Caerphilly* or Carmarthenshire* or Ceredigion* or Cardiganshire* or Conwy* or Aberconwy* or Colwyn* or Denbighshire* or Flintshire* or Gwynedd* or Caernarfonshire* or Merionethshire* or Anglesey* or Merthyr next Tydfil* or Monmouthshire* or Port next Talbot* or Pembrokeshire* or Powys or Rhondda* or Torfaen* or Wrexham*) 5592

#31 (Northern next Ireland* or Northern next Irish or Armagh* or Belfast* or Derry* or Lisburn* or Newry* or Antrim* or Ballymena* or Ballymoney* or Banbridge* or Carrickfergus or Castlereagh* or Coleraine* or Cookstown* or Craigavon* or Dungannon* or South next Tyrone* or Fermanagh* or Larne* or Limavady* or Magherafelt* or Moyle* or Mourne* or Newtownabbey* or North next Down* or Omagh* or Strabane*) 1679

#32 {or #26-#31} 224461

#33 #25 and #32 Publication Year from 2011 to 2014 268

#34 #25 Publication Year from 2011 to 2014 369

#35 #33 in Trials50

#36 #34 in Economic Evaluations 16

#37 #34 in Technology Assessments5

5: Source: Database of Abstracts of Reviews of Effects (DARE) - Issue 4 of 4, Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 11/12/14
Retrieved records: 15
Search strategy:

#1 [mh "Critical Care"] 1856
#2 [mh "Intensive Care Units"] 2640
#3 ("acute care" or "critical care" or "critically ill" or critical next illness*) 13291
#4 ("high dependency" near/2 (care or unit*)) 100
#5 "intensive care" 16402
#6 intensive next therapy next unit* 72
#7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs) 4260
#8 ("level 2 care" or "level 3 care" or "level two care" or "level three care") 3
#9 26516
#10 [mh ^"Catheter-Related Infections"] 187
#11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#12 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 607
#13 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1552
#14 (catheter-related or catheter associated) 3007
#15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 6
#16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 115
#17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated) 75

#18	((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti	19
#19	((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs))	72
#20	((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti	11
#21	((line-associated or line-related) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs))	43
#22	([mh ^Catheterization] or [mh ^"Catheterization, Central Venous"] or [mh "Catheterization, Peripheral"] or [mh ^"Cardiac Catheterization"] or [mh Catheters]) and ([mh ^Infection] or [mh ^"Bacterial Infections"] or [mh Sepsis] or [mh ^"Cross Infection"])	530
#23	([mh ^Catheterization/AE] or [mh ^"Catheterization, Central Venous"/AE] or [mh "Catheterization, Peripheral"/AE] or [mh ^"Cardiac Catheterization"/AE] or [mh Catheters/AE]) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)	648
#24	{or #10-#23}	3787
#25	#9 and #24	911
#26	[mh "Great Britain"]	5467
#27	(Britain* or British or GB or UK or United next Kingdom* or National next Health next Service* or NHS or Department next of next Health* or DoH)	116687

#28 (England* or English or Birmingham* or Bradford* or Brighton* or Bristol* or Cambridge* or Canterbury* or Carlisle* or Chelmsford* or Chester* or Chichester* or Coventry* or Derby* or Durham* or Ely* or Exeter* or Gloucester* or Hereford* or Hull* or Lancaster* or Leeds or Leicester* or Lichfield* or Lincoln* or Liverpool* or London* or Manchester* or Newcastle* or Norwich* or Nottingham* or Oxford* or Peterborough* or Plymouth* or Portsmouth* or Preston* or Ripon* or Salford* or Salisbury* or Sheffield* or Southampton* or "St Albans" or Stoke* or Sunderland* or Truro* or Wakefield* or Westminster* or Winchester* or Wolverhampton* or York* or Northumberland* or Tyne* or Cumbria* or Lancashire* or Blackpool* or Blackburn* or Darlington* or Stockton* or Middlesbrough* or Hartlepool* or Redcar* or Humber* or Merseyside* or Halton* or Warrington* or Cheshire* or Shropshire* or Telford* or Staffordshire* or Midlands or Warwickshire* or Rutland* or Northamptonshire* or Norfolk* or Suffolk* or Essex* or Southend* or Thurrock* or Hertfordshire* or Bedford* or Luton* or "Milton Keynes" or Buckinghamshire* or Gloucestershire* or Worcestershire* or Somerset* or Wiltshire* or Swindon* or Berkshire* or Medway* or Kent* or Sussex* or Surrey* or Hampshire* or Isle next of next Wight or Dorset* or Poole or Bournemouth* or Somerset* or Devon* or Torbay* or Cornwall* or Bolton* or Oldham* or Rochdale* or Stockport* or Tameside* or Trafford* or Wigan* or Knowsley* or Sefton* or "St Helens" or Wirral* or Barnsley* or Doncaster* or Rotherham* or Gateshead* or Dudley* or Sandwell* or Solihull* or Walsall* or Calderdale* or Kirklees) 156466

#29 (Scotland* or Scottish or Scots or Aberdeen* or Dundee* or Edinburgh* or Glasgow* or Inverness* or Perth* or Stirling* or Angus* or Argyll* or Bute* or Clackmannanshire* or Dumfries or Galloway* or Ayrshire* or Dunbartonshire* or Lothian* or Renfrewshire* or Falkirk* or Fife* or Highland* or Inverclyde* or Midlothian* or Moray* or Lanarkshire* or Kinross* or Grampian* or Strathclyde* or Tayside* or Orkney* or Shetland* or "Western Isles" or Arran* or Forth next Valley* or Cambuslang* or Rutherglen* or Strathkelvin*) 16752

#30 (Wales or Welsh or Bangor* or Cardiff* or Newport* or St next Asaph* or St next David* or Swansea* or Blaenau next Gwent* or Bridgend* or Caerphilly* or Carmarthenshire* or Ceredigion* or Cardiganshire* or Conwy* or Aberconwy* or Colwyn* or Denbighshire* or Flintshire* or Gwynedd* or Caernarfonshire* or Merionethshire* or Anglesey* or Merthyr next Tydfil* or Monmouthshire* or Port next Talbot* or Pembrokeshire* or Powys or Rhondda* or Torfaen* or Wrexham*) 5592

#31 (Northern next Ireland* or Northern next Irish or Armagh* or Belfast* or Derry* or Lisburn* or Newry* or Antrim* or Ballymena* or Ballymoney* or Banbridge* or Carrickfergus or Castlereagh* or Coleraine* or Cookstown* or Craigavon* or Dungannon* or South next Tyrone* or Fermanagh* or Larne* or Limavady* or Magherafelt* or Moyle* or Mourne* or Newtownabbey* or North next Down* or Omagh* or Strabane*) 1679

#32 {or #26-#31} 224461

#33 #25 and #32 Publication Year from 2011 to 2014 268

#34 #25 Publication Year from 2011 to 2014 369

#35 #33 in Trials50

#36 #34 in Economic Evaluations 16

#37 #34 in Technology Assessments5
#38 #34 in Other Reviews 15

6: Source: NHS Economic Evaluation Database (NHS EED) - Issue 4 of 4, Oct 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 11/12/14
Retrieved records: 16
Search strategy:

#1 [mh "Critical Care"] 1856
#2 [mh "Intensive Care Units"] 2640
#3 ("acute care" or "critical care" or "critically ill" or critical next illness*) 13291
#4 ("high dependency" near/2 (care or unit*)) 100
#5 "intensive care" 16402
#6 intensive next therapy next unit* 72
#7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs) 4260
#8 ("level 2 care" or "level 3 care" or "level two care" or "level three care") 3
#9 26516
#10 [mh ^"Catheter-Related Infections"] 187
#11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs) 117
#12 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 607
#13 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 1552
#14 (catheter-related or catheter associated) 3007
#15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 6
#16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)) 115
#17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated) 75

#18	((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti	19
#19	((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs))	72
#20	((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti	11
#21	((line-associated or line-related) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs))	43
#22	([mh ^Catheterization] or [mh ^"Catheterization, Central Venous"] or [mh "Catheterization, Peripheral"] or [mh ^"Cardiac Catheterization"] or [mh Catheters]) and ([mh ^Infection] or [mh ^"Bacterial Infections"] or [mh Sepsis] or [mh ^"Cross Infection"])	530
#23	([mh ^Catheterization/AE] or [mh ^"Catheterization, Central Venous"/AE] or [mh "Catheterization, Peripheral"/AE] or [mh ^"Cardiac Catheterization"/AE] or [mh Catheters/AE]) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)	648
#24	{or #10-#23}	3787
#25	#9 and #24	911
#26	[mh "Great Britain"]	5467
#27	(Britain* or British or GB or UK or United next Kingdom* or National next Health next Service* or NHS or Department next of next Health* or DoH)	116687

#28 (England* or English or Birmingham* or Bradford* or Brighton* or Bristol* or Cambridge* or Canterbury* or Carlisle* or Chelmsford* or Chester* or Chichester* or Coventry* or Derby* or Durham* or Ely* or Exeter* or Gloucester* or Hereford* or Hull* or Lancaster* or Leeds or Leicester* or Lichfield* or Lincoln* or Liverpool* or London* or Manchester* or Newcastle* or Norwich* or Nottingham* or Oxford* or Peterborough* or Plymouth* or Portsmouth* or Preston* or Ripon* or Salford* or Salisbury* or Sheffield* or Southampton* or "St Albans" or Stoke* or Sunderland* or Truro* or Wakefield* or Westminster* or Winchester* or Wolverhampton* or York* or Northumberland* or Tyne* or Cumbria* or Lancashire* or Blackpool* or Blackburn* or Darlington* or Stockton* or Middlesbrough* or Hartlepool* or Redcar* or Humber* or Merseyside* or Halton* or Warrington* or Cheshire* or Shropshire* or Telford* or Staffordshire* or Midlands or Warwickshire* or Rutland* or Northamptonshire* or Norfolk* or Suffolk* or Essex* or Southend* or Thurrock* or Hertfordshire* or Bedford* or Luton* or "Milton Keynes" or Buckinghamshire* or Gloucestershire* or Worcestershire* or Somerset* or Wiltshire* or Swindon* or Berkshire* or Medway* or Kent* or Sussex* or Surrey* or Hampshire* or Isle next of next Wight or Dorset* or Poole or Bournemouth* or Somerset* or Devon* or Torbay* or Cornwall* or Bolton* or Oldham* or Rochdale* or Stockport* or Tameside* or Trafford* or Wigan* or Knowsley* or Sefton* or "St Helens" or Wirral* or Barnsley* or Doncaster* or Rotherham* or Gateshead* or Dudley* or Sandwell* or Solihull* or Walsall* or Calderdale* or Kirklees) 156466

#29 (Scotland* or Scottish or Scots or Aberdeen* or Dundee* or Edinburgh* or Glasgow* or Inverness* or Perth* or Stirling* or Angus* or Argyll* or Bute* or Clackmannanshire* or Dumfries or Galloway* or Ayrshire* or Dunbartonshire* or Lothian* or Renfrewshire* or Falkirk* or Fife* or Highland* or Inverclyde* or Midlothian* or Moray* or Lanarkshire* or Kinross* or Grampian* or Strathclyde* or Tayside* or Orkney* or Shetland* or "Western Isles" or Arran* or Forth next Valley* or Cambuslang* or Rutherglen* or Strathkelvin*) 16752

#30 (Wales or Welsh or Bangor* or Cardiff* or Newport* or St next Asaph* or St next David* or Swansea* or Blaenau next Gwent* or Bridgend* or Caerphilly* or Carmarthenshire* or Ceredigion* or Cardiganshire* or Conwy* or Aberconwy* or Colwyn* or Denbighshire* or Flintshire* or Gwynedd* or Caernarfonshire* or Merionethshire* or Anglesey* or Merthyr next Tydfil* or Monmouthshire* or Port next Talbot* or Pembrokeshire* or Powys or Rhondda* or Torfaen* or Wrexham*) 5592

#31 (Northern next Ireland* or Northern next Irish or Armagh* or Belfast* or Derry* or Lisburn* or Newry* or Antrim* or Ballymena* or Ballymoney* or Banbridge* or Carrickfergus or Castlereagh* or Coleraine* or Cookstown* or Craigavon* or Dungannon* or South next Tyrone* or Fermanagh* or Larne* or Limavady* or Magherafelt* or Moyle* or Mourne* or Newtownabbey* or North next Down* or Omagh* or Strabane*) 1679

#32 {or #26-#31} 224461

#33 #25 and #32 Publication Year from 2011 to 2014 268

#34 #25 Publication Year from 2011 to 2014 369

#35 #33 in Trials50

#36 #34 in Economic Evaluations 16

7: Source: Cochrane Database of Systematic Reviews (CDSR) - Issue 12 of 12, December 2014

Interface / URL: Cochrane Library / Wiley Interscience
Search date: 17/12/14
Retrieved records: 11
Search strategy:

#1 [mh "Critical Care"] 1856
#2 [mh "Intensive Care Units"] 2640
#3 ("acute care" or "critical care" or "critically ill" or critical next illness*):ti,ab,kw 4650
#4 ("high dependency" near/2 (care or unit*)):ti,ab,kw 35
#5 "intensive care":ti,ab,kw 9523
#6 (intensive next therapy next unit*):ti,ab,kw 37
#7 (ITU or ICU or CCU or CICU or CITU or HDU or ITUs or ICUs or CCUs or CICUs or CITUs or HDUs):ti,ab,kw 3342
#8 ("level 2 care" or "level 3 care" or "level two care" or "level three care"):ti,ab,kw 3
#9 {Health and Social Care Information Centre, #1-`#8} 13254
#10 [mh ^"Catheter-Related Infections"] 187
#11 (CA-BSI or CA-BSIs or CABSI or CABSIs or CR-BSI or CR-BSIs or CRBSI or CRBSIs or CLA-BSI or CLA-BSIs or CLABSI or CLABSIs):ti,ab,kw 77
#12 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 607
#13 ((catheter* or microcatheter* or cannula* or microcannula* or canula* or microcanula*) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 1387
#14 (catheter-related or catheter associated):ti,ab,kw 2111
#15 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 6
#16 ((CVC or CVCs or CVL or CVLs or PICC or PICCs or PIV or PIVs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 93
#17 (CVC-related or CVCs-related or CVL-related or CVLs-related or PICC-related or PICCs-related or PIV-related or PIVs-related or CVC-associated or CVCs-associated or CVL-associated or CVLs-associated or PICC-associated or PICCs-associated or PIV-associated or PIVs-associated):ti,ab,kw 55

#18 ((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 19

#19 ((central next line* or venous next line* or intravenous next line* or vascular next line* or intravascular next line* or IV next line* or peripheral next line* or PIC next line* or CVP next line* or arterial next line* or intraarterial next line* or artery next line* or arteries next line* or art next line* or a next line* or IAC or IACs) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 38

#20 ((line-associated or line-related) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti 11

#21 ((line-associated or line-related) near/5 (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs)):ti,ab,kw 27

#22 ([mh ^Catheterization] or [mh ^"Catheterization, Central Venous"] or [mh "Catheterization, Peripheral"] or [mh ^"Cardiac Catheterization"] or [mh Catheters]) and ([mh ^Infection] or [mh ^"Bacterial Infections"] or [mh Sepsis] or [mh ^"Cross Infection"]) 530

#23 ([mh ^Catheterization/AE] or [mh ^"Catheterization, Central Venous"/AE] or [mh "Catheterization, Peripheral"/AE] or [mh ^"Cardiac Catheterization"/AE] or [mh Catheters/AE]) and (infect* or sepsis* or septic* or sepses or postsepsis* or bacteremi* or bacteraemi* or bacillemi* or bacillaemi* or fungemi* or funagemi* or HAI or HAIs or HCAI or HCAIs or BSI or BSIs):ti,ab,kw 623

#24 (or #10-#23) 2893

#25 #9 and #24 Publication Year from 2011 to 2014, in Cochrane Reviews (Reviews and Protocols) 11