NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: The 3M™ Tegaderm™ CHG I.V. securement dressing for central venous and arterial catheter insertion sites

Sponsor: 3M Health Care

Date sections A and B submitted: 18th Nov 2014

Date section C submitted: 16th Dec 2014

August 2011 (Version 1.1)

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with ‘see appendix X’.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Glossary of terms

Term	Definition
CR-BSI	Catheter Related Blood Stream Infection
CLABSI	Central Line Associated Blood Stream Infection
CFU	Colony-Forming unit;
ICU	Intensive Care Unit;
SAPS	Simplified Acute Physiology ;
SOFA	Sequential Organ Failure Assessment
IVCs	Intravascular catheters, both central venous and arterial
CHG	Chlorhexidine Gluconate

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Critically ill adult patients in intensive care or high dependency units who require a central venous or arterial catheter.	None	
Intervention	Swabbing with 2% chlorhexidine gluconate (CHG) in alcohol and Tegaderm CHG IV securement dressing	None	
Comparator(s)	1. Swabbing with 2% CHG in alcohol and sterile semi-permeable transparent dressing 2. Swabbing with 2% CHG in alcohol and CHG impregnated dressing	None	
Outcomes	Catheter related bloodstream infection (CR-BSI) 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	None	
Cost analysis	Two comparators will be considered: □ Swabbing with 2% CHG in alcohol and a sterile semi-permeable transparent dressing □ Swabbing with 2% CHG in alcohol and a CHG impregnated dressing Costs will be considered from an NHS and personal social services perspective. The time horizon for the	None	

	cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	None identified	None	
Special considerations, including issues related to equality	None identified	None	

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Brand name: 3M™ Tegaderm™ CHG Chlorhexidine Gluconate I.V. Securement Dressing,

Available in 4 sizes:

Ref	Size
1660R	7 x 8.5cm
1657R	8.5 x 11.5cm
1659R	10 x 15.5cm
1658R	10 x 12cm

2.2 What is the principal mechanism of action of the technology?

Securement of percutaneous devices, in particular to cover and protect central venous and arterial catheter insertion sites with the aim of providing an effective barrier against external contamination through release of chlorhexidine gluconate which has antiseptic action

3M™ Tegaderm™ CHG Chlorhexidine Gluconate I.V. Securement Dressing, is used to cover and protect catheter sites and to secure devices to skin. It is available in a variety of shapes and sizes. Tegaderm CHG dressing consists of a transparent adhesive dressing and an integrated gel pad containing 2% w/w chlorhexidine gluconate (CHG), an antiseptic agent with broad spectrum antimicrobial and antifungal activity. The gel pad absorbs fluid. The transparent film provides an effective barrier against external contamination including fluids (waterproof), bacteria, viruses and yeasts, and protects the I.V. site.

In vitro testing (time kill and zone of inhibition) demonstrates that the Tegaderm CHG gel pad has an antimicrobial effect against a variety of gram-positive and gram-negative bacteria, and yeast, including organisms most commonly associated with catheter-related bloodstream infections (CR-BSI).

Tegaderm CHG dressing is transparent, allowing continual site observation, and is breathable, allowing good moisture vapour exchange.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

For use in critically ill adult patients in intensive care or high dependency units who require a central venous or arterial catheter. Hospital Episodes Statistics (HES) data for England and Wales 2012/13 show that there were 237,710 adult ICU episodes in England, most of whom require a central venous catheter and/or arterial catheter.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

NICE clinical guideline 139, March 2012 provides guidance on the using dressings in adults and children with vascular access devices (central venous catheter (CVC) or peripherally inserted central catheter (PICC)) in primary and community care settings. The guideline recommends that the skin at the CVC insertion site, and the surrounding skin during dressing changes, should be decontaminated with chlorhexidine gluconate in 70% alcohol and be allowed to air dry.

Where the manufacturer's recommendations prohibit the use of alcohol with their catheters, an aqueous solution of chlorhexidine gluconate should be considered for use. It further recommends using a sterile, transparent semi-permeable membrane dressing to cover the vascular access device insertion site, and that the dressing should be changed every 7 days or sooner if it is no longer intact or moisture collects under it. A sterile gauze dressing, covered with a sterile transparent semi-permeable dressing, should be considered for use only if the patient has profuse perspiration, or if the vascular access

device insertion site is bleeding or oozing. The guideline states that systemic antimicrobial prophylaxis should not be used routinely to prevent catheter colonization or CR-BSI, either before insertion or during the use of a central venous catheter.

CG139 made no recommendations on CHG impregnated dressings. The full guideline states that they may be cost effective compared with sterile transparent semi-permeable membrane (film) dressings.

The **epic3 guideline** (Healthcare Infection Society, 2013) on preventing healthcare-associated infections in NHS hospitals in England recommends using a sterile transparent semi-permeable dressing to cover the intravascular insertion point as best practice in both adults and children. The guideline recommends, based on high-quality evidence (stated as Grade A), a single application of 2% CHG in 70% isopropyl alcohol (or povidone iodine alcohol for patients with sensitivity to CHG) to clean the central catheter insertion site during dressing changes, and allow to air dry. The guidance also recommends, that hospitals consider the use of a CHG impregnated sponge dressing in adults with a CVC, as a strategy to reduce CR-BSI.

NICE evidence update 64, Infection (September 2014) states that the evidence on which the epic3 recommendation (on CHG impregnated sponges in adults with a CVC) is based is unlikely to have an impact on NICE clinical guideline 139, and that further research is needed to establish the efficacy of CHG dressings applied to CHG-prepped skin to prevent CR-BSI in patients with venous access devices.

The Guidelines for the Prevention of Intravascular Catheter-Related Infections, (HICPAC 2011) provide guidance on use of dressings and chlorhexidine dressings.

A Category IA recommendation is to use either sterile gauze or sterile, transparent, semi permeable dressing to cover the catheter site.

Also, use a chlorhexidine-impregnated sponge dressing for temporary short-term catheters in patients older than 2 months of age if the CLABSI rate is not

decreasing despite adherence to basic prevention measures, including education and training, and appropriate use of chlorhexidine for skin antisepsis.

Category 1B - no recommendation is made for other types of chlorhexidine dressings which at that time were regarded as an unresolved issue.

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

Tegaderm CHG dressing is used as a direct replacement for either sterile gauze or sterile, transparent, semi permeable dressings in the local protocol describing management of the intravascular catheter insertion site and secural. Following the successful insertion of the intravascular catheter, the site is cleansed and skin antisepsis occurs in line with local protocol. The skin is allowed to air dry and the Tegaderm CHG dressing is applied so the gel pad covers the insertion site. The sterile tape strips may be applied either under or over the dressing to better secure the catheter in place. In common with sterile, transparent, semi permeable dressings, the dressing has a recommended maximum wear time of seven days. In common with all I.V. site dressings, the dressing should be changed where the protection of the site is compromised by adhesive failure or moisture has accumulated at the site.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

None known. Our experience from our communications with clinical professionals working in critical care units, is that the recommendations by NICE guideline 139 and epic3 guideline are generally followed with the majority of sites using 2% chlorhexidine gluconate in alcohol to provide skin antisepsis at the insertion site. Generally a sterile, transparent, semi permeable dressing is used to dress the site once the skin disinfectant is dry.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

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. In common with the current protocol of care the insertion site requires observing several times a day to check for any signs of inflammation or other indicators of infection or moisture accumulation.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

None are anticipated.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

None are anticipated.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None are anticipated**.**

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

None are anticipated

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in

section 3.9 that would no longer be needed with using this technology.

Not applicable

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

PDF copies of these documents accompanies this application

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The technology is CE marked and has licensed indications as follows: 3M™ Tegaderm™ CHG Chlorhexidine Gluconate IV Securement Dressing can be used to cover and protect catheter sites and to secure devices to skin. Common applications include central venous and arterial catheters, other intravascular catheters and percutaneous devices. Tegaderm CHG dressing is intended to reduce skin colonization and catheter colonization and to suppress re-growth of microorganisms commonly related to blood stream infections. Tegaderm CHG dressing is intended to reduce catheter-related bloodstream infections (CR-BSI) in patients with central venous or arterial catheters.

Authorisation was received in April 2009 and was updated to include the indication for reduction in CR-BSI in Feb 2014.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The technology is currently available in all territories that accept the CE mark for medical devices (EU, Australia), plus other territories including Canada, USA, Japan, China, South Africa, Brazil and Mexico,

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Not applicable

4.5 If the technology has been launched in the UK provide information on the use in England.

The technology has been available in the UK since 2009 with a revised version launched in 2012. Current estimates of use indicate approximately 15% use in the scoped population in England.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

A health economic analysis comparing the notified product to sterile semi-permeable transparent dressing has been prepared and is currently awaiting journal acceptance.

A comparative study at a major clinical centre in UK is ongoing with patient data collection ongoing. A poster presentation containing the results of the initial data analysis of a comparative study in 273 intensive care unit patients has been accepted for presentation at The Hospital Infection Society Conference, Lyon, Nov. 2014. This study was not powered to detect differences in CR-BSI 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.

3M Health Care collects medico-vigilance data on Tegaderm CHG dressing, the database being updated for each new event.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

Not applicable

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

None are anticipated

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None are anticipated

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

Not applicable

Bibliography for Section A

- O'Grady, N.P., Alexander, M., Burns, L.A., Dellinger, E.P., Garland, J., Heard, S.O., Lipsett, P.A., Masur, H., Mermel, L.A., Pearson, M.L., Raad, I.I., Randolph, A.G., Rupp, M.E., and Saint, S. Guidelines for the prevention of intravascular catheter-related infections. *American Journal of Infection Control* 2011; **39**(4 SUPPL.), S1-S34.

- Infection prevention and control. Nice Quality Standard, QS61, April 2014. Available from: http://www.nice.org.uk/guidance/QS61

- Infection: Prevention and control of healthcare-associated infections in primary and community care. NICE Clinical Guideline, CG139, March 2012. Available from: http://guidance.nice.org.uk/CG139

- NICE evidence update 64, Infection (September 2014) A summary of selected new evidence relevant to NICE clinical guideline 139 'Prevention and control of healthcare-associated infections in primary and community care' (2012). Available from: https://www.evidence.nhs.uk/ evidence-update-64

- Loveday HP, Wilson JA, Pratt RJ, et al. epic3: National evidence based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect 2014;86(Suppl. 1):S1eS70.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

A systematic review was undertaken in accordance with recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[1] The purpose of the review was to evaluate the effectiveness and safety of 3M™ Tegaderm™ CHG Chlorhexidine Gluconate I.V. Securement Dressing (Tegaderm CHG dressing) containing 2% chlorhexidine gluconate (3M Health Care, St. Paul, MN, USA) dressings compared to other dressings (used in standard or usual care) in patients (age >18 years) admitted to a critical care setting such as an intensive care unit (ICU) who required intravascular access – via an arterial catheter or central venous catheter or both – for at least 24 hours.

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

Systematic searches were carried out to retrieve relevant comparative studies from published and unpublished sources. For published studies, the following databases were searched on 23rd July 2013:

- MEDLINE and MEDLINE in Process: Ovid. 1946 to Present
- EMBASE: Ovid. 1974 to 2013 July 17
- Cochrane Library
- Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
- Cochrane Central Register of Controlled Trials (CCRT): Wiley Interscience. 1898-present
- Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
- Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
- NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present
- EconLit: Ovid. 1961 to June 2013

The search approach and strategies were designed to retrieve all studies irrespective of study design relating to the technology and relevant comparators. Comparators of interest included dressings used as part of standard care or usual care in patients with intravascular catheters. Such dressings included chlorhexidine-sponge dressings (Biopatch) and non-medicated (active) transparent film dressings (e.g. 3M™ Tegaderm™ HP Transparent Film Dressing and IV3000 dressing). Figure 1 and Figure 2

summarise the framework used for developing the respective search strategies. Searches for central venous catheterisation and arterial catheterisation with comparators were carried out separately (see Appendix 10.1).

Figure 1: Framework for the search strategy for the intervention

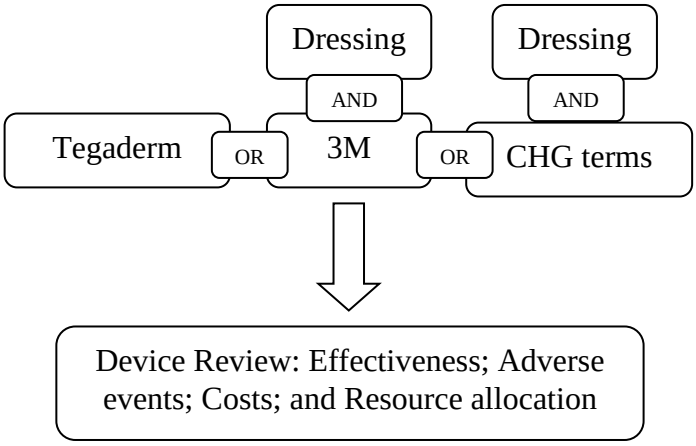
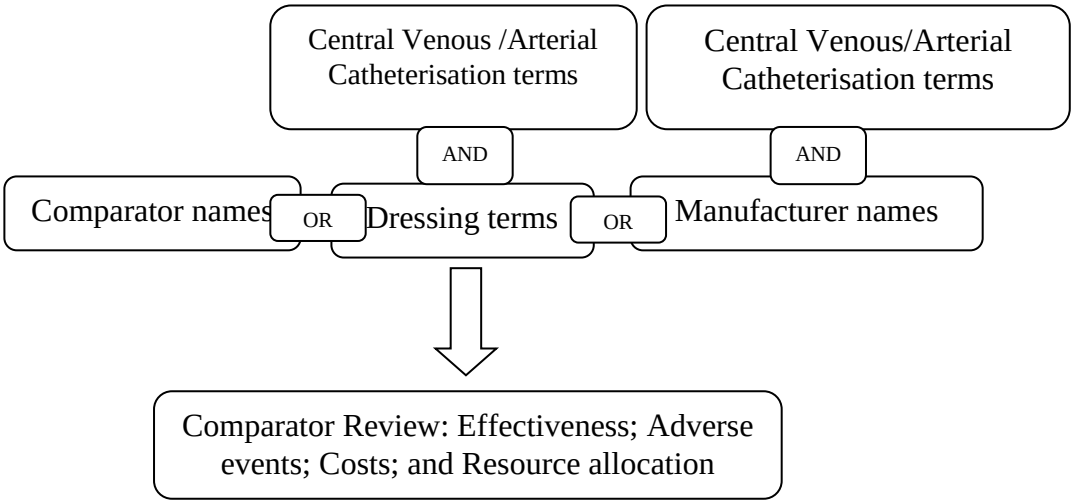


Figure 2: Framework for the search strategy for potential comparators



No limits in terms of date, language or study design were applied to the searches. All search strategies are provided in Section 10, Appendix 10.1.

Studies were also identified from reference tracking of included studies, identified reviews and relevant guidelines. Key investigators were also contacted for information about completed studies.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Grey literature searching included searches for conference abstracts, clinical trial records and medical device reports. Health agency websites were also searched. Sources searched included the following:

- Conference Proceedings Citation Index – Science (CPI-S): Web of Science. 1990-present
- Clinicaltrials.gov http://clinicaltrials.gov/ (accessed 30th July 2013 and 30th August)
- FDA (http://www.fda.gov/) Manufacturer and User Facility Device (MAUDE) (accessed 29th July 2013 and 30th August)
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
- EuroScan http://euroscan.org.uk/ (accessed 29th July 2013)
- MHRA http://www.mhra.gov.uk/ (accessed 29th July 2013 and 30th August)
- EMEA http://www.ema.europa.eu/ (accessed 29th July 2013)

Additionally, key investigators were contacted for information about unpublished or on-going studies.

7.2 Study selection

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Published studies

The aim of the systematic review was to evaluate the effectiveness and safety of Tegaderm CHG dressings compared to other dressings (as earlier described) in patients (aged>18 years) admitted to a critical care setting

requiring intravascular access – via an arterial catheter or central venous catheter or both. Outcome data considered were those that were assessed using reliable and valid methods. The primary outcome of interest was the incidence of catheter-related blood stream infection (CR-BSI). The choice of the primary outcome was based on empirical evidence.[2-4] According to the Guidelines for the Prevention of Intravascular Related Infections:[5]

'CR-BSI is a clinical definition, used when diagnosing and treating patients, that requires specific laboratory testing that more thoroughly identifies the catheter as the source of the (bloodstream, infection) BSI.'

Secondary outcomes considered included:

(i) Outcomes relating to effectiveness: incidence of catheter colonisation; incidence of skin colonisation;

(ii) Outcomes relating to safety: number of events or frequency of adverse events (including serious adverse events);

(iii) Outcomes relating to performance: number of events or frequency of catheter failure resulting from forced or accidental dislodgement, dislocation or removal, dressing change due to dislodgement or soiling etc.

The review also sought to identify non-randomised, comparative studies (with sample size > 10 and loss to follow-up < 50%) that provided data for (ii) and (iii) to ensure that additional information on outcomes other than effectiveness was captured in the review.

The pre-defined eligibility criteria relating to population, intervention, comparators, outcomes and search limits were the same for published and unpublished evidence. Criteria for considering published studies for this review are summarised in Table B1 on the following pages.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Populations	Patients (age ≥ 18 years) admitted to an intensive care unit (ICU) or any critical care setting requiring an intravascular catheter (IVC) inserted after admission for at least 48 hours. IVCs considered included: (i) Short-term central venous catheters (CVCs) inserted via the subclavian, internal jugular or femoral vein (ii) Long-term CVCs inserted peripherally via the cephalic, basilic or brachial vein (peripherally inserted catheters, PICCs) (iii) Arterial catheters inserted via the radial, ulnar, brachial, femoral or dorsalis pedis artery
Interventions	Intervention (i) Chlorhexidine-containing Tegaderm dressing (Tegaderm CHG dressing) Comparators Any standard intravascular dressings used in routine care including: (i) chlorhexidine-sponge dressing (Biopatch) (ii) any transparent film dressing including Tegaderm non-medicated dressings, IV 3000 (iii) gauze and tape, etc. (iv) no dressing Duration of dressing: at least 24 hours
Outcomes	Outcomes relating to effectiveness: (i) Incidence of catheter related blood stream infection

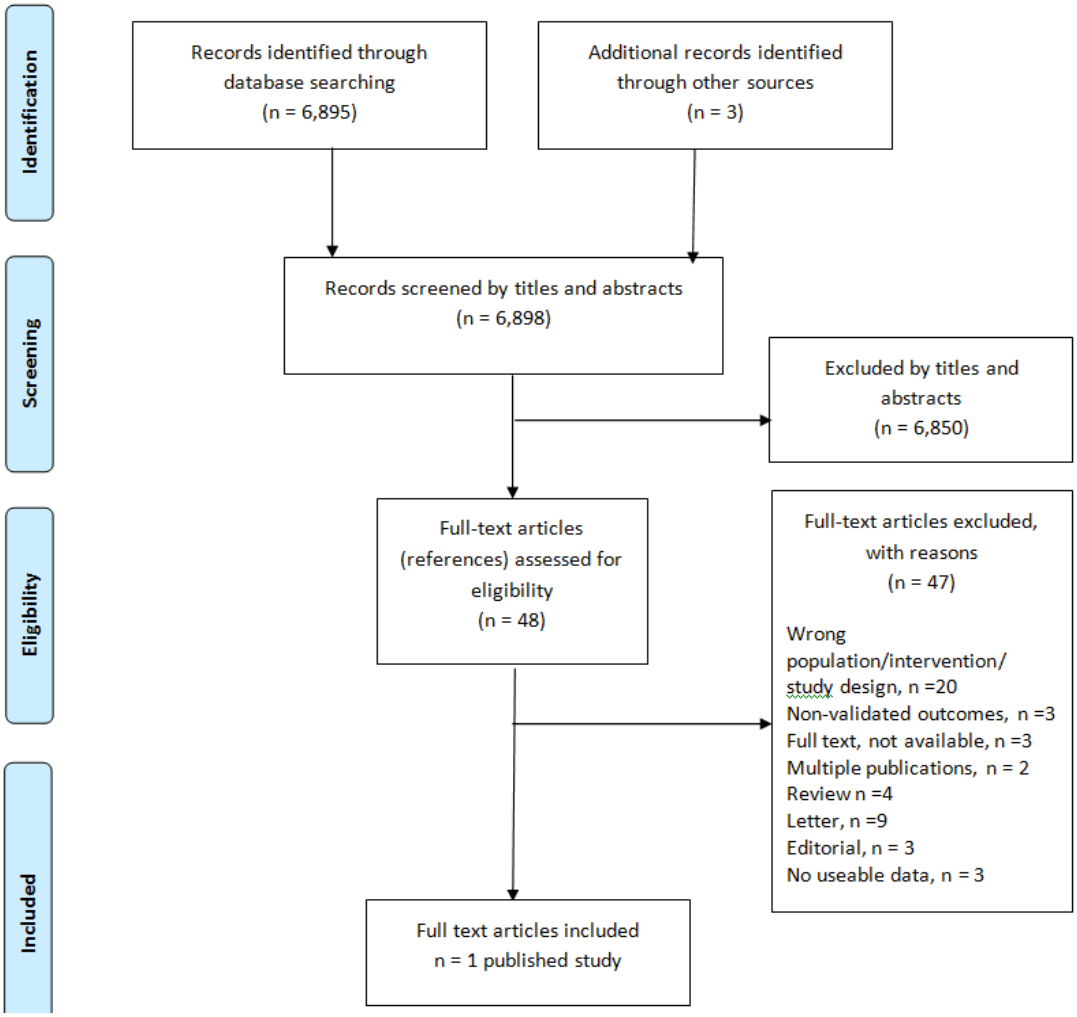
	(primary outcome) (ii) Skin colonisation (iii) Catheter colonisation Outcomes relating to safety: (i) Serious adverse events* including death, anaphylactic shock (ii) Other adverse events including contact dermatitis, skin allergies Outcomes relating to performance: (i) Catheter security or movement or dislodgement (ii) Frequency of dressing change due to dislodgement, soiling etc.
Study design	(i) Randomised controlled trials only for effectiveness outcomes (ii) Comparative studies with at least 10 patients and/ or loss to follow-up < 50% for safety and performance outcomes
Language restrictions	English
Search dates	None
Exclusion criteria	
Populations	(i) Patients (age < 18 years) admitted to ICU in need of intravascular access (ii) Patients (age ≥ 18 years) with IVCs inserted prior to admission on ICU or requiring an IVC for less than 24 hours (iii) Adult patients requiring IVCs but not in a critical

	setting, e.g. haemodialysis unit (iv) Insufficient information to identify relevant patient population
Interventions	(i) Unspecified Tegaderm dressing type (ii) Insufficient details to identify type of dressing
Outcomes	(i) Relevant outcomes not reported according to allocated treatment (ii) Insufficient information to assess validity and reliability of reported outcomes
Study design	(i) Cross-over randomised trials (ii) Cluster-randomised trials (iii) Comparative studies with less than 10 patients and/ or loss to follow-up > 50%
Language restrictions	Non-English
Search dates	None
*A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening (i.e. at risk of death at the time of the event), requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, congenital anomaly or birth defect. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf)	
Abbreviations: CHG, chlorhexidine gluconate; CVC, central venous catheter; ICU, intensive care unit; IVC, intravascular catheter	

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

See Figure 3 Flow chart (adapted)[1]: Study selection for clinical effectiveness review of Tegaderm CHG dressing (below).

Figure 3: Flow chart (adapted)[1]: Study selection for clinical effectiveness review of Tegaderm CHG dressing



Study selection was undertaken using a two-step process:

At the outset, all titles were examined for inclusion by one reviewer using the pre-specified eligibility criteria summarised in Table B1. Any citations that clearly did not meet the inclusion criteria (i.e. non-human, unrelated to dressings for IVC exit sites) were excluded. Subsequently, all abstracts and full text articles were examined by one reviewer and checked by a second reviewer. The decisions were coded and recorded in a Reference Manager database by the one reviewer. Disagreements were resolved by discussion between the two reviewers. During this stage of study selection, identified multiple publications of the same study were linked and considered as a single report to provide the most recent or comprehensive evidence from the study.

Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Populations	Patients (age ≥ 18 years) admitted to an intensive care unit (ICU) or any critical care setting requiring an intravascular catheter (IVC) inserted after admission for at least 48 hours. IVCs considered included: (i) Short-term central venous catheters (CVCs) inserted via the subclavian, internal jugular or femoral vein (ii) Long-term CVCs inserted peripherally via the cephalic, basilic or brachial vein (peripherally inserted catheters, PICCs) (iii) Arterial catheters inserted via the radial, ulnar, brachial, femoral or dorsalis pedis artery
Interventions	Intervention (i) Chlorhexidine-containing Tegaderm dressing (Tegaderm CHG dressing) Comparators Any standard intravascular dressings used in routine care including: (i) chlorhexidine-sponge dressing (Biopatch) (ii) any transparent film dressing including Tegaderm

	non-medicated dressings, IV 3000 (iii) gauze and tape, etc. Duration of dressing: at least 24 hours
Outcomes	Outcomes relating to effectiveness: (i) Incidence of catheter related blood stream infection (primary outcome) (ii) Skin colonisation (iii) Catheter colonisation Outcomes relating to safety: (i) Serious adverse events* including death, anaphylactic shock (ii) Other adverse events including contact dermatitis, skin allergies Outcomes relating to performance: (i) Catheter security or movement or dislodgement (ii) Frequency of dressing change due to dislodgement, soiling etc.
Study design	Comparative studies with at least 10 patients and/ or loss to follow-up < 50% However, comparative studies were limited to randomised controlled trials only for effectiveness outcomes
Language restrictions	English
Search dates	None
Exclusion criteria	
Populations	(i) Patients (age < 18 years) admitted to ICU in need of intravascular access

	(ii) Patients (age ≥ 18 years) with IVCs inserted prior to admission on ICU or requiring an IVC for less than 24 hours (iii) Adult patients requiring IVCs but not in a critical care setting, e.g. haemodialysis unit (iv) Insufficient information to identify relevant patient population
Interventions	(i) Unspecified Tegaderm dressing type (ii) Insufficient details to identify type of dressing
Outcomes	(i) Relevant outcomes not reported according to allocated treatment (ii) Insufficient information to assess validity and reliability of reported outcomes
Study design	(i) Cross-over randomised trials (ii) Cluster-randomised trials (iii) Comparative studies with less than 10 patients and/ or loss to follow-up > 50%
Language restrictions	Non-English
Search dates	None
*A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening (i.e. at risk of death at the time of the event), requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, congenital anomaly or birth defect. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf)	
Abbreviations: CHG, chlorhexidine gluconate; CVC, central venous catheter; ICU, intensive care unit; IVC, intravascular catheter	

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

After de-duplication of retrieved records, there were 6,895 citations obtained from database searching. Three additional records[6-8], including a report of an interim analysis of a terminated study, were obtained following contact with investigators. Of the retrieved records, 1 published study[9] met the pre-specified inclusion criteria. A flow chart outlining the process of study selection is presented below. A list of excluded studies with reasons is presented in the *Section B supplementary file Tegaderm CHG, table A.* Of these, there were 3 RCTs[7;10;11] that were not eligible for inclusion in this review. The studies contributed no data in relation to pre-specified effectiveness outcomes. Additionally, reported outcomes were nursing satisfaction and performance outcomes using non-validated methods. A summary of outcomes reported in the 3 studies are presented in *Section B supplementary file Tegaderm CHG, table B.*

Section B Supplementary file_

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

The details of all published and unpublished studies that compare the technology with other treatments for the relevant group of patients should be presented using tables B3 and B4 respectively. The studies that compare the intervention directly with the appropriate comparator(s) referred to in the decision problem should be clearly highlighted. If there are none, please state this. All types of studies should be considered, including observational studies such as cohort, case series and case-control studies, and single case reports and qualitative studies when relevant to the scope.

The list of relevant studies must be complete and will be validated by independent searches conducted by the External Assessment Centre.

Published studies should be referenced by first author name and year of publication. Unpublished studies should be referenced by first author and date of report. Full details of each reference should be provided in the reference list after section 9. In addition, list any trial short names if useful.

Table B3 List of relevant published studies

Primary study reference	Clinical trial Identifier/acronym	Population	Intervention	Comparator
Maryniak 2009[10]	NR	Patients with CVCs [Acute medical unit] (n=217)	Tegaderm CHG dressing (n=107)	standard transparent dressing (IV3000™, Smith & Nephew) (n = 110)
Olson 2008[6;11]	NR	Patients with CVCs and PICCs [ICUs, acute and sub-acute medical-surgical units] (n = 63)	3M™ Tegaderm™ CHG (chlorhexidine gluconate) dressing (n = 33)	3M ™Tegaderm™ IV transparent film dressing (n = 30)
Rupp 2008 [7]	NR	Patients with CVCs [Setting , not reported] (n=60)	3M™ Tegaderm™ CHG (chlorhexidine gluconate) dressing (n=30)	standard transparent dressing (IV3000™, Smith & Nephew) (n = 30)
Timsit 2012[9]	NCT 01189682/ Timsit 2012	Patients with CVCs and/or	3M™ Tegaderm™ CHG	3M Tegaderm™ HP Transparent Film

		arterial catheters [ICUs] (n = 1,879)	(chlorhexidine gluconate) dressing (n = 938)	Dressing [highly adhesive dressing] (n =465) 3M Tegaderm™ Transparent Film Dressing [standard breathable, hypoallergenic dressing] (n = 476)

Table B4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Scopettuolo 2012[8]	(NCT01142934)	601 patients (ICU and non-ICU settings including General surgery and Palliative care)	3M™ Tegaderm™ CHG (chlorhexidine gluconate) dressing (n = 302)	standard Tegaderm dressing without CHG (n = 299)

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

Five publications[6;8,7;10;11] including one abstract of a conference poster were identified that compared the intervention of interest, Tegaderm CHG (chlorhexidine gluconate) dressing to relevant comparators. Of these, three reports were excluded as these studies did not contribute data to the primary outcome, incidence of CR-BSI. Additionally, all three studies reported nursing satisfaction and performance outcomes related to use of the dressings under

investigation. These outcomes were evaluated with instruments or scales that could not be validated. A summary of the outcomes presented in these studies are shown in supplementary file, table B.

Unpublished evidence retrieved was related to an interim analysis of a terminated study[8] comparing Tegaderm CHG dressing to standard Tegaderm dressing without CHG. The study with a start date, October 2009, was terminated because of slow recruitment of participants. Information on the clinicaltrial.gov web-page projected a sample size of 1,200 participants. The interim report, dated November 2012, indicated that there were 'approximately 640 patients' enrolled at the time of analysis. However, the document noted that 4 of the 302 patients in the intervention group and 11 of the 299 patients in the comparator group developed CR-BSI. Furthermore, the study setting included ICU and non-ICU setting such as general surgery and palliative care units. As the data presented in the interim report did not lend itself to abstracting data for the relevant patient population, that is, patients in ICUs only, this report was excluded from the current review.

Overall, one study was considered eligible for inclusion in this systematic review. This study conducted in France from 31st May 2010 to 29th July 2011 by Timsit and colleagues[9], was a large, multicentre randomised controlled trial (n = 1,879 patients).

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Data extraction and quality assessment were conducted independently by two reviewers. Disagreements were resolved by discussion between the two reviewers. The study design and methodology used in the Timsit 2012 study[9] is summarised in Table B5. The study, conducted in 12 medical and surgical ICUs of 7 university and 4 general hospitals in France, was a 2:1:1 assessor-

blinded randomised trial (n = 1,879 patients) that compared three different transparent dressings used a part of standard care in patients with intravascular catheters. The dressings evaluated were Tegaderm CHG dressing and two non-chlorhexidine dressings: (1) 3M™ Tegaderm™ HP Transparent Film Dressing, a highly adhesive dressing and (2) 3M™ Tegaderm™ Transparent Film Dressing, a standard breathable, hypoallergenic dressing.

Eligible patients (aged >18 years) were individuals with CVCs and/ or arterial catheters required for a minimum duration of 48 hours. Patients with peripherally inserted venous catheters, haemodialysis catheters, pulmonary arterial catheters, antiseptic- or antibiotic-impregnated catheters or catheters inserted prior to ICU admission were excluded from the study. Patients with known allergies to chlorhexidine were also excluded.

All study centres followed locally accepted recommendations similar to those of the Centres for Disease Control and Prevention principles[5] for catheter insertion and care. Preferred insertion sites were the subclavian vein for CVCs and the radial artery for arterial catheters. Catheter care bundle included maximal sterile barrier safety measures (that is the use of surgical hand antisepsis, wearing of a sterile gloves, mask, cap and gown and using large sterile drape) at the time of catheter insertion. Antiseptic skin preparation with alcoholic povidone-iodine(PVI) or alcoholic chlorhexidine solution was undertaken during catheter insertion and change of dressing. Dressing change was performed on Day 1 (24 hours after catheterisation), then on Day 3 or Day 7 as per local protocol. However, immediate change of dressing was performed if there was soiling or leaking of the applied dressing. Intravascular catheters were removed immediately if a catheter-related infection (CRI) was suspected or when the catheter was no longer needed.

The study evaluated a number of relevant outcomes as summarised in Table B5. The primary outcomes of the study was the incidence of catheter-related infections (CRI) for chlorhexidine dressing versus non-CHG dressings and the incidence of catheter colonisation for highly adhesive dressings versus standard dressing (non-CHG dressings). CRI was limited to catheter-related

clinical sepsis or CR-BSI. Secondary outcomes assessed included the rate of dressing change due to detachment, skin colonisation and incidence of CR-BSI. A post-hoc analysis was also conducted to estimate rates of central line-associated bloodstream infection (CLABSI) as defined by the Centers for Disease Control and Prevention.[5]

Descriptive statistics used for categorical variables and continuous variables representing characteristics of patients, dressings and catheters were numbers (percentage) or median (inter-quartile ranges) respectively. Variables were analysed using the chi-square test or Mann-Whitney tests as appropriate. Analysis followed an intent-to-treat approach and was stratified by ICUs. As it was expected that eligible patients may have more than one catheter *in situ*, the effect of clustering (that is multiple catheters per patient) was addressed by using a marginal Cox model for clustered data. However, for skin colonisation, the effect of clustering was not considered. As an alternative, skin colonisation was categorised into 4 distinct classes based on colony-forming units (CFUs) of skin cultures. These were as follows: (i) sterile, (ii) CFU < 1 log 10, (iii) CFU = 1 -2 log 10, and (iv) CFU ≥ 2 log 10. Skin counts of CFUs between treatment groups (CHG dressings and non-CHG dressings) were compared by performing a Mann-Whitney test. Risks of major CRIs and catheter colonisations for treatment groups were presented as Kaplan Meier plots.

Table B5 Summary of methodology for randomised controlled trials

Study name	Timsit 2012 [9]
Objectives	To establish the effect of chlorhexidine-impregnated dressings and strongly adherent dressings on the reduction of catheter-related infection (CRI)and catheter colonisation rates in patients admitted to an intensive care unit (ICU)requiring an intravascular catheter for a minimum duration of 48 hours
Location	Twelve medical and surgical ICUs of 7 university and 4 general hospitals in France
Design	Multicentre, single-blinded[1], 2:1:1 randomised controlled trial
Duration of study	13 months (31st May 2010 to 29th July 2011)
Sample size	1,879 patients Total number of catheters, n = 4,163 (central venous catheters, n=1,962; arterial catheters, n = 2,201) Total number of catheter-days, n = 34,339 catheter days
Inclusion criteria	Patients (age, 18 years old or older) admitted to an ICU and requiring an intravascular catheter for at least 48 hours
Exclusion criteria	Patients allergic to chlorhexidine or transparent dressings. Catheter types excluded were as follows: antibiotic or antiseptic - impregnated catheters haemodialysis catheters; pulmonary arterial catheters and peripherally inserted venous catheters
Method of randomisation	Block randomisation using a web-based random number generator, stratified according to ICUs. Within each permuted block, there were 4 allocations to the chlorhexidine-containing dressing (Tegaderm CHG) and two allocations each to the non-chlorhexidine dressings, (1) highly adhesive dressing (Tegaderm HP Transparent Film Dressing) and (2) standard breathable, hypoallergenic dressing (Tegaderm Transparent Film Dressing)
Method of blinding	Outcome assessors - microbiologists, an external investigator, a clinical research monitor together with an independent adjudication committee - were masked to study groups.

Intervention(s) (n =) and comparator(s) (n =)	Intervention: chlorhexidine-containing dressings (Tegaderm CHG), n = 938 patients (2,108 catheters) Comparators: non-CHG dressings (1)highly adhesive dressing (Tegaderm HP Transparent Film Dressing), (n = 465 patients; 988 catheters) and (2) standard breathable, hypoallergenic dressing (Tegaderm Transparent Film Dressing), (n = 476 patients; 1,067 catheters)
Baseline differences	At baseline, patients in treatment group were comparable with respect to age, gender, Simplified Acute Physiology II (SAPS II) scores, Sequential Organ Failure Assessment (SOFA) scores and the presence of at least one chronic disease. Additionally, the main reason for admission of patients (septic shock, cardiogenic shock, de novo respiratory failure, coma, trauma and need for mechanical ventilation) was similar between treatment groups. However, compared to the non-CHG group, there were more patients with haematological malignancies (3.3% versus 2.3%) and metastatic cancer (6.6% versus 5.9%) in the CHG group.
Duration of follow-up, lost to follow-up information	48 hours after discharge from ICU. We have discussed with the investigators and they report no patients were lost to follow up.
Statistical tests	Analyses were stratified by ICUs and undertaken using an intention-to-treat approach. Where appropriate, continuous data between study groups were compared using the Mann-Whitney test. The chi-squared test was used for categorical data. Risk of major CRI and catheter colonisation for each study group were plotted in Kaplan-Meier curves. A marginal Cox model was used to address possible clustering for individual patients with more than one catheter *in situ.* Cochran-Armitage test.
Primary outcomes (including scoring methods and timings of assessments)	(1) Major CRI [for chlorhexidine dressings versus non-chlorhexidine dressings] • A major CRI was considered as a catheter-related clinical sepsis or CR-BSI. Catheter related clinical sepsis was evidence of (i)a body temperature ≤ 36.5°C or ≥ 38.5°C; (ii)catheter colonisation;(iii) pus at the site of catheter insertion or resolution of clinical sepsis

	following removal of catheter [occurring within 24 hours and before any change in anti-microbial treatment] and (iv)absence of any other source of infection. • A CR-BSI is defined under 'Secondary outcomes'. In the event of a suspected major CRI, at least one peripherally obtained blood sample was taken for microbiological culture. These samples could be obtained at the time of catheter removal or with the catheter in situ. If the catheter was removed, a catheter tip culture was also performed. An external investigator assisted by a senior clinical research monitor, both blinded to the study groups collated all information from medical charts and case reports for a masked independent adjudication committee to classify all events according to agreed internationally validated criteria.[12;13] (2) Incidence of catheter colonisation [for highly adhesive non-chlorhexidine dressings versus standard non-chlorhexidine dressing] • If the catheter was removed, catheter colonization was defined as positive quantitative catheter-tip culture ≥1000 colony-forming units per millilitre (CFU/ml) using the vortexing technique or ≥100 CFU/ml using the sonication method. • When the catheter was *in situ,* catheter colonisation was considered in the event of a positive culture of blood sampled from the catheter hub.

Secondary outcomes (including scoring methods and timings of assessments	(1) Rate of dressing change due to detachment • According to the study protocol, dressing changes occurred 24 hours after catheter insertion and then every 3 or 7 days according to standard procedures in participating ICUs. Dressings were changed immediately if it was soiled or if there was a leakage at the site. No information was available describing dressing change due to detachment. (2) Incidence of catheter-related bloodstream infection(CR-BSI) • CR-BSI was defined as clinical evidence of (i) one or more positive peripheral blood culture taken either within 48 hours or immediately before catheter removal; (ii) positive quantitative culture of catheter tip [defined as growth ≥ 100 CFU/ml using the sonication technique or ≥1,000 CFU/ml using the vortexing technique for the similar micro-organism (same species and susceptibility pattern) as identified in peripheral blood culture] or a differential time-to-positivity of 2 hours or more for simultaneously sampled blood and catheter cultures [in patients who had to keep catheters in situ after ICU discharge]; (iii) no other source of infection. (3) Incidence of skin colonisation • This outcome was based on the number of colony-forming units in a semi-quantitative culture over a 48-hour period obtained by pressing the centre of a sterilised nutritive plate of antiseptic -neutralising containing trypticase-soya agar (Count-TactTM, 3P Pack+, BiomerieuxTM, Crapone, France) over the insertion site for 10 seconds. (4) Incidence of contact dermatitis or skin allergy • This was assessed by a dermatologist.
[1] The study was masked to the adjudication committee and microbiologists who	

processed samples of catheter and skin cultures but not to the study investigators and ICU staff.

Table B6 Summary of methodology for observational studies

Study name: Not applicable
Objective
Location
Design
Duration of study
Patient population
Sample size
Inclusion criteria
Exclusion criteria
Intervention(s) (n =) and comparator(s) (n =)
Baseline differences
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up
Statistical tests
Primary outcomes (including scoring methods and timings of assessments)
Secondary outcomes (including scoring methods and timings of assessments)

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Not applicable

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

Not applicable

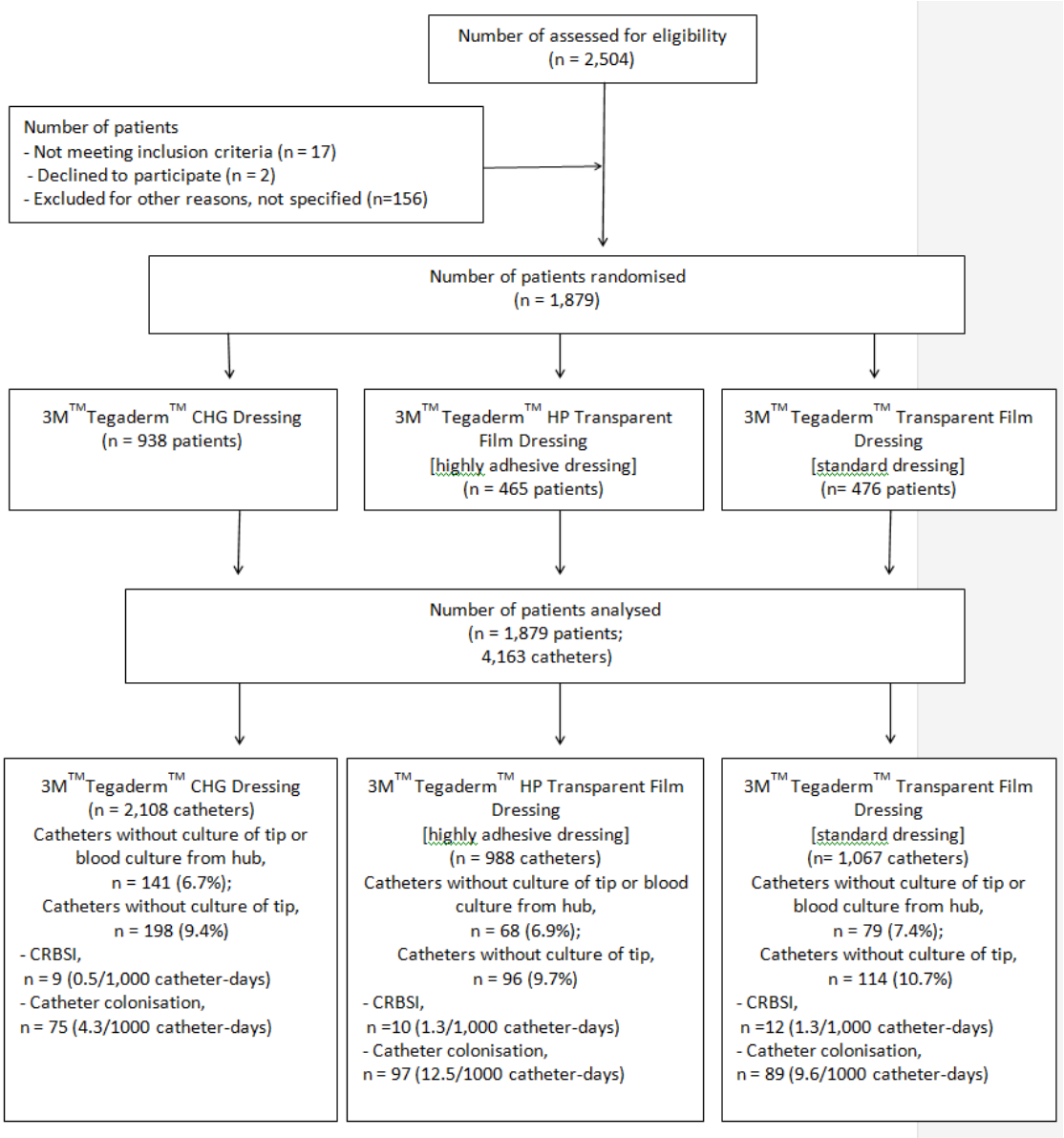
7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

A post-hoc sub-group analysis was conducted for patients with CVCs and arterial catheters. The rationale for this analysis was not reported by the investigators.

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

The number of eligible patients enrolled and analysed in this study is summarised in the Figure 4, flow chart below.

Figure 4 Flow chart of patients showing number of eligible patients enrolled and analysed in the included study



The investigators are not able to provide any explanation for the reasons that the 156 patients were excluded. The 17 patients assessed not to meet the inclusion criteria were under the age of 18 at that time.

It is recommended that details of the numbers of patients that were eligible to enter the study(s), randomised and allocated to each treatment are presented as CONSORT flow charts if possible (see www.consort-statement.org/consort-statement/).

7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

In total, 22 patients in the CHG group had dressings with Tegaderm CHG dressing discontinued because they developed severe dermatitis. Patients were maintained in the original randomized group (ITT analysis) and infection, colonization data from these was included in the analysis according to their randomization.

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

7.5.2 Quality assessment

The methodological quality of included randomised control trial was assessed by one reviewer using the criteria proposed by Centre for Reviews and Dissemination. Decisions relating to items assessed are summarised and presented in Table B7.

Table B7 Critical appraisal of randomised control trials

Study name	Timsit 2012[9]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study**
Was randomisation carried out appropriately?	Yes	Randomisation was achieved by using a web-based random number generator to obtain blocks of 8 (4 allocations to CHG dressings and 2 for each of the non-CHG dressings). Randomisation was stratified by ICUs.
Was the	Yes	The method used was not described;

concealment of treatment allocation adequate?		however the report indicated that investigators were not aware of block size or permutation procedure.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	At baseline, patients in treatment group were comparable with respect to age, gender, the presence of at least one chronic disease, Simplified Acute Physiology II (SAPS II) and Sequential Organ Failure Assessment (SOFA) scores.
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)?	Yes	Outcome assessors - microbiologists, an external investigator, a clinical research monitor together with an independent adjudication committee were blinded to treatment group. Blinding of care providers and patients to the interventions used in this study would be challenging. Lack of blinding in this case could have increased the risk of performance bias. However, the use of blinded outcome assessors and an independent adjudication committee helps to improve the validity of outcome reporting in this study.
Were there any unexpected imbalances in drop-outs between groups?	Not clear	In the CHG dressing group, the intervention was discontinued in 22 patients who developed severe contact dermatitis. Five patients in the non-CHG group also developed severe dermatitis.

If so, were they explained or adjusted for?		Further information relating to data collection and analysis of this sub-group of patients was not available.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The study protocol was not accessible. However, reported outcomes were those listed in the clinical trial record available at http://clinicaltrials.gov/show/NCT01189682 (last accessed 15 November 2013)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The investigators advice there is no missing patient data due to adverse events.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B8 Critical appraisal of observational studies

Study name Not applicable		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

The included study, a 2:1:1 assessor-blinded study[9], evaluated 3 different transparent dressings used in the standard care for patients with intravascular catheters. The dressings evaluated were Tegaderm CHG dressing and two non-chlorhexidine dressings: (1) Tegaderm HP Transparent Film Dressing, a highly adhesive dressing and (2) Tegaderm Transparent Film Dressing, a standard breathable, hypoallergenic dressing. For this clinical review, the comparisons of interest are between CHG-impregnated dressings and non-CHG dressings as a single treatment group. There is a strong justification for pooling of the data from the standard dressings and the highly adhesive dressings groups in regard of the data that are drawn from these two study groups. The term “highly adhesive dressings” is used in the Timsit 2012 paper as a descriptor for sterile semi-permeable transparent film I.V. dressings that are regarded as “highly permeable” to moisture vapour. “Standard dressings” sterile semi-permeable transparent film dressings are composed of adhesive transparent dressings with a standard level of permeability to moisture vapour. Two RCTs[14;15] that compared the CR-BSI rates of highly adhesive dressings with standard dressings in a patient population receiving therapy with central venous catheters have been published. In both studies, there was no significant difference between the rates of CR-BSI found in the standard dressing and the highly adhesive dressing (high permeability).

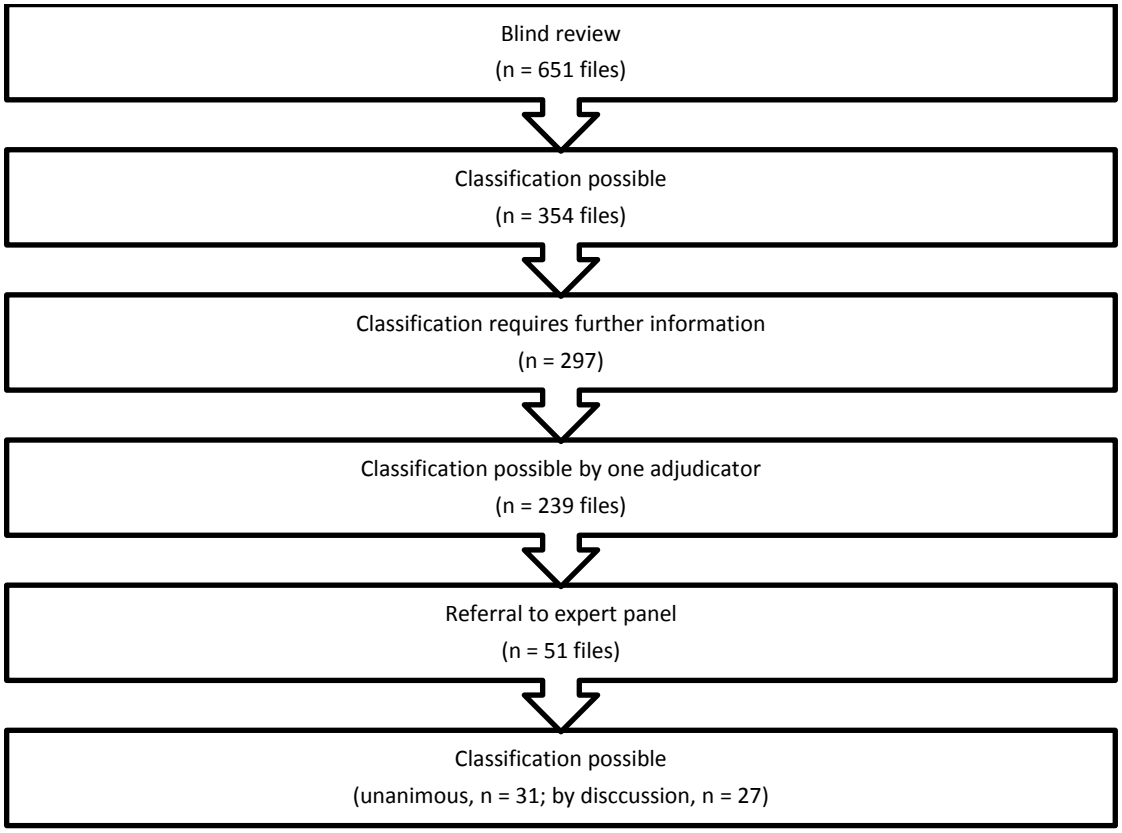
A total of 1,879 patients (4,163 catheters and 34,339 catheter days) were randomised to the two treatment groups (CHG-impregnated dressing [Tegaderm CHG dressing]; n = 938 patients and 2,108 catheters) versus non-CHG dressing ([Tegaderm HP Transparent Film Dressing and Tegaderm Transparent Film Dressing]; n = 941 patients and 2,055 catheters). The primary outcome was the incidence of a major CRI, which included CR-BSI.

Other outcomes of interest were catheter colonisation and the incidence of contact dermatitis. Based on a 3% catheter-related infection (CRI) rate in patients requiring at least 2 catheter with an intra-class correlation of 0.02, 16 it was hypothesised that CHG-impregnated dressing would decrease the CRI rate by 61%. Using an $\alpha = 5\%$ and $1-\beta = 80\%$, an adequately powered study was expected to have a sample size of 1,888 patients (>3,776 catheters). A p-value ≤ 0.05 was considered statistically significant. The presence of multiple catheters in a patient (clustering effect) was addressed by using a marginal Cox model. The marginal Cox model allows placing the catheter as a statistical unit and takes into account the correlation between two catheters in the same patient. Based on a conservative assumption, the statistical unit is the catheter whereas the unit of randomization is the patient.

By the end of the study period, there had been 14, 019 changes of dressings. Dressings were performed earlier than schedule in 72.8% sites of arterial catheters. . Early dressing changes were performed more frequently for jugular and femoral sites (71.3%) than for subclavian sites (50.1%) for patients with CVCs.

An independent adjudication panel assessed files to categorise events relating to pre-specified end-points. Overall, a total of 651 catheter files were subjected to blind review by the independent adjudication committee. The figure below is a summary of how outcomes (events) were classified.

Figure 5, Flow chart describing classification of outcomes by the independent adjudication committee



At the time of time of database lock, there were 9 CR-BSIs observed in patients in the Tegaderm CHG group compared to 22 cases in the non-CHG group (0.5 per 1,000 catheter-days versus 1.3 per 1,000 catheter-days; hazard ratio [HR], 0.402, 95% [CI] confidence interval, 0.186 to 0.868); p = 0.02). There were also fewer cases of catheter colonisation in the CHG-impregnated dressing group (n =75) compared to the non-CHG group (n = 186), [4.3 per 1,000 catheter-days versus 10.9 per 1,000 catheter-days; HR, 0.412, 95% CI, 0.306 to 0556); p < 0.0001]. Patients in the CHG dressing group also had a lesser degree of skin colonisation than those in the comparator group. The incidence of CR-BSI and catheter colonisation reported in the Timsit study are presented in Table B9 together with outcomes reported for the post-hoc analyses of dressings for CVCs and arterial catheters. Post-hoc analyses did not demonstrate the effect of heterogeneity between CHG-impregnated dressing and catheter types (CR-BSI, p = 0.512; colonization, p = 0,111, Gail and Simon test).

Figure 6, Kaplan-Meier plots for incidence of CR-BSI for Tegaderm CHG versus non-chlorhexidine dressings[9]

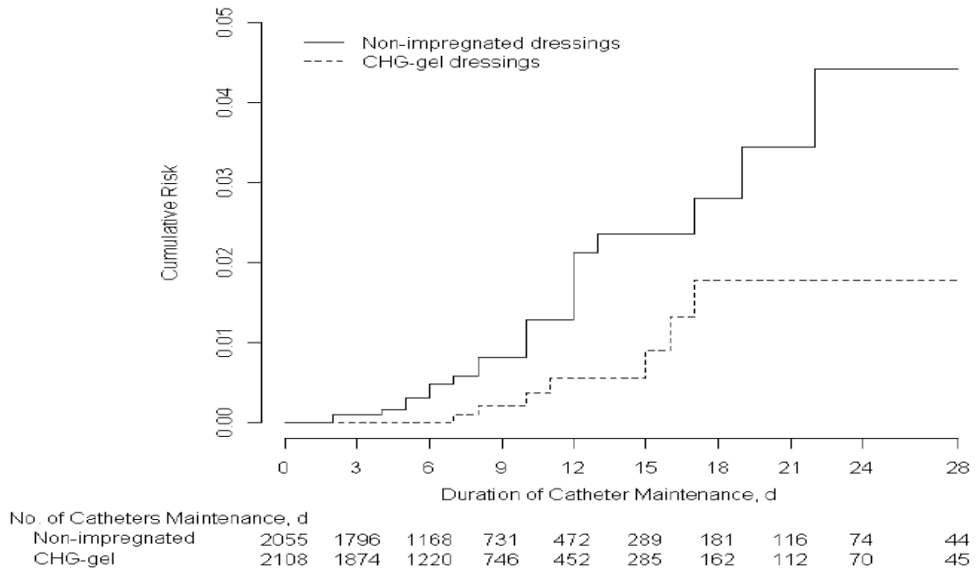


Figure 7, Kaplan-Meier plots for incidence of catheter colonisation for Tegaderm CHG dressing versus non-chlorhexidine dressings[9]

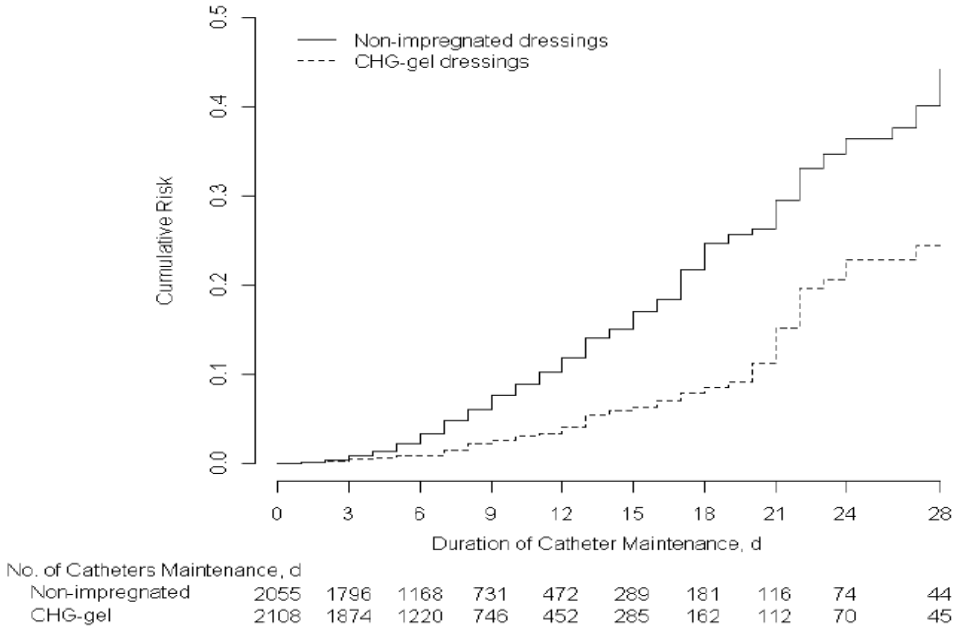


Table B9 Outcomes from published study

Study name	Timsit el al. 2012[9]		
	Treatment	All intravascular	938 patients;

Size of study group		catheters	2,108 catheters
		CVCs only	759 patients; 980 catheters
		Arterial catheters only	814 patients; 1,128 catheters
	Control	All intravascular catheters	941 patients (2,055 catheters)
		CVCs only	772 patients; 982 catheters
		Arterial catheters only	852 patients; 1,073 catheters
Study duration	Time unit	After 48 hours or within 7 days of ICU discharge	
Type of analysis	Intention-to-treat/per protocol	Intention–to–treat	
Outcome	Name	CR-BSI (all intravascular catheters)	
	Unit	Hazard ratio	
Effect size	Value	0.402	
	95%CI	0.186–0.868	
Statistical test	Type	Marginal Cox model	
	P value	P = 0.02	
Outcome	Name	CR-BSI (CVCs only)	
	Unit	Hazard ratio	
Effect size	Value	0.296	
	95%CI	0.095 to 0.922	
Statistical test	Type	Marginal Cox model	
	P value	P = 0.036	
Outcome	Name	CR-BSI (arterial catheters only)	
	Unit	Hazard ratio	
Effect size	Value	0.513	
	95%CI	0.151 to 1.740	
Statistical test	Type	Marginal Cox model	
	P value	P = 0.284	

Outcome	Name	Catheter colonization (all intravascular catheters)
	Unit	Hazard ratio
Effect size	Value	0.412
	95%CI	0.306 to 0.556
Statistical test	Type	Marginal Cox model
	P value	P < 0.0001
Outcome	Name	Catheter colonization (CVCs only)
	Unit	Hazard ratio
Effect size	Value	0.503
	95%CI	0.340 to 0.746
Statistical test	Type	Marginal Cox model
	P value	P = 0.0006
Outcome	Name	Catheter colonization (arterial catheters only)
	Unit	Hazard ratio
Effect size	Value	0.316
	95%CI	0.208 to 0.480
Statistical test	Type	Marginal Cox model
	P value	P < 0.0001
Abbreviations: CI, confidence interval; CVC, central venous catheters		

The incidence of skin colonisation was assessed by the number of CFUs in a semi-quantitative culture on a sterilised nutritive plate of antiseptic - neutralising containing trypticase-soya agar (Count-Tact™, 3P Pack+, Biomerieux™, Crapone, France). Skin colonisation was grouped into 4 distinct classes: (i) sterile, (ii) CFU < 1 log 10, (iii) CFU = 1 -2 log 10, and (iv) CFU ≥ 2 log 10. Colony-forming units between treatment groups (CHG-impregnated dressings and non-CHG dressings) were compared using a Mann-Whitney test. Skin cultures were performed following the removal of 2,965 catheters. Of these, 31% (n = 918 cultures) were sterile. Culture positivity rates were lower in the CHG groups compared to the non-CHG group (see Extra Table A below).

Extra Table A comparing semi-quantitative skin colonisation between treatment groups

Count-Tact groups of skin cultures	Tegaderm CHG dressing (n = 1,567 catheters)	non-CHG dressings (n = 1,398)
sterile	534 (34.1)	384 (27.5)
CFU < 1 log 10 [1 to 9 CFU]	325 (20.7)	249 (17.8)
CFU = 1 -2 log 10 [10 to 49 CFU/ 50 to 99 CFU]	379 (24.2)	336 (24.0)
CFU ≥ 2 log 10 [Equal to or greater than 100 CFU]	329 (21)	429 (30.7)

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

Not applicable

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The search approach and strategies described in Section 7.1 was designed to retrieve all studies irrespective of study design relating to the technology and

comparators i.e. methodological filters was not applied to the searches. It was envisaged that the strategies developed in section 7.1 would retrieve all the adverse events studies relating to Tegaderm CHG dressing and relevant comparators. See section 10 appendix 10.1 for strategies.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

Table B10 Adverse events across patient groups

	Intervention *% of patients (n =)*	*Comparator* *% of patients (n =)*	*Relative risk* *(95%CI)*
Severe contact dermatitis	*2.3% (n = 938)*	*0.5% (n = 941)*	*4.4 (1.7 to 11.6)*
Abbreviations: CI, confidence interval			

The Timsit 2012 study[9] reported no systemic adverse reactions to CHG. However, there were 22 cases of severe contact dermatitis requiring discontinuation of treatment in the Tegaderm CHG dressing group whereas 5 cases of severe dermatitis were reported in the non-CHG dressing group ($p < 0.0001$). Contact dermatitis in a patient was considered if it occurred for a single catheter site. The findings suggest that patients treated with CHG dressings may be more inclined to develop severe dermatitis compared to those receiving non-CHG dressings (relative risk, 4.4; 95% confidence interval, 1.7 to 11.6), however, the investigators noted that severe contact dermatitis was more common in patients with damaged skin, subcutaneous oedema and multiple organ failure.[9]

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

Searches were undertaken in national databases for records reporting or suggesting adverse events related to Tegaderm CHG dressing. Only one relevant record was retrieved from the Medicines and Healthcare products Regulatory Agency (MHRA) web-page [http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON197918?tabName=Problem, search date 23October 2013] whereas 109 records were obtained from the U.S Food and Drug Administration (FDA) Manufacturer and User Facility Device (MAUDE) database. [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm, search date: 29 July 2013].

Adverse events reported on MHRA web-page referred to all devices and products containing chlorhexidine including wipes, antiseptic creams, skin preparations, antimicrobial dressing and central venous catheters. This record related to a warning issued about the risk of anaphylaxis. This was based on 2 reports. One was related to the incidence of an anaphylactic reaction to a CHG-containing skin wipe in a patient before cannulation while the second report described a cardiac arrest in a patient with known chlorhexidine allergy following insertion of CHG-impregnated catheter.

Adverse events reported in the MAUDE database (see Extra Table B below) described events in a non-standardised manner. In a number of records, it was not possible to ascertain the occupation of the reporter, the type of intravascular catheter/setting or details about dressing procedures. Most of the reported adverse events were local reactions, often occurring within the first 48 hours of dressing application. A number of reports indicated that patients had skin reactions and described these in diverse terms such as “redness and maceration at the line insertion site with severe irritation and drainage”, "mild erythema and yellowish debris", "white pustule areas, reddish/brown drainage and flaking of skin" or "red, swollen, macerated, 1.25cm in diameter, 100% slough, no granulation". It is uncertain how the

severity of these reactions were classified as the outcomes were occasionally presented as “skin healed, no further treatment needed” or that the skin was “improving” or “remained “unchanged”. However, there were 7 reports suggesting to the presence of an eschar (an area of necrotic or dead skin) [Report numbers 50;62;78;79;80;81 and 83, Table] at the site of dressing. Furthermore, two cases of death were documented in patients who were immune-compromised. In both circumstances, the deaths could not or were not directly linked to Tegaderm CHG dressing [Report numbers 108 and 109].

Extra Table B, Adverse events related to Tegaderm CHG dressing reported on MAUDE database

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
1.	nurse	NR	NR	PICC	For antibiotics	NR	6 weeks	Skin maceration	PICC line removed, Dressing change every 48 hours	Skin condition improved
2.	nurse	NR	NR	PICC	For antibiotics	NR	NR	Skin maceration	Discontinued use of Tegaderm CHG	Condition improved after 2 days
3.	nurse	NR	NR	PICC	For antibiotics	NR	NR	Skin maceration	Discontinued use of Tegaderm CHG	Condition improved within 3 days
4.	nurse	NR	NR	PICC	For antibiotics	NR	NR	Skin maceration with severe itching	PICC line removed	Skin condition improved
5.	nurse	NR	no skin sensitivities, dermatological pathologies or allergies	CVC (not specified)	For chemotherapy and TPN	NR	NR	Redness, swelling, blisters, rash, itching and pain	CVC removed, Tegaderm dressing discontinued, topical cream applied	It is not known when the reaction resolved.
6.	nurse	NR	no skin sensitivities, dermatological pathologies or allergies	CVC (not specified)	For chemotherapy and TPN	NR	NR	Redness, swelling, blisters, rash, itching and pain	CVC removed, Tegaderm dressing discontinued, topical cream applied	It is not known when the reaction resolved.
7.	nurse	NR	Patient with no skin sensitivities, dermatological pathologies or allergies	CVC (not specified)	For chemotherapy and TPN	NR	NR	Redness, swelling, blisters, rash, itching and pain	CVC removed, Tegaderm dressing discontinued, topical cream applied	It is not known when the reaction resolved.
8.	nurse	NR	Patient with no skin sensitivities, dermatological pathologies or allergies	CVC (not specified)	For chemotherapy and TPN	NR	NR	Redness, swelling, blisters, rash, itching and pain	CVC removed, Tegaderm dressing discontinued, topical cream applied	It is not known when the reaction resolved.
9.	nurse	NR	Patient with spontaneously dislodged catheter	Tunnelled silicone dialysis catheter	NR	NR	2 days	Skin maceration and infection	New catheter inserted, positive skin culture, antibiotics given	Skin condition healed and infection cleared

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
10.	physician	NR	NR	Subclavian CVC	NR	Dressing had been in place for 4 days	NR	Redness and yellowish discolouration of skin	Discontinued use of Tegaderm CHG	Skin condition improved, no resulting sickness
11.	nurse	NR	NR	PICC	For antibiotics	Dressing had been in place for 8 days	NR	"mild erythema and yellowish debris" under CHG gel pad	Catheter removed, negative skin culture	Skin condition healed and no further treatment was needed
12.	nurse	NR	NR	PICC	For antibiotics	Dressing had been in place for more than 24 hours and several dressing changes had been completed. Catheter secured with statlock.	NR	"white pustule areas, reddish/brown drainage and flaking of skin" under CHG gel pad.	Catheter removed, no culture performed	Skin healed, no further treatment needed
13.	not applicable'	NR	Dressing had been exposed to moisture while showering	Subclavian CVC	NR	Dressing had been in place for more than 24 hours and several dressing changes had been completed.	NR	erythema and ulceration	IV antibiotics and antiseptics, catheter was not removed	Skin condition 'improving'
14.	not applicable'	NR	Patient had a shower with catheter and dressing in place	Subclavian CVC	NR	Dressing had been in place for more than 24 hours and several dressing changes had been completed.	NR	erythema and ulceration	IV antibiotics and antiseptics, catheter was not removed	Skin condition 'improving'
15.	nurse	NR	Dressing had been exposed to moisture while showering. Patient did not have pre-existing skin condition.	Subclavian CVC	NR	Previous duration of dressing use unknown. No stabilization device was used under the dressing. Skin was	NR	erythema and ulceration under CHG gel pad	Catheter removed, IV antibiotics given	NR

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
			Catheter was inserted in a another hospital.			prepped with chloraprep during dressing changes				
16.	nurse	NR	NR	Subclavian CVC	NR	NR	NR	Suspected infection ate insertion site (site developing hole and oozing)	Catheter removed, dressing changed to gauze and IV 3000	outcome of incident reported as 'improving'
17.	nurse	NR	Patient was receiving chemotherapy; had an ulcerated anal wound	PICC	NR	Skin was prepped with chloraprep and alcohol sani-cloth CHG 2%. The dressing was in place for more than 24 hours before the symptoms developed on the day of the dressing change. Securement with statlock	NR	Skin reaction - redness of exit site with an area of exudate	Oral antibiotics, dressing changed to gauze and IV 3000	outcome of incident reported as 'improving'
18.	nurse	NR	Patient was receiving chemotherapy; had an ulcerated anal wound	PICC	NR	Skin was prepped with chloraprep and alcohol sani-cloth CHG 2%. The dressing was in place for more than 24 hours before the symptoms developed on the day of the dressing change. Securement with statlock	NR	Skin reaction - redness of exit site and 'some necrosis	Oral antibiotics, catheter removed, wound packed with silver aquacell and dressed	reported as unknown
19.	nurse	NR	Diagnoses - pulmonary	Internal	For antibiotics	The patient's skin was	NR	Skin reaction - "redness	Catheter removed,	outcome of the

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
			respiratory failure, emphysema, sacral decubitus	jugular CVC	and blood products	prepped with chloraprep. Catheter was secured wi.th sutures. The dressing had been in place for more than 24 hours and several dressing changes had been completed.		at insertion site, maceration in a square pattern around site"	Tegaderm CHG discontinued, frequency of dressing changes increased	incident was reported as improving
20.	nurse	NR	NR	vascular access device (not specified)	For antibiotics, iv fluids and blood products	The patient's skin was prepped with chloraprep. Catheter secured with retention sutures. The dressing had been in place for more than 24 hours and several dressing changes had been completed.	NR	Skin reaction - "redness and drainage at the insertion site with maceration of the skin",	Catheter was removed, Tegaderm dressing was discontinued	outcome of incident reported as 'unchanged'
21.	nurse	NR	NR	vascular access device (not specified)	For antibiotics, iv fluids and blood products	The patient's skin was prepped with chloraprep. The dressing had been in place for more than 24 hours and several dressing changes had been completed.	NR	Infection - "redness and maceration at the line insertion site with severe irritation and drainage"	Catheter was removed, Tegaderm dressing was discontinued	outcome of incident reported as ' unchanged'
22.	not applicable'	NR	NR	vascular access device (not specified)	For antibiotics	The patient's skin was prepped with chloraprep. Catheter	NR	Skin reaction - "redness and maceration at the insertion site and	Catheter was removed, Tegaderm dressing was discontinued,	outcome of incident reported as 'unchanged'

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						secured with retention sutures. The dressing had been in place for more than 24 hours and several dressing changes had been completed.		yellowish drainage under the CHG gel pad"		
23.	not applicable'	NR	Diagnoses - pulmonary (aspiration, pna, chf, copd, pacemaker). Topical antiobiotic applied for a partial thickness wound	CVC (not specified)	For antibiotics	The patient's skin was prepped with chloraprep. Catheter secured with retention sutures. The dressing had been in place for more than 24 hours and several dressing changes had been completed.	NR	Skin reaction - "red, swollen, macerated, 1. 25cm in diameter, 100% slough, no granulation",	Catheter was removed, Tegaderm dressing was discontinued	outcome of incident reported as 'unchanged'
24.	not applicable'	NR	NR	PICC	NR	The dressing was in place for more than 24 hours before the symptoms developed. The symptoms did not occur with the first use of the Tegaderm CHG dressing. An unknown number of Tegaderm CHG dressings were used.	NR	Infection - painful ' nickel-sized redness with purulent discharge	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of incident reported as 'improving'
25.	not applicable'	NR	NR	PICC	NR	The dressing was in place for more than	NR	Infection - red copious grey drainage - The	Catheter was removed, Tegaderm dressing was	outcome of incident reported as

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						24 hours before the symptoms developed. The symptoms did not occur with the first use of the Tegaderm CHG dressing. An unknown number of Tegaderm CHG dressings were used		outcome of the skin reaction was reported as an infection (lumbar osteomyelitis)'	discontinued. No further treatment needed	'improving'
26.	not applicable'	NR	NR	PICC	NR	Multiple dressing changes had been completed using Tegaderm CHG and the dressing was in place for more than 24 hours before the symptoms developed.	NR	Infection - The diagnosis was classified as an infection (lower extremity cellulitis).	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of incident reported as 'improving'
27.	not applicable'	NR	NR	PICC	NR	The dressing was in place for more than 24 hours before the symptoms developed. The symptoms did not occur with the first use of the Tegaderm CHG dressing. An unknown number of Tegaderm CHG dressings were used	16 days	Grey slough with erythema and purulent drainage	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of incident reported as 'unchanged'
28.	nurse	NR	NR	PICC	For antibiotics	The Tegaderm CHG dressing was in place	NR	"an enlarged insertion site and surrounding area	Catheter was removed, Tegaderm dressing was	outcome of incident reported as

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						for more than 24 hours before the symptoms developed. However, the symptoms did not occur with the first use of the Tegaderm CHG dressing. There were multiple dressing changes of the Tegaderm CHG dressing.		that looked like white fungus. "	discontinued. Dressing with gauze and telfa instituted	'improving'
29.	nurse	NR	NR	PICC	NR	The Tegaderm CHG dressing was in place for more than 24 hours before the symptoms developed. However, the symptoms did not occur with the first use of the Tegaderm CHG dressing. There were multiple dressing changes of the Tegaderm CHG dressing.	NR	Purulent discharge	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of incident reported as 'improving'
30.	not applicable'	NR	NR	PICC	NR	The Tegaderm CHG dressing was in place for more than 24 hours before the	NR	skin maceration	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of incident reported as 'unchanged'

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						symptoms developed. However, the symptoms did not occur with the first use of the Tegaderm CHG dressing. There were multiple dressing changes (more than four) of the Tegaderm CHG dressing				
31.	not applicable'	NR	NR	PICC	NR	It was reported that the dressing was exposed to moisture while bathing/showering. The dressing was in place for more than 24 hrs before the symptoms developed. The symptoms did not occur with the first use of the Tegaderm CHG dressing. A total of three Tegaderm CHG dressings were used.	NR	Skin maceration - redness, blistering	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of incident reported as 'unknown' as patient did not return to clinic
32.	not applicable'	NR	NR	PICC	NR	The dressing was in place for more than 24 hrs before the	NR	Itchiness with 'bumpy rash and breakdown of skin'	Catheter was removed, Tegaderm dressing was discontinued. No further	outcome of incident reported as 'unknown' as patient

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						symptoms developed. The symptoms did not occur with the first use of the Tegaderm CHG dressing. It is unknown the number of times that a Tegaderm CHG dressing was used.			treatment needed	did not return to clinic
33.	nurse	NR	NR	PICC	NR	The dressing had been in place for more than 24 hours and several dressing changes had been completed.	NR	Sin irritation - 'reddened skin which appeared excoriated and macerated with a blister and clear drainage'	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	Skin healed, no further treatment needed
34.	NR	NR	Patient, receiving post-surgical care, diagnosis -unknown	NR	NR	The dressing was in place for more than 24 hours before the symptom developed. Multiple dressings had been applied.	NR	yellowing of the skin'	Catheter was removed, Tegaderm dressing was discontinued. No further treatment needed	outcome of the incident - 'improving' .
35.	NR	NR	NR	NR	NR	The dressing was in place for more than 24 hours before the symptoms developed. Only one dressing was applied. Prior to the dressing application, a clinical wipe was used	NR	Mild skin reaction	IV Vancomycin for 2 days. Catheter was not removed	Skin reaction improved. No further treatment needed
36.	nurse	NR	NR	PICC	For antibiotics and	The dressing was in place for more than	NR	Skin irritation - redness and inflammation around	Catheter removed, CHG dressing discontinued	outcome of the skin reaction improved

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
					chemotherapy	24 hours before the symptoms had developed. Only 1 dressing was applied.		the insertion site		and no further treatment was needed
37.	not applicable'	NR	NR	NR, (femoral site)	NR	The dressing was in place for more than 24 hours before the symptoms had developed. Only 1 dressing was applied.	NR	Mild small spots in the femoral site, under the Tegaderm gel dressing)	Catheter removed	NR
38.	Physician	NR	NR	PICC	NR	The dressing was in place over 24 hrs before the symptoms developed. Overall, the dressing had been in place for 7 days. However, the symptoms did not occur with the first use of the dressing.	NR	Skin irritation with purulent discharge and blisters, followed by enlargement of the insertion site	Catheter was removed; CHG dressing was discontinued; warm compresses were applied to the skin area	outcome of the skin reaction improved and no further treatment was needed
39.	nurse	NR	NR	PICC	NR	The dressing was in place over 24 hours before the symptoms developed. However, the symptoms did not occur with the first use of the Tegaderm CHG dressing.	NR	skin irritation of redness, excoriated, blistering, and drainage	Catheter was removed; CHG dressing was discontinued; warm compresses were applied to the skin area	outcome of the skin reaction improved and no further treatment was needed
40.	nurse	NR	NR	PICC	NR	The dressing was in place over 24 hours	NR	skin irritation - redness around the insertion site	Catheter was removed and the use of the	outcome of the skin reaction improved

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						before the symptoms developed. The symptoms did not occur with the use of the first Tegaderm CHG dressing. More than four Tegaderm CHG dressings were used.			Tegaderm CHG dressing was discontinued	and no further treatment was needed.
41.	nurse	NR	NR	PICC	NR	The dressing was in place over 24 hours before the symptoms developed. The symptoms did not occur with the use of the first Tegaderm CHG dressing. More than four Tegaderm CHG dressings were used.	NR	skin irritation - redness, itchiness, drainage and white blisters under the gel dressing	Catheter was removed and the use of the Tegaderm CHG dressing was discontinued	outcome of the skin reaction improved and no further treatment was needed.
42.	nurse	NR	NR	NR	NR	NR	NR	Skin irritation under the entire dressing	Catheter removed, topical antibiotic cream (mupirocin) was applied.	outcome of skin - 'unknown'
43.	nurse	NR	NR	NR	NR	NR	NR	Skin irritation under the entire dressing	Catheter removed.	outcome of skin - 'unknown'. No further treatment was needed.
44.	nurse	NR	NR	PICC	NR	Multiple dressing changes had been completed using	NR	Report indicates that the *Patient developed "denuded, grey, necrotic*	Catheter removed	NR

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						Tegaderm CHG.		*skin with odour and drainage"*		
45.	nurse	NR	NR	PICC	NR	NR	NR	Skin maceration - 'patient developed macerated erythematous denuded skin with greyish bumps and drainage under the gel dressing'	Catheter was removed and the use of the Tegaderm CHG dressing was discontinued	outcome of the skin condition improved and no further treatment is needed.
46.	nurse	NR	NR	NR	NR	NR	NR	CR-BSI and/or a skin reaction (2 cases reported by a health facility	NR	NR
47.	nurse	NR	NR	PICC	NR	NR	NR	Skin reaction - 'grey, mushy skin and pink satellites under the Tegaderm CHG pad (at the iv site)'.	Catheter was removed and the use of the Tegaderm CHG dressing was discontinued	outcome of skin - 'unknown'. No further treatment was needed.
48.	nurse	NR	NR	PICC	NR	NR	NR	Skin reaction - 'itchiness, redness and skin blistering under dressing and beyond		NR
49.	nurse	NR	Patient was receiving chemotherapy via the vascular access device (as an out-patient)	NR	For chemotherapy	Dressing was in place for nine days as patient was out of town. Patient replaced dressing with dry sterile gauze due to increasing skin irritation.	NR	Skin reaction - Redness and skin blistering under entire dressing	Tegaderm dressing discontinued; replaced with dry sterile dressing	Skin reaction improving
50.	not applicable'	NR	NR	Subclavian CVC	For antibiotics and IV fluids	The dressing was exposed to sweat	NR	Erythema, redness and eschar under gel pad	Tegaderm dressing discontinued; topical antibiotics applied	Skin -healed
51.	nurse	NR	NR	PICC line	NR	NR	NR	Skin reaction - mushy	Tegaderm dressing	Skin - improving. No

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
				catheter (not specified)				and grey area under the gel pad	discontinued; picc line / catheter were removed	further treatment needed.
52.	nurse	NR	NR	PICC	NR	NR	NR	Dislodgement of PICC line due to gel pad being stuck to the catheter	NR	No further treatment needed
53.	nurse	NR	NR	CVC - internal jugular	NR	NR	NR	Skin - "breaking down, red and burning"	CVC relocated	No further information was provided by the health facility
54.	nurse	NR	Bone marrow' patient	PICC	NR	NR	NR	Extensive breakdown of skin under gel pad	PICC line relocated; dressing changed to Biopatch; negative culture (not specified)	NR
55.	nurse	NR	NR	NR	NR	NR	NR	Skin reaction -redness, saturated and 'lifted' dressing	NR, other treatments listed in report were Biatain and Opsite 30000	NR
56.	nurse	NR	NR	NR	NR	NR	NR	Skin reaction -itchiness, soaked and disintegrated gel pad	NR	NR
57.	nurse	ER	NR	PICC line catheter (not specified)	NR	The dressing was exposed to sweat	NR	Skin irritation - burning, itchiness, induration, redness	Tegaderm dressing discontinued; catheter removed	Condition improved
58.	nurse	NR	NR	CVC (right subclavian)	NR	NR	NR	Redness at insertion site with grey/yellow areas	Tegaderm dressing discontinued; CVC removed	Condition - had improved
59.	nurse	NR	An immunosuppressed, multiple myeloma patient. Although, a tunnelled aphaeresis	NR	NR	NR	NR	Separation of gel pad from transparent film	NR	NR

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
			Patient with catheter in place on the neck, this site was not dressed with a CHG-containing dressing. Two days prior to this report, patient was diagnosed with a 'line infection' with the probable source being the tunnelled catheter. It is not clear which site/ catheter was dressed with Tegaderm CHG							
60.	nurse	NR	Previous reactions to adhesive products. .	CVC (left intra jugular vein).	NR	Chloraprep 2% for skin prep was used	NR	Mild skin reaction under the gel pad	NR	Patient healed after the incident
61.	nurse	NR	Paraplegic patient with multiple problems	PICC	NR	NR	NR	Positive blood culture (unspecified) Catheter tip culture yielded one colony of Pseudomonas aeruginosa	PICC line removed, systemic antibiotics (vancomycin, cefepime,linezold and flagyl) given	Patient - improving
62.	nurse	NR	Patient with burns and a healed donor site, prviously dressed with Biopatch	PICC	For TPN	NR	NR	Blisters, erythema, macerated skin, eschar under the gel dressing and pus from the insertion site	PICC line removed; Tegaderm dressing discontinued; the site cleansed with normal saline and wrapped with gauze and Biopatch. Within 24 hours of treatment, a white	Patient - improving

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
									eschar developed under the Biopatch dressing. Subsequently, dressing was limited to gauze only. Cause of infection, unknown. Possible allergy to CHG	
63.	Other health care professional (not specified)	NR	NR	PICC	NR	NR	NR	Skin reaction - irritation, induration, ulceration area around insertion site with hard yellow slough	PICC line removed, Tegaderm dressing discontinued; area cleansed with alcohol followed by application of sterile 2x2 (gauze) secured by kerlix wrap	Skin reaction - healed
64.	nurse	N/a	Out-patient with a PICC line	PICC	NR	NR	NR	Skin reaction - irritation, ulceration area around insertion site with hard yellow slough	PICC line removed, Tegaderm dressing discontinued; area cleansed with alcohol followed by application of sterile 2x2 (gauze) secured by kerlix wrap. No cultures were performed and no medication given	Skin - healed after approximately 1 week
65.	nurse	NR	NR	catheter (not specified)	NR	NR	NR	Redness of skin under dressing with 'hard' pus around insertion site	Catheter removed; silvasorb and centurion transparent dressing applied. Negative culture (unspecified)	Skin reaction - improving

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
66.	nurse	NR	NR	catheter (not specified)	NR	NR	NR	Possible maceration - red/yellow/white/grey area under the gel pad	NR	Skin condition - improving. No further treatment needed
67.	nurse	NR	Patient enrolled in a trial	NR	NR	NR	NR	Fungaemia	NR	NR
68.	nurse	NR	NR	catheter (not specified)	NR	NR	NR	Skin redness and 'yellowish pus-looking drainage ' under gel pad	Catheter removed; ointment (unspecified) applied	Skin condition - improving. No further treatment needed
69.	nurse	NR	patient undergoing kidney dialysis	translumbar catheter		NR	NR	Yellow material, with intense itching, irritation and redness under the dressing'	Catheter removed	Cultures for bacteria and fungus-negative; skin reaction - healed
70.	Other health care professional (not specified)	NR	Patients in the health facility were allowed to shower	NR	NR	NR	NR	Possible maceration - 'fungal growth-like, white skin, yeasty, sloughy like a burn'. Dressing soaked and disintegrating	Report indicates that no additional information was available.	No further information provided
71.	Other health care professional (not specified)	NR	Patients in the health facility were allowed to shower	NR	NR	NR	NR	Possible maceration - 'fungal growth-like, white skin, yeasty, sloughy like a burn'. Dressing soaked and disintegrating	Report indicates that no additional information was available.	No further information provided
72.	Other health care professional (not specified)	NR	NR	NR	NR	NR	NR	Yellow tissue under gel pad and transparent film	NR	Skin - improving
71.	Other health care professional (not specified)	NR	Patients in the health facility were allowed to shower	NR	NR	NR	NR	Possible maceration - 'fungal growth-like, white skin, yeasty, sloughy like a burn'. Dressing soaked	Report indicates that no additional information was available.	No further information provided

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
								and disintegrating		
74.	nurse	NR	NR	dialysis catheter	NR	NR	NR	creamy looking substance with redness and skin irritation under the gel pad.'	Catheter removed, culture for bacteria and fungi; topical antibiotics applied	Negative cultures. Area - healed
75.	nurse	NR	Patient with heart failure awaitng transplant	catheter (not specified)	NR	NR	NR	redness with 'yellow malodorous discharge around the catheter and under the dressing'	Catheter removed, culture for bacteria and fungi; topical antibiotics applied	Negative cultures; skin - improving
76.	nurse	NR	NR	dialysis right subclavian catheter	NR	NR	NR	yellow exudate with redness at the insertion site under gel pad'	catheter removed; catheter tip and blood culture performed	results were negative for CR-BSI
77.	Other (not specified)	NR	Patient had a nasogastric tube and a drainage onto the neck and into the dressing.	CVC	For TPN	NR	NR	Severe itchiness and blistering with a yeast-like appearance under gel pad	Catheter removed; Dressing discontinued and cavilon non-sting barrier film applied	Area - healed
78.	Other (not specified)	NR	NR	CVC (right subclavian)	For antibiotics and TPN	The catheter was secured with sutures. Alcohol and duraprep had been used on the skin prior to dressing application.	NR	"eschar with reddened excoriated skin under gel pad. "	Catheter removed; blood culture performed IV antibiotics given, Lotrisine cream applied to area	Negative culture; area-healed
79.	Other health care professional (not specified)	NR	NR	CVC (right subclavian)	For antibiotics, blood products, and IV fluids	Chloraprep had been used on the skin prior to dressing application	NR	redness and eschar under the gel pad	Catheter removed; catheter tip and blood cultures performed Silvadene applied locally	Negative culture; area-improving
80.	Other health care professional (not specified)	NR	NR	CVC (right subclavian)	For antibiotics, blood products, and IV fluids	Chloraprep had been used on the skin prior to dressing application	NR	redness and eschar under the gel pad	Catheter removed; catheter tip and blood cultures performed Silvadene applied locally	Negative culture; area-improving

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
81.	Other health care professional (not specified)	NR	Patient with excessive sweating	CVC (left subclavian)	For antibiotics and IV fluids	Povidone iodine, chloraprep, and duraprep had been used on the skin prior to dressing application	NR	"erythema, redness, and eschar" under the CHG gel pad.	Catheter removed; Silvadene applied locally	Area - healed
82.	Other health care professional (not specified)	NR	Patient with excessive sweating	CVC (right subclavian)	For antibiotics and IV fluids	Povidone iodine, chloraprep, and duraprep had been used on the skin prior to dressing application	NR	"a white/grey colour, redness and skin breakdown" under the CHG gel pad	Catheter removed; cultures of catheter tip and insertion site performed; Silvadene applied locally	Negative culture; area - improving
83.	Other health care professional (not specified)	NR	Patient with excessive sweating	CVC (right subclavian)	For antibiotics and IV fluids	Povidone iodine, chloraprep, and duraprep had been used on the skin prior to dressing application	NR	"eschar with reddened grey/white matter" under the CHG gel pad.	Catheter removed; culture of insertion site performed; Silvadene applied locally	Negative culture; area - improving
84.	Other health care professional (not specified)	NR	Trauma patient	CVC (subclavian)	NR	NR	NR	"white area with black" under the dressing, (gel pad soaked with blood and fluid)	Catheter and dressing removed; culture of catheter tip	Negative culture; area -healed
85.	not applicable	NR	NR	CVC (subclavian)	NR	NR	NR	'redness and sloughing of the skin - looked like a second degree burn'	Catheter removed; topical antibiotics applied	Patient - improving
86.	not applicable	NR	Elderly patient	PICC	NR	NR	NR	Redness and maceration around insertion site	PICC line removed; Tegaderm dressing discontinued; culture of catheter tip	Negative culture. Skin reaction - healed
87.	nurse	NR	Medical-surgical	PICC	NR	NR	NR	Redness and blistering	PICC line replaced with	Site - healing

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
			patient					underneath the dressing (no differentiation between gel pad and transparent film)	peripheral IV line for vascular access. No medical treatment given. No cultures performed	
88.	nurse	NR	Medical-surgical patient	PICC	NR	NR	NR	Redness and blistering underneath the dressing (no differentiation between gel pad and transparent film)	PICC line replaced with peripheral IV line for vascular access. No medical treatment given. No cultures performed	Site - healing
89.	Other health care professional (not specified)	NR	Dialysis patient with Tegaderm CHG dressing applied in another facility	PICC	NR	NR	NR	Maceration around an enlarged insertion site	PICC removed	Patient discharged
90.	Other (not specified)	NR	Neurology patient	PICC	NR	NR	9 days	White material under the gel pad' at the femoral site (it is not clear if patient had other catheters in addition to the PICC line which is usually inserted in the arm)	Culture of catheter tip and skin	Catheter tip culture, negative; skin culture yielded < 15 colonies of E. Coli. No further information
91.	Other (not specified)	NR	NR	PICC	NR	Dressing had be in place for 9 days	NR	Dislodgement of PICC line (1 to 4 cm) due to gel pad being stuck to the catheter and white slough peeling from skin when removing dressing	PICC line maintained. No further information	Patient - improving
92.	Other (not specified)	NR	NR	PICC	NR	Several dressings had been used on this patient and the	NR	Erythema and white material at subclavian insertion site	PICC line removed; site cleansed with sterile saline	Spontaneous resolution of condition

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
						dressing was in place >24 hours before condition was noticed.				
93.	Other (not specified)	NR	Elderly neurology patient	CVC (right subclavian) Arterial catheter (left radial)	NR	NR	NR	White material at insertion site	CVC removed; cultures of insertion site and catheter tip for bacteria and fungi	Negative cultures
94.	Other (not specified)	NR	Heart transplant patient receiving hydrocortisone, prednazone, and prograft. Patient had profuse sweating.	CVC (internal jugular)	NR	NR	NR	White material under soaked gel pad. Peeling of skin during removal of dressing	Cultures (not specified) performed	No further information available
95.	not applicable	NR	NR	PICC	NR	NR	NR	Redness and blistering under dressing.	Tegaderm dressing discontinued; PICC line relocated to contralateral arm; Douderm applied locally	Area - healing
96.	nurse	ICU	NR	CVC (subclavian)	NR	Dressing was in place for five days until condition developed.	NR	Redness of skin noticed through dressing, followed by skin abrasion and 'pus(s)-like exudate	Tegaderm dressing discontinued; catheter removed; wound swabs taken; skin cleansed with saline. Wound was left uncovered following prior application of povidine iodine for 3 hours	Negative culture. No further information available
97.	nurse	NR	In-patient being	PICC	For antibiotics	NR	NR	Reddened skin with thick	PICC removed; another	Patient - healed. No

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
			treated for an fungal infection					yellow 'cheesy' exudate around insertion site accompanied by a full body skin rash	PICC line placed in the other arm. No culture performed	further information provided
98.	Other (not specified)	NR	Patient had two PICC line dressed with Tegaderm CHG. Lines were place sequentially as patient complained of itchiness with the first PICC line.	PICC	NR	NR	NR	Itchiness with red bumps and white substance under the gel pad	Culture of both catheter tips; Tegaderm dressing discontinued; oral antihistamine (bendryl) given	Patient - healed
99.	physician	NR	Patient receiving treatment for 'gastrointestinal issues and dehydration'	PICC	For antibiotics and TPN	Patient's dressing was changed twice within 24 hours due to dislodgement of the PICC line	NR	Skin necrosis preceded by redness at the insertion site	Dressing discontinued	Skin grafting performed
100.	Other health care professional (not specified)	NR	NR	NR	NR	NR	NR	Infection - 'green drainage' at (insertion) site	Catheter removed; Culture (not specified) performed	Positive culture for enterococcus resistant to cephalosporins, immunogylcosides, clinomycin, and a sulfa-type antibiotic; patient - healed
101.	Other health care professional (not specified)	NR	NR	NR	NR	NR	NR	Dermatitis (presumed)	Catheter removed	Patient - improving
102.	Other health	NR	NR	NR	NR	NR	NR	Redness, inflammation	Catheter removed and a	Patient developed

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
	care professional (not specified)							and oozing under gel pad	new catheter replaced	pneumothorax following second catheterisation; Catheter removed; Patient - healed
103.	Other health care professional (not specified)	NR	NR	NR	NR	NR	NR	Redness, inflammation and oozing under gel pad	Catheter removed	Patient - healed
104.	not applicable	NR	Patient complained of itching and had changed dressing frequently at home during the past few days in an effort to relieve symptoms.	PICC	NR	NR	NR	Cellulitis - areas of redness, swelling and ulceration under dressing	PICC line removed and new line placed in other arm; site was cleansed with water and hibliclens; topical and systemic antibiotic treatment given for cellulitis. Culture taken	Culture results, not known. No further information available
105.	nurse	NR	Patient had no pre-existing skin condition or history of reaction to adhesives or preps. Statlock in place.	PICC	NR	Chloraprep was used for skin preparation	NR	green slough (extensive) under the CHG gel pad around insertion site	PICC line removed and a new line was placed; a different dressing (not specified) was applied.	NR
106.	nurse	NR	Patient had no history of reaction to adhesive or CHG.	PICC	For TPN	Symptoms developed 24 hours after the dressing was applied. Chloraprep was used for skin preparation.	NR	Redness and discharge around insertion site	PICC line removed and placed in a different site; Tegaderm dressing discontinued	Area - beginning to heal
107.	nurse	NR	Patient had 3 central lines	PICC CVC (subclavian)	NR	NR	NR	Eschar (at all 3 sites)	PICC line removed and placed in a different site	NR

Report number	Reporter Occupation	Critical care setting	Patient characteristics	Intravascular catheter type	Indication for intravascular catheter	Dressing details	Length of intravascular use	Reported AE	Intervention/outcome following incidence of AE	Final outcome following intervention
				Dialysis catheter						
108.	Other (not specified)	NR	Elderly 'compromised' Patient with pleural effusion (fluid in lungs), decubitus, and had a percutaneous endoscopic gastroscopy (PEG)tube.	PICC 'Line' (not specified)	NR	Patient developed skin condition 3 days after dressing was applied	NR	Maceration, ulceration and redness under CHG (gel)	The line was removed the following month, and a PICC inserted.'	Death [Facility reported that death was related to lung problems and unrelated to CHG or sepsis.] Negative skin culture
109.	medical professional (not specified)	NR [patient was later moved to ICU]	Very sick and immune-compromised patient with fragile skin	CVC (not specified)	For chemo-therapy and TPN	NR		large skin tear (size and shape) under CHG pad'	Neosporin given and 4 x 4's applied without tape or adhesive	Infection Death

Abbreviations: CHG, chlorhexidine gluconate; CVC, central venous catheter; IV, intravenous; NR, not reported; PICC, peripherally-inserted central catheter

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

In general, the risk of an anaphylactic reaction in patients treated with any CHG-containing medicine or device needs to be assessed in those with known or unknown sensitivity to CHG. The Tegaderm CHG dressing is associated with skin reactions of varying severity and presentation.

Overall, the available safety profile of Tegaderm CHG dressing suggests that local adverse events may be more common in most patients. However, there is a small risk of anaphylaxis (a serious adverse event) in a selected population of treated individuals.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not applicable

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

The findings of the pivotal study reported by Timsit et al., suggest that Tegaderm CHG, a sterile semi-permeable transparent dressing with a 2% (w/w) chlorhexidine-impregnated hydrophilic gel pad, reduces the risk of CR-BSI by 60% (0.5 per 1,000 catheter-days versus 1.3 per 1,000 catheter-days; hazard ratio [HR], 0.402, 95% [CI] confidence interval, 0.186 to 0.868); p = 0.02) in critically ill patients requiring intravascular catheters (arterial catheters and CVCs) for short periods.[9] The beneficial effect of this CHG-impregnated dressing was also demonstrated in the reduction of catheter colonisation rates and skin colonisation rates in treated patients. However, compared to sterile semi-permeable transparent dressings for critically ill patients with IVCs, Tegaderm CHG dressing was associated with an increased incidence of severe contact dermatitis ($p < 0.001$).

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The included study[9] is an adequately powered, multicentre randomised controlled trial (n =1,879 patients). It is believed that the findings of this study could be transferable to settings with care bundles similar to those used in the participating centres. Although, double blinding was not achieved in the conduct of this study, the use of blinded assessors and an independent

adjudication committee guaranteed the validity of key study end-points such as CR-BSI and catheter colonisation.

One limitation of this study is the use of surrogate end-points. The study assessed skin colonisation and catheter colonisation. The use of surrogate end-points have been noted to introduce statistical and clinical misinterpretations, thereby threatening the validity of results.[17] However, it is important to note that the surrogate end-point, catheter colonisation which was used in the Timsit study[9], has been shown to closely correlate with CR-BSI.[18]

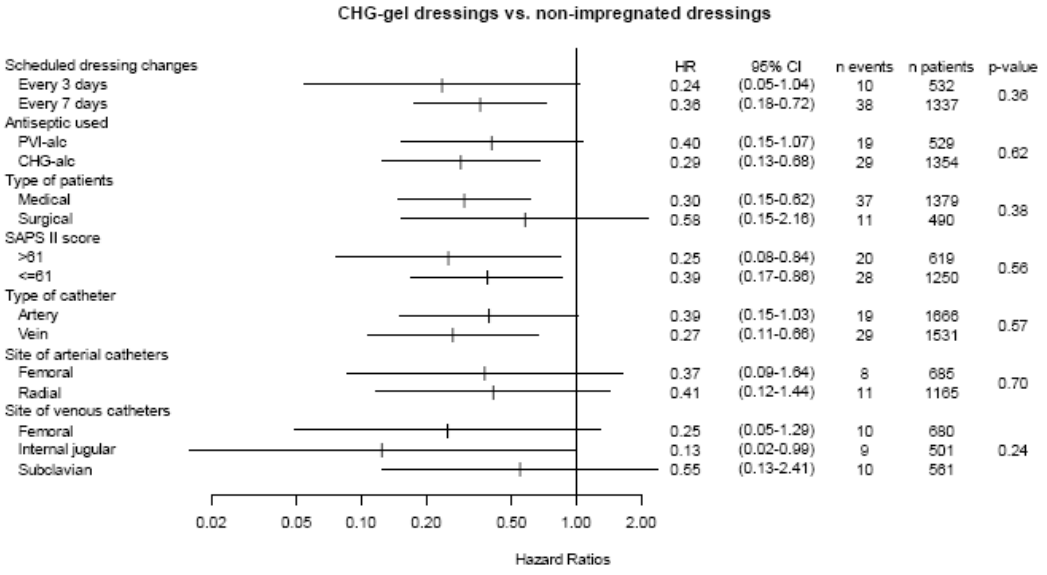
7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

Extra Table C, relevance of the evidence base to the scope

Criterium	Scope	Timsit 2012[9]
Population	Critically ill adult patients in intensive care or high dependency units who require a central venous or arterial catheter.	1,879 Intensive care unit patients
Intervention	Swabbing with 2% chlorhexidine gluconate (CHG) in alcohol and Tegaderm CHG IV securement dressing	Both CHG in alcohol and povidone iodine alcohol used as skin prep. Of 1,883 patients where the data was recorded, 71.9% of patients were treated with CHG in alcohol. The chart below (Figure 8) presents hazard ratios for patient characteristics or aspects of care. The data presented shows no significant difference in hazard ratios (p=0.62) between methods of skin antisepsis[9]. We conclude that the overall results of this study would be similar to those reported if all patients included had been treated with a CHG in alcohol skin antiseptic.
Comparators	Swabbing with 2% CHG in alcohol and sterile semi-permeable transparent dressing Swabbing with 2% CHG in alcohol and CHG impregnated dressing	The comparators in the pivotal study are sterile semi-permeable transparent dressings. See above comments on skin antisepsis. No randomised controlled studies in critically ill adult patients were found comparing Tegaderm CHG with other CHG containing dressings. A study in volunteers indicates that the maintenance of reduction of skin colonisation is similar between the Tegaderm CHG and a CHG containing sponge dressing on skin prepped with 2% CHG in alcohol.[19]

Outcomes	The outcome measures to consider include: • CR-BSI and associated antimicrobial use • Skin colonisation and catheter colonisation • Length of stay in critical care/high dependency • Mortality due catheter related infections • Dermatitis • Local site infection • Quality of life • Device-related adverse events, including adverse events caused by contact with chlorhexidine	Relevance of outcomes examined in Timsit 2012 are listed below: • CR-BSI – primary outcome, no data reported on antimicrobial use • Skin at catheter site and catheter colonisation are secondary outcomes • Length of stay in ICU reported for the intervention and the comparators • Mortality due to catheter related infections not reported in this study • Incidence dermatitis reported in this study • Local site infection not reported • Quality of life not reported in this study • Adverse events including those related to CHG are reported in the study

Figure 8, Efficacy of chlorhexidine-gel dressings. Sensitivity analysis. HR and 95%CI represent the effect for each subgroup. The p-value tests the heterogeneity of CHG-gel dressing effect between subgroups. A P value >0.05 indicates the absence of significant differences of effects between subgroups.[9]



A recent comparative study available only as a pre-publication poster and received after completion of the systematic review, has compared sterile semi-permeable transparent film dressings (n= 137) with Tegaderm CHG

dressing (n=136) in an intensive care population who were all swabbed with 2% CHG in alcohol skin preparation.[20] The results showed significantly lower levels of both aerobic and anaerobic bacteria at skin and suture sites under the Tegaderm CHG dressing ($p<0.001$). Also incidence of colonisation of the intra-dermal section of the CVC was significantly lower in the Tegaderm CHG group ($p=0.037$).

This evidence indicates that compared to the protocol of swabbing with 2% CHG in alcohol/ use of sterile semi-permeable transparent dressing, use of swabbing with 2% CHG in alcohol *and* Tegaderm CHG dressing reduces skin colonisation at the site of intravascular catheters, thereby reducing a major risk factor for infection.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

We are not aware of any factors that would adversely influence the use of and outcomes associated with use of Tegaderm CHG dressing in the care of critically ill patients with intravascular catheter in routine clinical practice. Patient recruitment in the pivotal study[9] took place in a group of 12 French ICUs where the reported patient demographics are similar to those generally found in routine clinical practice in critical care in England and Wales. All study centres followed locally accepted practice recommendations similar to those of the Centres for Disease Control and Prevention principles[5] for catheter insertion and care. These recommendations have been very influential on the development of the NICE and epic3 guidelines that strongly influence patient care in England and Wales. The levels of CR-BSI reported for the comparator (sterile semi-permeable transparent film dressing) 1.3 per 1,000 catheter days. This rate of infection is comparable with the 1.48 CVC-BSI per 1,000 catheter days reported in a UK national programme to reduce CR-BSI in intensive care units.[21]

No cases of systemic chlorhexidine sensitivity were found in the pivotal study[9], however, 22 occurrences of severe dermatitis requiring withdrawal of

Tegaderm CHG dressing occurred during this study, a rate of 1.1 per 100 patients.

The evidence from the pivotal study[9] was collected from patients who were expected to receive care through an intravascular catheter for more than 48 hours. This is not a selection that is currently recognised in clinical practice.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

A search of the 3M Health Care post market surveillance data base has shown a reduction in reported skin reactions associated with Tegaderm CHG dressing that was coincidental to the introduction of a modified design of this device with a high breathability film. The level of skin irritation found by Timsit et al has not been reported from routine use of Tegaderm CHG dressing across a broader patient population.

Patients with known sensitivities to chlorhexidine products should be excluded from treatment with Tegaderm CHG dressing.

Figure 9, 3M Health Care Medico-vigilance data for Tegaderm CHG dressing, 2010-2013

This figure contained information that was submitted as commercial-in-confidence and has been redacted.

In the pivotal study[9] an inclusion criterion was for patients who were expected to receive therapy via an intravascular catheter for more than 48 hours. After discussion with clinicians this is not a practical approach to selecting patients for care with Tegaderm CHG dressing since it is difficult to predict how long a critical care patient will require arterial or central venous access. In view of this it is proposed to recommend the dressing for all critical care patients receiving therapy through intravascular catheters.

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Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

a) Electronic databases

Studies were identified by searching the following electronic databases and research registers:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (OvidSP) 1948 to August 2013
- EMBASE (OvidSP) 1980 to August 2013
- Cumulative Index to Nursing and Allied Health Literature (EBSCO host) 1982 to August 2013
- Cochrane Database of Systematic Reviews (Wiley Online) 1996 to August 2013

- Cochrane Central Register of Controlled Trials (Wiley Online) 1898 to August 2013
- Health Technology Assessment Database (Wiley Online) 1995 to August 2013
- Database of Abstracts of Review of Effects (Wiley Online) 1995 to August 2013
- NHS Economic Evaluation Database (Wiley Online) 1995 to August 2013
- BIOSIS Previews (ISI Web of Knowledge) 1969 to August 2013
- Science Citation Index Expanded (Web of Science) 1899 to August 2013
- Conference Proceedings Index-Science (Web of Science) 1990 to August 2013
- EconLit (OvidSP) 1961 to August 2013
- UK Clinical Research Network (CRN) Portfolio Database (NIHR) 2001 to October 2012
- National Research Register (NRR) Archive (NIHR) 2000 to September 2007.
- Current controlled trials 2000 to October 2012
- ClinicalTrials.gov (US NIH) 2000 to October 2012

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). All resources were initially searched from inception to October 2012. With the exception of the four research registers, updated searches to August 2013 were conducted on the remaining electronic databases.

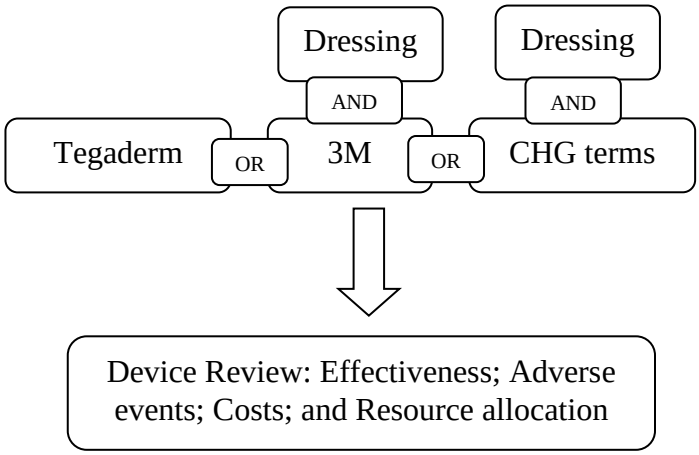
b) Other resources

To identify additional published, unpublished and ongoing studies, the reference lists of all relevant studies (including existing systematic reviews) were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index

- Science) was undertaken to identify articles that cite the relevant articles. In addition, systematic keyword searches of the World Wide Web were undertaken using the Google search engine and key experts in the field were contacted.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

Figure x: Framework for the search strategy



No limits in terms of date, language or study design were applied to the searches. Studies were also identified from reference tracking of included studies, identified reviews and relevant guidelines. Key investigators were also contacted for information about completed studies.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Studies were selected for inclusion according to pre-determined inclusion and exclusion criteria. Studies were included if they reported an economic

evaluation of interventions for reducing catheter related infections for patients in acute setting.

Studies that performed economic evaluations alongside trials were excluded if they did not extrapolate the outcomes beyond the trial duration as these economic analyses are only valid for the trials under consideration. Studies that were considered to be methodologically unsound, that were not reported in sufficient detail to extract costs and outcome estimates (including abstracts) or did not report an estimate of cost-effectiveness (e.g. costing studies) were also excluded. Papers not published in the English language were also excluded.

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer. Any citations that clearly do not meet the inclusion criteria were excluded. Second, and all abstracts and full text articles were examined independently by two reviewers and any disagreements in the selection process were resolved through discussion

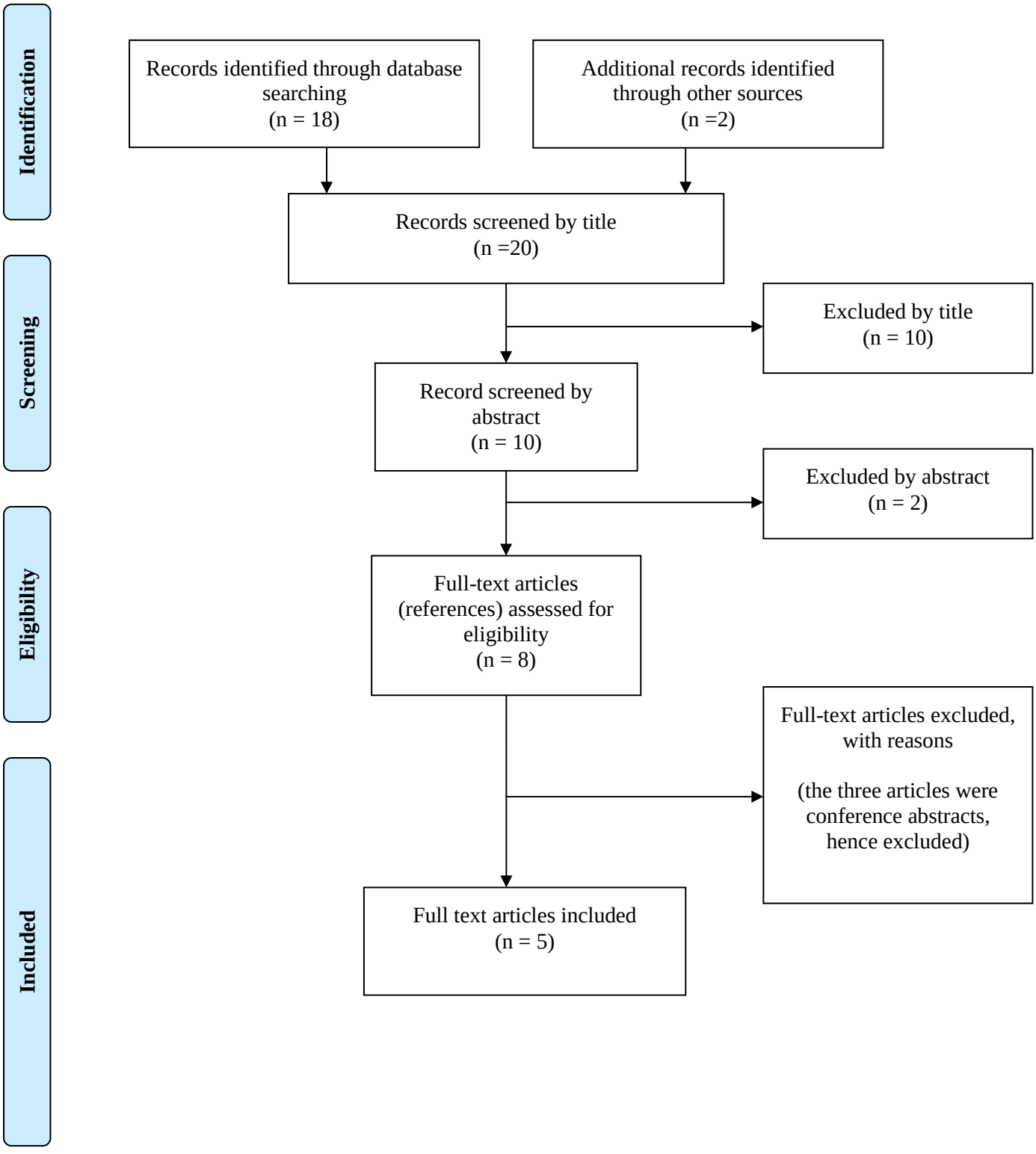
Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients cared for in an acute setting.
Interventions	Interventions for reducing of catheter related infections
Outcomes	Studies that report an economic evaluation
Study design	All designs
Language restrictions	Papers reported in the English language
Search dates	23rd July 2013
Exclusion criteria	
Population	Patients cared for outside the acute setting
Interventions	None
Outcomes	None
Study design	Studies that performed economic evaluations alongside trials that did not extrapolate the outcomes beyond the trial duration as these economic analyses were only seen as valid for the trials under consideration. Studies that were considered to be methodologically

	unsound, Studies that were not reported in sufficient detail to extract costs and outcome estimates (including abstracts) Studies that did not report an estimate of cost-effectiveness (e.g. costing studies)
Language restrictions	Papers not published in the English language.
Search dates	23rd July 2013

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 1 : Study flow chart (adapted): cost-effectiveness review



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Table C2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Veenstra et al: 1999[1]	US	Decision analytic model of CHG impregnated and standard CVCS	Patients with high risk of CRIs	Antiseptic coated catheters - $336 vs Standard catheters - $532	CRBSI, death and related costs	Antiseptic impregnated catheters are cost saving
Crawford et al: 2004[2]	US	Trial based CBA of CHG impregnated and standard CVCS	Patients of all Philadelphia area hospitals	Chlorhexidine dressing - $637.54 vs Standard dressing - $1322.4 (figures shown are at the higher CRBSI	local infections CRBSIs, and deaths	CHG dressings would reduce costs, local infections and CRBSIs, and deaths

				incremental cost of $25000)		
Hockenhull et al: 2008[3]	UK	Decision analytic model of anti-infective CVCs and standard CVCs	Patients requiring CVCs in UK	anti-infective central venous catheters save an estimated £138.20 per patient vs standard practice	CRBSIs	anti-infective CVCs are cost saving
Ye et al: 2011[4]	US	Decision analytic model of CHG-impregnated dressing to standard care	Patients requiring CVCs	CHG-impregnated dressing - $712,129 vs Standard care - $1,607,947 (Based on a hospital inserting 3,078 CVCs per year)	CRBSIs, local infections, and ITU bed days	CHG dressing is a cost-effective CRBSI prevention treatment option

Schwebel et al: 2012[5]	France	Trial based evaluation of 3- and 7- day CHG- vs standard dressings	Patients from 7 ICUs in France	Chlorhexidine gluconate-impregnated sponges for catheter dressings saved money vs standard dressing decreasing the cost per catheter by at least $83	CRBSIs, catheter-related infection	CHG dressings save money

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Study name: Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;282:554-560[1]		
Study design	Decision analytic model based on data from randomised controlled trials, meta-analyses and case controlled studies and US safety databases	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Objective to estimate the incremental clinical and economic outcomes associated with the use of antiseptic-impregnated vs standard catheters
2. Was the economic importance of the research question stated?	Yes	See, Introduction
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payers
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The interventions were chosen for comparsion in view of the availability of a meta-analysis comparing these interventions
5. Were the alternatives being compared clearly described?	Yes	Antiseptic coated catheters is a generic term for a specific device containing chlorhexidine and silver suphadiazine
6. Was the form of economic evaluation stated?	Yes	Decision analytic model based on data from randomised controlled trials, meta-analyses and case controlled studies and US safety databases
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999;281:261-267
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	

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)?	Yes	Published as a separate meta-analysis
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	See Outcome assessment and sensitivity analysis
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	No direct measure of costs
14. Were productivity changes (if included) reported separately?	No	
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	Table 2
17. Were the methods for the estimation of quantities and unit costs described?	Yes	From published studies
18. Were currency and price data recorded?	Yes	USD
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	See Figure 1
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No Yes	Parameters discussed
22. Was the time horizon of cost and benefits stated?	Not clear	
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?	N/A	
26. Were the details of statistical test(s) and	N/A	

confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	See Figure 2 and 3
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Not clear	Costs benefits reported were incremental however the absence of an incremental cost-effectiveness ratio was explained
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	.Our analysis indicates that the use of antiseptic-impregnated central venous catheters results in both decreased costs and decreased morbidity and mortality in hospitalised high risk patients
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Discussion of patient populations and catheter types were made.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Crawford AG, Fuhr, Jr. JP, Rao B. Cost–Benefit Analysis of Chlorhexidine Gluconate Dressing in the Prevention of Catheter-Related Bloodstream Infections. Infection Control and Hospital Epidemiology, Vol. 25, No. 8 (August 2004), pp. 668-674[2]	
Study design	RCT based Cost-benefit analysis of CHG impregnated sponges versus standard treatment for central venous catheters (CVCs). CBA presented as Budget Impact expressed as

	potential annual US net benefits	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To compare the costs with the benefits of using chlorhexidine gluconate sponges on central venous catheters and to determine the effectiveness of these in reducing local infections and catheter-related bloodstream infections (CRBSIs), costs, and mortality.
2. Was the economic importance of the research question stated?	Yes	Catheter-related bloodstream infections significantly associated with increased hospital stay and costs. The importance of addressing the financial implication of adopting this strategy is justified in the introduction
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Hospital perspective at the national level
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The superior clinical efficacy of using CHG sponges vs. standard dressings to prevent CRBSI has been previously proven. This work addresses the financial implication of adopting this strategy.
5. Were the alternatives being compared clearly described?	No	Although there is a clear identification of the CHG impregnated treatment, the comparator is not clearly described (mentioned as control or standard treatment).
6. Was the form of economic evaluation stated?	Yes	CBA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Type of evaluation chosen to evaluate net financial benefits
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	However, the source data for efficacy has not been published in peer-reviewed journal (Manufacturer data on file and presentation in a congress)
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or	N/A	

meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Decision analysis evaluated averted CRBSI treatment cost per patient resulting from chlorhexidine dressing use
12. Were the methods used to value health states and other benefits stated?	Yes	Costs estimations of chlorhexidine dressing versus standard treatment, averted cost of treating local infection and CRBSI
13. Were the details of the subjects from whom valuations were obtained given?	No	Description of the population studies in the RCT are not given No direct measure of costs
14. Were productivity changes (if included) reported separately?	N/A	
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?	No	
17. Were the methods for the estimation of quantities and unit costs described?	N/A	Estimated from published data and from a public healthcare database
18. Were currency and price data recorded?	Yes	USD
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	Figure. Decision analysis model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	The model follows the approach proposed by Veenstra et al. for the cost-effectiveness of antibiotic-coated catheters.
22. Was the time horizon of cost and benefits stated?	No	The reader can only assume from the results that the time horizon was one year (annual benefits)
23. Was the discount rate stated?	No	Costs estimated are not related to an specific year and there is no mention to discount rate
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No stochastic data analysis performed
27. Was the approach to sensitivity analysis described?	Yes	The sensitivity analyses employed two estimates of the baseline rate of catheter-related BSI in U.S.; three estimates of the number of catheters used annually in U.S. hospitals, and two estimates of the cost of catheter-related BSI based on the literature.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Based on published data and taken a conservative approach
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	The study pointed out potential financial benefits of chlorhexidine dressings.
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Several methodologic limitations, restricting the generalizability of the findings have been addressed in the discussion
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, Gamble C, McLeod C, Walley T and Dickson R. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in

preventing bloodstream infections: a systematic review and economic evaluation. *Health Technology Assessment* 2008; Vol. 12: No. 12[3]		
Study design	Health Technology Assessment of anti-infective central venous catheters (AI-CVCs) compared to standard CVCs, including meta-analyses on the effectiveness, a review of health-economic evidence and an economic evaluation using a decision analytic model built for the UK. **The current quality assessment will focus on last of these three aspects.**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	The objective was to analyse the economic performance (cost effectiveness and potential cost-savings) of using AI-CVCs to reduce the number of CRBSIs in patients requiring a CVC. The analysis comprised a basic decision-analytic model exploring a range of possible scenarios for the UK.
2. Was the economic importance of the research question stated?	Yes	See Executive Summary page xi
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Payer: NHS in England and Wales. None of the previously conduct were directly relevant to the UK NHS. The decision-analytic model and built and used to fill this gap
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Alternatives (AI-CVCs vs. standard CVCs) were identified in the systematic review of published studies
5. Were the alternatives being compared clearly described?	Yes	AI-CVCs included three categories of coated catheters (antiseptic externally coated, antiseptic both ext. and internally coated and antibiotic coated). Standard CVC have no anti-infective coating
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	3 out 4 published studies previously analysed by the authors were CEA; this type of economic evaluation is recognized as appropriate for assessing technologies for preventing infections (health outcomes expressed in natural units: number of infections

		prevented
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Literature
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Effectiveness based on a meta-analysis of several published
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)?	Yes	First part of the publication
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	CE criterion: Cost per CRBSI avoided
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	No direct measure of costs
14. Were productivity changes (if included) reported separately?	N/A	
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	Table 21
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Chapter Baseline assumptions; page 76
18. Were currency and price data recorded?	YES	GBP
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	Figure 27
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	The authors decided to use a very simple decision-tree model
22. Was the time horizon of cost and benefits stated?	Yes	1 year
23. Was the discount rate	N/A	

stated?		
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No statistics provided; no ICs for the estimates was given
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? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Table 22 and 22
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	Use of AI-CVCs instead of standard CVCs can lead to decreased medical costs
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	The discussion points out that several key parameters (e.g. costs and health outcomes associated with hypersensitivity, local infections, assumptions about attributable mortality and specification of CVC type) were not included in the model. Also mention lack of local data and advise interpretation with caution
36. Were generalisability issues addressed?	Yes	Authors emphasized that the size of the benefit assumed from AI-CVCs compared with standard CVCs is the result of a meta-analysis which included a mix of high-risk (ICU, surgery, cancer) and low-risk (hospital) patients. In

		addition, the analysis does not differentiate between types of AI-CVC.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C3 Quality assessment of health economic studies

Study name: Ye X et al:Economic impact of use of chlorhexidine-impregnated sponge dressing for prevention of central line-associated infections in the United States. Am J Infect Control 2011;39:647-654.[4]		
Study design:	Economic analysis using data from peer-reviewed published studies to populate a decision model.	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	to perform a cost-effectiveness evaluation of the use of the CHG-impregnated sponge dressing compared with standard care from a hospital perspective
2. Was the economic importance of the research question stated?	Yes	There are few data on the cost-effectiveness of measures to prevent CR-BSI from a hospital perspective thus, further high-quality cost-effectiveness assessment is needed to facilitate the decision-making process.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	US health care decision makers in the hospital setting, and a hospital perspective was adopted for the analysis
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	The comparators in the economic evaluation described as CHG impregnated sponge dressing (ie, CHG-impregnated sponge dressing + chlorhexidine skin preparation + transparent film dressing) versus standard care (ie, chlorhexidine skin preparation and transparent film dressing alone).
6. Was the form of economic evaluation stated?	Yes	Decision analytic model as a structured representation of ‘‘real-world’’ health care activities incorporating event probabilities, resource utilization, costs, and patient outcomes
7. Was the choice of form of economic evaluation justified in relation to the questions	No	

addressed?		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	The clinical and economic data used to populate the decision analytic model were obtained from the published literature.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	NA	
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)?	Yes	efficacy estimates for CHG-impregnated sponge dressing with standard or impregnated catheters were weighted equally in calculating the clinical impact of CHG-impregnated sponge dressing
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	CHG-impregnated sponge dressing demonstrated a reductionof CR-BSIs by 69% in standard CVCs when compared with standard care in critically ill patients. When used in combination with impregnated catheters, CHG-impregnated sponge dressing delivered an incremental reduction of 44% in CR-BSIs compared with impregnated catheters alone
12. Were the methods used to value health states and other benefits stated?	NA	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Each cost was described individually
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	

20. Were details of any model used given?	Yes	The model was described and also stated to be interactive with assumptions easily modifiable for sensitivity analyses and to adjust for differences across hospitals and health care systems.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	See 20
22. Was the time horizon of cost and benefits stated?	No	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Alternate plausible estimates or confidence interval values of estimates were used when available. When other parameter estimates were not available or appropriate, a range of +25% of the base case value was implemented.
28. Was the choice of variables for sensitivity analysis justified?	Yes	The number of CVCs was not evaluated in a sensitivity analysis because the results were directly proportionate to the number of CVCs.
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	Because the technology was economically ‘‘dominant’’ a cost-effectiveness ratio does not need to be calculated because it would not cost health care payers incremental dollars to derive the additional benefit

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Presented in the form of a chart (Fig 1)
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	CHG-impregnated sponge dressing is a cost-effective and cost savings treatment option for patients requiring CVCs. The use of the CHG-impregnated sponge dressing with standard care will result in better clinical outcomes for patients and lower total health care costs compared with standard care alone.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Two key limitations to the study were cited
36. Were generalisability issues addressed?	Yes	The results of this study may not be applicable to smaller hospitals or hospitals with lower rates of CVC insertion. This analysis was also conducted from the perspective of a US hospital payer, and the results of the evaluation would differ from a different payer perspective or in a different country.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Schwebel C, Lucet JC, Vesin A et al. Economic evaluation of chlorhexidine-impregnated sponges for preventing catheter-related infections in critically ill adults in the Dressing Study. *Crit Care Med* 2012;40:11-17. [5]		
Study design	Trial based evaluation	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Not clear	Objective stated as to assess the economic impact of the use of CHG sponge dressings for arterial or central vein catheters from an ICU perspective
2. Was the economic importance of the research question stated?	Yes	See introduction to the publication
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	ICU patients, geography not mentioned
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Standard dressings
5. Were the alternatives being compared clearly described?	Not clear	detailed in separate study publication: see 8
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Not expressly stated why
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. JAMA 2009 Mar 25;301(12):1231-41.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	Referred to reference above where full details are available
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	Yes	In model presented in Figure 1

evaluation clearly stated?		
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?	No	
14. Were productivity changes (if included) reported separately?	Yes	In the Online supplement
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	See Electronic Material 2 in the Online supplement
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Micro-costing study
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Exchange rate used stated (€ to $) based on the 2007 eschange rte of 1$ = 0.73€
20. Were details of any model used given?	Yes	See Figure 1
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No Yes	
22. Was the time horizon of cost and benefits stated?	N/A	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	One way and two way sensitivity analyses conducted
28. Was the choice of variables for sensitivity analysis justified?	No	However, One way analysis showed that the most sensitive parameter was the rate of major

		catheter related infection.
29. Were the ranges over which the parameters were varied stated?	Yes	Figure 2
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Sensitivity analyses includes baseline rates of MCRI & implementation of swabbing with standardised skin preparation with 2% CHG solution was mentioned but not resolved
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	See Timsit 2009
33. Was the answer to the study question given?	Not clear	We conclude that the use of CHG Sponges is cost saving in ICUs even when the baseline MCRI is low
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Results were obtained from a large teaching hospital which may limit relevance to other institutions.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

A *de novo* economic model was developed as there were no UK based studies that addressed the cost-effectiveness of Tegaderm CHG against standard dressing.

The objectives of the cost-effectiveness analysis were to:

1. Estimate the costs and consequences of different interventions (Tegaderm CHG, Tegaderm, etc) implemented to reduce catheter related events in an acute setting
2. Identify the strategy that is most likely to be cost-effective for patients in an acute setting requiring an intravascular catheter (IVC)

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Patients (age ≥ 18 years) admitted to an intensive care unit (ICU) or any critical care setting requiring an intravascular catheter (IVC) inserted after admission for at least 48 hours. IVCs considered included:

(i) Short-term central venous catheters (CVCs) inserted via the subclavian, internal jugular or femoral vein and long-term CVCs inserted peripherally via the cephalic, basilic or brachial vein (peripherally inserted catheters, PICCs)

(ii) Arterial catheters inserted via the radial, ulnar, brachial, femoral or dorsalis pedis artery

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

There are two comparators in the scope:

1. Swabbing with 2% CHG in alcohol and sterile semi-permeable transparent dressing which **is** a comparator in the model

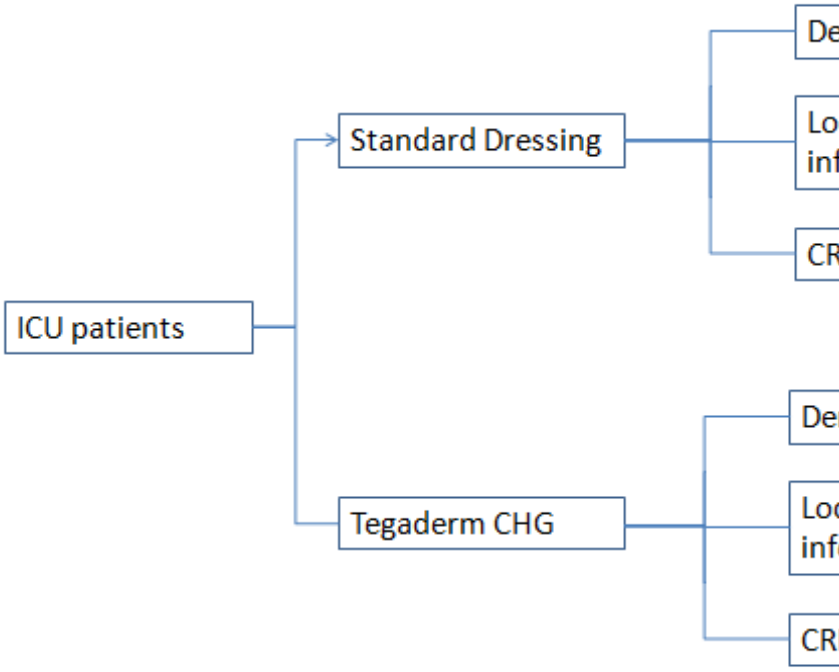
2. Swabbing with 2% CHG in alcohol and CHG impregnated dressing is **not** part of the model due to lack of any direct comparative evidence.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

Figure 2 shows the structure of the model

Figure 2



9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

A *de novo* economic model was developed using Excel to explore the costs and health outcomes associated with use of Tegaderm CHG and standard care (non-antimicrobial dressings) for critical care patients receiving therapy via intravascular catheters. The economic perspective of the model is the NHS in England and Wales with the structure of the mode shown in Figure 2.

Tegaderm CHG dressing can be regarded as a disease prevention product. The results from the Timsit 2012 publication demonstrate a significant reduction in CR-BSI. This complication associated with the use of IVCs affects a minority of critical care patients but leads to significantly longer stays in critical care. The costs associated with longer stays in critical care have been employed in the model as representative of the costs associated with CR-BSI.

Local site (insertion site) infection is a complication of patient treatment with IVCs. It is a local infection of the intra-cutaneous tract of IVCs. Removal of the IVC and insertion of the site is a consequence of this condition. The costs of treatment of local site infection have been included in the model.

There are a proportion of patients who have a dermatitis when Tegaderm CHG dressing is used. The costs of treatment of dermatitis at the catheter insertion site have been included in the model.

In Section 3.3 we described how Tegaderm CHG dressing can be readily substituted into the catheter site care protocol for intravascular catheters. The need for training in application of the product is based around supplier led drop in sessions that are fitted around patient care. In view of this no provision for costs of training have been included in the model.

The model assigned each patient with an indwelling intravascular catheter and a standard dressing, a baseline risk of associated dermatitis, local infection at the catheter insertion site and CR-BSI. The risks of these events for patients with a Tegaderm CHG were estimated by applying the effectiveness parameters from the clinical review to the baseline risks. 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 CR-BSI. Results were estimated as mean values of 1000 probabilistic sensitivity analysis (PSA) runs, each run with a different estimate for the risks, hazard ratios (HR), and costs sampled from probability distributions representing uncertainty in the parameter estimates.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

The different interventions (Tegaderm CHG and standard care) were applied to a hypothetical cohort of patients with catheters in acute setting. The model assigned each patient a probability of CR-BSI, dermatitis and local infection depending upon whether they had Tegaderm CHG or standard dressings. Costs were also accrued through costs of intervention (i.e. Tegaderm CHG). Hospital treatment costs depended on whether the patients had CR-BSI, dermatitis or local infection.

9.1.7 Define what the model's health states are intended to capture.

The model's health states are intended to capture only conditions that add to cost. The outcomes included in the model were (a) CR-BSI, (b) local site infection and, (c) dermatitis.

In the development of the model, parameters in addition to these were considered for inclusion but then rejected on further examination. One of these was that the Tegaderm CHG dressing would decrease the numbers of patients with suspected CR-BSI. The costs of diagnosis of sepsis, including blood cultures and techniques for assessment of suspected CR-BSI were also considered for inclusion in the model. However, a recent audit of the ICU at University Hospital Birmingham Prof Elliott, personal communication) did not show any differences in rates of suspected sepsis between those patients who had Tegaderm CHG dressings as compared to those who received non-antimicrobial dressings. In view of this, these potential costs were omitted from the model.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	The model took a short time horizon	Hospital length of stay is assumed to be 10 days	Ye et al: 2011[4]
Discount of 3.5% for costs	No discount rate was used	the model took a short time horizon so discounting was not considered necessary	NA
Perspective (NHS/PSS)	The economic perspective of the model was the NHS in England and Wales	Scope of the review was England and Wales	NA
Cycle length	N/A	NA	NA
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

The outcomes included in the model are (a) catheter blood stream infection, (b) local site infection, (c) dermatitis. The model estimated the number of these events in the patient cohort by using a probability of these events depending upon the type of intervention. The effectiveness parameters for Tegaderm CHG were estimated from Timsit et al[7], the only relevant study identified in a systematic review.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Due to the short time horizon in the study matching the time horizon in practice no extrapolation was made

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final

clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Catheter colonisation is often used as a surrogate outcome for CR-BSI and has been shown to have a good correlation with this outcome (Rinders et al[6]). Timsit et al 2012[7] reports data comparing catheter colonisation in patients cared for with non-antimicrobial dressings and Tegaderm CHG dressing. However, since significant differences in CR-BSI were reported directly in Timsit 2012[7] we have determined there would be little value in including surrogate outcomes based on catheter colonisation in the model.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The impact of contact dermatitis and local infection were included in the cost analysis.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

- *The criteria for selecting the experts:*

The criteria for selecting the clinical advisers was based on their levels of expertise in a relevant clinical area and credibility with the intended target audience. Consideration was given to levels of heterogeneity amongst experts resulting in selections from different clinical areas (Infection Prevention and Critical Care). To mitigate concerns around whether different categories of participants produce different results discussion and review with a panel within the company the following descriptions for expert advisers was defined:

a) Facility lead clinician in critical care and experience in the use of Tegaderm CHG dressing in clinical practice

b) Facility lead in infection prevention, lead author in Medline listed in publications on catheter related infections, and experience in the use of Tegaderm CHG dressing in clinical practice

- *the number of experts approached*

Four clinical experts were approached who were employees of NHS England Trusts where Tegaderm CHG dressing was in use in critical care units. Two of these experts provided opinion on the design of the model and the inclusion of model parameters that were relevant to clinical practice. The two experts selected were experienced in their fields of Infection Prevention or Critical Care.

1.Professor Tom Elliott, Consultant Microbiologist / Deputy Medical Director, University Hospital Birmingham

2. Dr Tony Whitehouse, Consultant Critical Care and Anaesthesia

While Professor Elliott has considerable experience in the research into interventions and causes of CR-BSI, Dr Whitehouse has considerable experience in the daily care of critical care patients.

- *the number of experts who participated*

Two experts participated as the sponsor's clinical advisers and gave comment on the economic model

- *declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought*

Professor Tom Elliott, Consultant Microbiologist / Deputy Medical Director, University Hospital Birmingham has received unrestricted research grants from 3M and Carefusion companies. He has also served as a speaker in

symposia and has participated in scientific boards for 3M and Carefusion companies in the past 5 years.

Dr Tony Whitehouse, Consultant Critical Care and Anaesthesia, University Hospital Birmingham has no conflicts of interest to declare

- *the background information provided and its consistency with the totality of the evidence provided in the submission*

A draft publication was written and sent to the clinical advisers for their review and comments. The publication described the health economic model and the assumptions that were made regarding the following:

- *the method(s) used to collect and collate the opinions*

A draft publication was authored and sent to the clinical advisers for their review and comments. The publication described the Timsit 2012 study and a health economic model and the assumptions that were made in building the model. Criticism was received and parameters changed according to a consensus approach.

- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*

Information was gathered by telephone and direct interview with the clinical advisers and later by comments provided on the draft publication. Due to the small number of participants telephone interviews replaced traditional questionnaires, the responses were aggregated and then clarified by further discussion with each individual participant (via a further call or face-to-face interview). The clarified opinions were embedded into the publication which was then provided to the experts for further individual comment.

- *the questions asked*

1 Average length of stay of patients in critical care.

2 Extra length of stay where CR-BSI occurs.

3 Levels of severe dermatitis observed during clinical use of Tegaderm CHG dressing.

4 Costs that are associated with CR-BSI and candidates for inclusion in the model.

5 The potential for a reduction in numbers of incidences of diagnosis of sepsis for critical care patients treated with Tegaderm CHG dressing.

6 The relevance of the health economic model structure to the needs of NHS facilities.

- *whether iteration was used in the collation of opinions and if so, how it was used*

Not used

- *the uncertainly around these values should be addressed in the sensitivity analysis.*

Length of stay due to CRBSI: Schwebel et al[5] reported that the mean additional hospital length of stay for patients with CR-BSI is 11 days. In Europe, additional length of stay in ICU has been reported as 9 to 10 days Timsit[7]. However the experts regarded this as maybe longer than that seen in many ICUs in the UK where it was considered that the average length of stay for a CR-BSI patient will vary between 6 days (first 2 days in ICU and rest of the 4 days in general medical ward) and 10 days (first 3 days in ICU and the rest of the 7 days in general medical ward).

Levels of severe dermatitis: There was no report of severe dermatitis related to the CHG gel dressing.

Cost of CRBSI: The clinical experts felt that the cost of an average day in a UK ICU to be between £1,800-£2,400 with an additional £100 for the consultant time and consumables. This figure in combination with the extra ward based costs of £480 per day results in an average extra total cost of around £9,750. They also estimated that in clinical practice approximately 50% of intravascular catheters are removed due to suspected CR-BSI and if they are subsequently replaced the cost is estimated to be £140 (acquisition cost of catheter £35; X-ray for confirming position of catheter £50 plus consumables of £15 plus staff costs to carry out the procedure at £40.00). In view of this a figure of £140 for catheter replacement has been included in the total cost of CR-BSI, which results in the overall CRBSI cost of £9,890. This figure is very similar to that used in a HTA report by Hockenhull et al[3] in 2008 who reported a mean CR-BSI cost of £9,148, that when inflated to present day costs using the hospital and community health services (HCHS) pay and price index[10] is £9,905. Thus, the cost of CR-BSI used in the model is £9,900 as shown in Table C5.

The potential for a reduction in numbers of incidences of diagnosis of sepsis for critical care patients treated with Tegaderm CHG dressing: A recent audit of the ICU at University Hospital Birmingham did not show any differences in rates of suspected sepsis between those patients who had Tegaderm CHG dressings as compared to those who received non-antimicrobial dressings. In view of this, these potential costs were omitted from the model.

Relevance of the model: The model was considered to be a relevant structure to the needs of NHS facilities by the experts.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Parameter	Mean	Distribution	Source
Average length of catheterisation	10 days	Normal (10,2)	Timsit et al (7)
Baseline risks			
CR-BSI risk (per 1000 catheter days)	1.48/1000 catheter days	Normal	Bion et al (8)
Local site infection risk (per patient)	0.1	Normal (0.1, 1)	Ye et al (4)
Dermatitis risk (per catheter)	0.0026	Normal (0.0026,0.0002)	Schwebel et al(5), Timsit et al(7)
HRs for Tegaderm CHG			
CR-BSI	0.402 (0.186–	Lognormal (-0.911,0.393)	Timsit et al(7)
Local site infection	0.402 (0.186–	Lognormal (-0.911,0.393)	Timsit et al(7), Ye et al (4)
Dermatitis (as RR)	4.4 (1.7–11.6)	Lognormal (1.482 -0.489)	Timsit et al(12)
Costs (in £)			
Unit non antimicrobial transparent film dressings	£1.34	Fixed	3M
Unit Tegaderm CHG cost	£6.21	Fixed	3M
CR-BSI	£9,900	Gamma (198,50)	Hockenhull et al(3)
Local site infection	£250	Gamma (50,5)	Saint et al(9)

Dermatitis	£150	Gamma (30,5)	Schwebel et al(5)

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Patients entering ICU are reimbursed via HRG4 based on a locally agreed tariffs with the CCG which are calculated based on the likely length of stay. The total cost of in-patient care is also reimbursed via HRGs, these HRGs attract a national tariff and have a long stay trim point (based on admission method). Once the long stay trim point has been exceeded reimbursement attracts a per-day long stay (or "excess bed days") payment

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

L91.1 – open insertion of central venous catheter
L91.2 – insertion of central venous catheter after NEC
L91.3 – attention to central venous catheter after NEC
L91.4 – removal of central venous catheter

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

The resources included in the model are those associated with the treatment, where appropriate, for any local infections at the catheter insertion site, CR-BSI, and dermatitis. It was assumed that all other initial treatment resource

use were the same and were not included in the model. The Tegaderm CHG dressing is readily adopted into clinical practice and can directly replace non-antimicrobial transparent film dressing in the care pathways for arterial and central venous catheters. Therefore no additional staff costs were included in the model.

We have conducted a targeted literature review to identify the unit costs for these events than a systematic search of all relevant resource data. The costs were identified from previous HTAs and validated using expert clinical input.

The main driver in the model was CR-BSI, which included diagnosis, catheter replacement and the associated increased length of stay. Schwebel et al[5] reported that the mean additional hospital length of stay for patients with CR-BSI is 11 days, which resulted in a reported cost estimate of CR-BSI in excess of $25,000 (14;18). In Europe, additional length of stay in ICU has been reported as 9 to 10 days[7]. However, this was regarded as longer than that seen in many ICU in the UK by our clinical experts, who considered that the average length of stay for a CR-BSI patient will vary between 6 days (first 2 days in ICU and rest of the 4 days in general medical ward) and 10 days (first 3 days in ICU and the rest of the 7 days in general medical ward). In a UK hospital the cost of an average day in the ICU has been determined as being between £1,800-£2,400 with an additional £100 for the consultant time and consumables. This figure in combination with the extra ward based costs of £480 per day results in an average extra total cost of around £9,750. Also, it is estimated that in clinical practice approximately 50% of intravascular catheters are removed due to suspected CR-BSI and if they are subsequently replaced the cost is estimated to be £140 (acquisition cost of catheter £35; X-ray for confirming position of catheter £50 plus consumables of £15 plus staff costs to carry out the procedure at £40.00). In view of this a figure of £140 for catheter replacement has been included in the total cost of CR-BSI, which results in the overall CRBSI cost of £9,890. This figure is very similar to that used in a Health Technology Assessment (HTA) report by Hockenhull et al[3] in 2008 who reported a mean CR-BSI cost of £9,148, that when inflated to present day costs using the hospital and community health services (HCHS) pay and

price index (20), is £9,905. Thus, the cost of CR-BSI used in the model is £9,900 as shown in Table C5.

The cost of treatment for a local site infection was reported as $400 by Saint et al[9] and it was considered that a cost of £250 for treatment of local infection in UK was a reasonable estimate and was therefore adopted in the model as shown in Table 1.

The costs of treating dermatitis were taken from Schwebel et al[5] who reported that contact dermatitis requires four standard dressings, removal of the catheter and insertion of a new catheter. They used a micro costing approach to estimate the total costs as $228. We considered that the equivalent cost of £150 for treatment of dermatitis was acceptable, and this was used in the model as shown in Table C5.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

The model and its outputs were shared with two clinical advisers. Because the model is driven primarily by extra length of stay for patients with CRBSI this was discussed and validated with two clinical advisors:

1. Professor Tom Elliott, Consultant Microbiologist / Deputy Medical Director, University Hospital Birmingham

2. Dr Tony Whitehouse, Consultant Critical Care and Anaesthesia, University Hospital Birmingham

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

The technology (Tegaderm CHG): is available in 4 sizes and the prices are as follows:

	Size	Price	Proportion used
Tegaderm CHG 1660R	7 x 8.5cm	£5.68	<5%
Tegaderm CHG 1657R	8.5 x 11.5cm	£6.21	85%
Tegaderm CHG 1659R	10 x 15.5cm	£7.17	13%
Tegaderm CHG 1658R	10 x 12cm	£5.52	<5%

Clearly Tegaderm CHG 1657 is the most commonly used so the price used in the model is £6.21

The Comparator 1:

In the model the standard dressing used is Tegaderm 1635 but Smith and Nephew's iv 3000 is another commonly used dressing and has been included here for reference.

Prices are as follows:

	Price (inc VAT)
Tegaderm 1635	£1.34
IV3000 10x12cm	£1.61

Comparator 2

Ethicon's Biopatch comes in one size only and requires a cover dressing which could potentially be various sizes and makes. Tegaderm 1635 is a commonly used cover dressings so the price has been included below**.**

	Price
Ethicon Biopatch	£5.16
Cover dressing (assume Tegaderm 1635)	£1.34

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The list prices were used in all cases

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£6.21 x 3 = £18.63	Price – NHSSC The average length of stay for a patient with an intravascular catheter in situ on ICU is estimated to be 10 days (Ref: Ye. et al) and with the prescribed time for standard dressing being between 3 and 7 days, this resulted in a conservatively estimated three non-antimicrobial transparent film dressings required per patient.
Consumables (if applicable)	NA It was assumed that all other initial treatment costs eg swabbing were the same and therefore not included in the model.	N/A
Maintenance cost	NA	N/A
Training cost	None	N/A
Other costs	None	N/A
Total cost per treatment/patient	£18.63	

Table C7 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	1.34 x 3 = £4.02	NHSSC The average length of stay for a patient with an intravascular catheter in situ on ICU is estimated to be 10 days (Ref: Ye. et al) and with the prescribed time for standard dressing being between 3 and

		7 days, this resulted in an estimated three non-antimicrobial transparent film dressings required per patient.
Consumables (if applicable)	NA It was assumed that all other initial treatment costs eg swabbing were the same and therefore not included in the model.	N/A
Maintenance cost	None	N/A
Training cost	None	N/A
Other costs	None	N/A
Total cost per treatment/patient	£4.02	

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Given that the model is a decision tree, rather than a Markov model, it does not include health states per se. However, the model includes different outcomes (CR-BSI, local site infection and, dermatitis) and the costs associated with these outcomes are described in section 9.3.3 and summarised in Table C8.

Table C8 List of health states and associated costs in the economic model

The model developed was based upon a short time frame and a Markov modelling approach wasn't used so for the costs refer to Table C5

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table C9 List of adverse events and summary of costs included in the

cost model

Adverse events	Items	Value	Reference
Contact Dermatitis	Catheter removal	£25 ($38.2)	Schwebel et al[5]
	Four standard dressings	£24 ($36.3)	As above
	Catheter insertion	£101 ($153.4)	As above
	Total	£150	

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Although there are potential other costs eg ongoing social care, these were not considered as part of the evaluation.

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

None were considered relevant to this evaluation

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented

and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The main cost drivers are the CRBSI costs. Thus, sensitivity analysis was performed around the baseline CRBSI risks and unit cost of CRBSI.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic sensitivity analysis was performed around the baseline CR-BSI risks and unit cost of CR-BSI as they are identified as the key cost drivers. The parameters used in the deterministic sensitivity analysis are presented in Table C10.1

Probabilistic sensitivity analysis was performed and cost-effectiveness analyses results were estimated as mean values of 1000 probabilistic sensitivity analysis runs, each run with a different estimate for the risks, HRs, and costs sampled from the probability distributions reported in Table C5. The sources for these parameters are also provided in Table C10.3 (reproduced from Table C5).

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

	Basecase	Low estimate	High estimate
Baseline CRBSI risk (per 1000 catheter days)	1.48	0.5	2.5

CRBSI cost	£9,900	£5,000	£15,000

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis

Not applicable

Table C10.3 Variable values used in probabilistic sensitivity analysis

Parameter	Mean	Distribution	Source
Average length of catheterisation	10 days	Normal (10,2)	Timsit et al[7]
Baseline risks			
CR-BSI risk (per 1000 catheter days)	1.48/1000 catheter days	Normal	Bion et al[8]
Local site infection risk (per patient)	0.1	Normal (0.1, 1)	Ye et al[4]
Dermatitis risk (per catheter)	0.0026	Normal (0.0026,0.0002)	Schwebel et al[5], Timsit et al[7]
HRs for Tegaderm CHG			
CR-BSI	0.402 (0.186–	Lognormal (-0.911,0.393)	Timsit et al[7]
Local site infection	0.402 (0.186–	Lognormal (-0.911,0.393)	Timsit et al[7], Ye et al [4]
Dermatitis (as RR)	4.4 (1.7–11.6)	Lognormal (1.482,-0.489)	Timsit et al[7]
Costs (in £)			
Unit non antimicrobial transparent film dressings	£1.34	Fixed	3M
Unit Tegaderm CHG cost	£6.21	Fixed	3M
CR-BSI	£9,900	Gamma (198,50)	Hockenhull et al[3]

Local site infection	£250	Gamma (50,5)	Saint et al[9]
Dermatitis	£150	Gamma (30,5)	Schwebel et al[5]

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

All the parameters in the model are included in the probabilistic sensitivity analysis except the unit costs of standard dressings and Tegaderm CHG dressings, as they can be considered constant.

Deterministic sensitivity analysis was performed around the baseline CR-BSI risks and unit cost of CR-BSI as they are identified as the key cost drivers. The rest of the parameters do not influence the results as much as these two parameters, as observed in section 9.5

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11 Base-case results

	Total per patient cost (£)
Technology (Tegaderm CHG)	£99.63
Comparator 1 (Standard dressing)	£176.89
...	

9.5.2 Report the total difference in costs between the technology and comparator(s).

Total savings per patient - £77.26

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12 Summary of costs by category of cost per patient

	Tegaderm CHG	Non-antimicrobial transparent film dressings	Increment	Absolute increment	% absolute increment
Dressing costs	£18,633	£4,021	£14,612	£14,609	12.54%
CR-BSI	£64,056	£146,657	-£82,601	£83,667	71.80%
Local site infection	£11,120	£25,041	-£13,921	£13,833	11.87%
Dermatitis	£5,818	£1,175	£4,643	£4,425	3.80%
Total	£99,627	£176,894	-£77,267	£116,535	100%

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

The model does not include health states *per se*. However, the costs for the different outcomes included in the model are presented in Table C12.

Table C13 Summary of costs by health state per patient

Please refer to Table C12 for the costs of the different outcomes included in the model.

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Please refer to Table C12 for the costs of the different outcomes included in the model.

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

Sensitivity analysis was performed around the baseline CR-BSI risks and unit cost of CR-BSI as they are identified as the key cost drivers. At a lower CR-BSI baseline risk of 0.5 per 1,000 catheter days, the mean cost savings were £22,700 and at a higher estimate of 2.5 per 1,000 catheter days, the mean cost savings were £135,280. At a lower cost estimate of CR-BSI of £5,000, the mean cost savings were £35,930 while the cost savings were £118,870 at a higher estimate of £15,000.

Table xxx: Cost savings in deterministic sensitivity analysis

	Baseline CRBSI risk	CRBSI cost
Basecase	-£77,267	-£77,267
Low estimate	-£22,700	-£35,930
High estimate	-£135,280	-£118,870

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Not applicable

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

We estimated the costs that would be expected in a typical service for 1,000 patients who require a short term intravascular catheter located in an ICU where Tegaderm CHG was the routine dressing instead of a non-antimicrobial transparent film dressing. The model showed use of Tegaderm CHG results in an overall saving of £77,267 per 1,000 patients i.e. an average cost saving of £77 per patient. Tegaderm CHG has a 98.5% probability of being cost saving compared to standard dressings. The total cost savings is provided as a breakdown of the individual cost differences as shown in Table C12.

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

Our analyses suggest that Tegaderm CHG is a cost saving strategy when implemented for care of patients with intravascular catheters in ICU (see section 9.5.8). Tegaderm CHG results in an overall savings of £77,267 per 1,000 patients i.e. an average cost saving of £77 per patient compared to standard care with a 98.5% probability of being cost saving compared to standard dressings. Most of the savings described are due to a reduction in suspected and confirmed CR-BSI. There are higher costs associated with the acquisition of CHG dressings but the savings in reduced event rates more than offset these costs associated with the technology.

The results were robust to sensitivity analyses performed on the baseline CR-BSI risks and unit cost of CR-BSI (see section 9.5.6). However, the lower the CR-BSI baseline risk and cost of CR-BSI, the lower the cost savings. Similarly, the higher the baseline risk of CR-BSI and the cost of CR-BSI, the higher the average cost savings.

9.5.10 What are the key drivers of the cost results?

The baseline CR-BSI risks and unit cost of CR-BSI are the key cost drivers. Sensitivity analysis performed around using lower and high estimates of the parameters identified that the conclusions are robust, as presented in section

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

None

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

No sub-group analysis was undertaken for the reasons expressed under 9.6.5. Define the characteristics of patients in the subgroup(s).

9.6.2 Describe how the subgroups were included in the cost analysis.

Not applicable

9.6.3 Define the characteristics of patients in the subgroup(s).

Not applicable

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

No subgroup analysis was undertaken in the cost analysis

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered

No subgroups are considered separately in this submission. All critical care patients receiving intravascular catheters were included in the model. There is the opportunity to provide sub-group models that are based on patients receiving either arterial or central venous catheters. However, these patients should not be considered as discreet sub-groups. There is a considerable overlap in patient populations receiving arterial and central venous catheters. Many critical care patients simultaneously receive therapy via these two types of catheter. In the pivotal study, the incidence of colonisation, major-CRI, and CR-BSI was not different between arterial catheters and CVCs. Timsit et al[7] A sensitivity analysis comparing CR-BSI in arterial and central

venous catheters showed no significant difference in hazard ratios (arterial catheters HR 0.39 (0.09-1.64), CVCs HR 0.27 (0.11-0.66)) Timsit et al[7] In view of this evidence we conclude that a sub-group analysis would provide little additional value to the cost analysis.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model was quality-assured by replicating it in another software (DecisionPro^{TM}) and comparing the results with the original (Excel$^{TM)}$ model, which allowed the verification of the model calculations.

For cross validation, the results of the model were also compared with other published cost-effectiveness analyses studies of CHG impregnated devices including other CHG dressings. Our findings for Tegaderm CHG are in line with those reported in previous studies for antimicrobial devices used to prevent catheter related infections (see section 9.8.1 for details).

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of the models were also compared with other published cost-effectiveness analyses studies of CHG impregnated devices including other CHG dressings. The analysis reported by Veenstra et al[1] compared the number of CR-BSIs associated with CHG impregnated and standard intravascular catheters and suggested that antiseptic impregnated catheters are cost saving. Crawford et al[2] performed a trial based evaluation and concluded that CHG sponge dressings would reduce costs, local infections

and CR-BSIs, and associated mortality. Similarly, Hockenhull et al[3] developed a decision analytic model for patients requiring central venous catheters (CVCs) in UK and suggested that anti-infective CVCs are cost saving. More recently, Ye et al[4] suggested that a CHG dressing is also a cost-effective CR-BSI prevention treatment option. Furthermore, Schwebel et al[5] performed a trial based evaluation comparing both 3- and 7- day CHG-dressing with standard dressings and concluded that CHG dressings are associated with financial savings. Our findings for Tegaderm CHG are, therefore, in line with those reported in previous studies for antimicrobial devices used to prevent catheter related infections.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The analysis has some limitations. Any modelling process involves simplifications and assumptions that may not accurately reflect local clinical practice. Owing to the lack of detail of cost estimates in research studies included in the analysis, scenarios were developed and their costs were independently reviewed by clinical experts. The uncertainties about the assumptions made in the estimation of these costs (especially CR-BSI costs) were tested using scenario analysis and the conclusion that Tegaderm CHG is cost saving remains valid in these analyses.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A clinical study designed to directly measure the economic outcomes would clearly be advantageous

References

1 Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. JAMA 1999;282:554-560

2 Crawford AG, Fuhr JP, Jr., Rao B, Crawford AG, Fuhr JPJ, Rao B. Cost-benefit analysis of chlorhexidine gluconate dressing in the prevention of catheter-related bloodstream infections. Infection Control & Hospital Epidemiology 2004;25:668-674.

3 Hockenhull JC, Dwan K, Boland A et al. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess 2008;12:iii-xii, 1.

4 Ye X,Rupnow M, Bastide P et al. Economic impact of use of chlorhexidine-impregnated sponge dressing for prevention of central line-associated infections in the United States. Am J Infect Control 2011;39:647-654.

5 Schwebel C, Lucet JC, Vesin A et al. Economic evaluation of chlorhexidine-impregnated sponges for preventing catheter-related infections in critically ill adults in the Dressing Study. Crit Care Med 2012;40:11-17.

6 Rijnders BJ, Van WE, Peetermans WE. Catheter-tip colonization as a surrogate end point in clinical studies on catheter-related bloodstream infection: how strong is the evidence? Clin Infect Dis 2002; 35: 1053-8.

7 Timsit JF, Mimoz O, Mourvillier B et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults.

American Journal of Respiratory & Critical Care Medicine 2012; 186: 1272-8.

8 Bion Bion J, Richardson A, Hibbert P, et al. 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf 2013 Feb;22(2):110-23.

9 Saint S, Veenstra DL, Lipsky BA. The clinical and economic consequences of nosocomial central venous catheter-related infection: are antimicrobial catheters useful? Infect Control Hosp Epidemiol 2000;21:375-380.

10 Curtis L. Unit costs of health and social care 2013.

12 Appendices

12.1 Appendix 1: Search strategy for published clinical evidence (and adverse events) (section 7.1.1)

The following information should be provided:

12.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Please see search strategy report below for identity of databases used. Databases include:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library
- Web of Science Conference Proceedings
- Econ Lit

12.1.2 The date on which the search was conducted.

The searches were conducted on the 23rd July 2013

12.1.3 The date span of the search.

The searches spanned 1946 to July 2013. Dates for individual databases are identified below:

- Medline/ Medline (R) In-Process 1946 to date of search
- Embase 1974 to 17th July 2013
- The Cochrane Library Various (see report)

- Web of Science C. P. 1990 to date of search
- Econ Lit 1961 to June 2013

12.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search approach and strategies described in Section 7.1 was designed to retrieve all studies irrespective of study design relating to the technology and comparators i.e. methodological filters was not applied to the searches. It was envisaged that the strategies developed in section 7.1 would retrieve all the adverse events studies relating to Tegaderm CHG dressing and relevant comparators.

Please see Search Strategy Report below.

12.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Not applicable

12.1.6 The inclusion and exclusion criteria.

See Table B1, Selection criteria used for published and unpublished studies

12.1.7 The data abstraction strategy.

Data extraction

Data extraction was undertaken by one reviewer and checked by a second reviewer. Discrepancies will be resolved by discussion between two reviewers. If required, a designated member of the 3M team (or the project team) was consulted. Details of eligible studies were extracted into a piloted data extraction. The following data was extracted from the eligible study:

1. Study characteristics

2. Patient and baseline characteristics
(including diagnosis/ age/sex/medications)
3. Details relating to CVC
4. CVC type [short-term or long-term; tunnelled or non-tunnelled etc]
   (i) Insertion: site [subclavian; internal jugular; femoral etc]
   (ii) Insertion procedure: [use of maximal sterile barrier procedures; performed by trained staff; method of skin preparation]
   (iii) Length of catheter insertion (days)
   (iv) Use of antibiotic lock solution
5. Details relating to dressing [type of dressing; dressing change protocol]
6. Details relating to outcomes
7. Details relating to primary outcome (CR-BSI)

(i) Clinical diagnosis –
- Confirmation of the presence or absence of signs of bacteraemia or fungaemia
- Evidence of systemic infection (fever, chills +/- hypotension)
- Catheter in situ or catheter removed

(ii) Laboratory diagnosis –
- Relating to peripheral blood culture
- Presence or absence of positive culture
- Relating catheter culture
- Source of culture (catheter tip/ hub/segment)
- Method for obtaining culture (Roll/ vortexing/sonication)
- Culture medium (type/ presence of absence of CHG inhibitors)
- Diagnostic method (semi-quantitative/ quantitative/ differential time to positivity)
- Rates per treatment arm

8. Details relating to secondary outcomes

(i) Skin colonisation
- Assessment methods used
- Rates per treatment arm

(ii) Catheter colonisation
- Assessment methods used
- Rates per treatment arm

(iii) Adverse events
- Assessment methods used
- Rates per treatment arm

(iv) Additional outcomes
- Assessment methods used
- Rates per treatment arm
-

Details for [4] to [10] were extracted per treatment arm to enable pair-wise comparison.

Quality assessment

The methodological quality of the included studywas assessed using the criteria proposed by Centre for Reviews and Dissemination. Items of quality assessment will be incorporated into the data extraction form. Items evaluated included the following:

1. Random sequence generation
2. Allocation concealment
3. Baseline comparability
4. Pre-specified eligibility criteria
5. Blinding (outcome assessors [blinding of care-givers/patients may be difficult to achieve in most studies])
8. Reporting of the primary outcome (as a point estimate with a measure of variability)
9. Inclusion of an intention-to-treat analysis

Disagreements were resolved through discussion with or without referral to a third party..

No formal quality assessment was undertaken for non-RCT evidence or unpublished evidence relating to adverse events.

A sample of the data extraction form is presented below:

Sample: Data Extraction Form

STUDY CHARACTERISTICS	Reference ID
	Study ID
	Study design
	Country of study
	Setting
	Description of critical care unit
	Study duration
	Funding
	Sample size(total)
	Catheters (total)
	Intervention
	Control
	Length of follow-up (all)
	Length of follow-up (intervention)
	Length of follow-up (control)
	Primary outcome(s)
	Definition(s)
	Secondary outcome(s)
	Definition(s)
PATIENT AND BASELINE CHARACTERISTICS	Inclusion criteria
	Exclusion criteria
	Age, mean(years)
	Gender(%males)

			Diagnosis
			Co-treatments
			Length of stay, ICU (days)
CHARACTERISTICS OF INTRAVASCULAR CATHETERS			CVC type
			Insertion site
			Number of lumens
			Coating of catheter
			Indication for catheter
Length of time(days) during which CVC was in situ		Intervention	mean
			SD
		Control	mean
			SD
		All patients	mean
			SD
Description of catheter care protocol			Pre-insertion
			Post-insertion
			Catheter removal, if infection is suspected
			Description of health practitioner who inserted the catheter
			Was health practitioner trained? Yes or no or not reported
INTERVENTIONS		Description of intervention	Dressing type
			Description of health practitioner dressing CVC site
			Was the health practitioner trained? Yes or no or not reported
		Description of control	Dressing type
			Frequency of dressing change per care protocol
			Description of health practitioner dressing CVC site
			Was the health practitioner trained? Yes or no or not reported
Length of time(days) during which dressing was in situ		Intervention	mean
			SD
		Control	mean
			SD
		All patients	mean
			SD
OUTCOMES	Criteria for assessing catheter-related infection		
	Clinical diagnosis		Evidence of systemic infection (fever, chills +/- hypotension)
			Confirmation of the presence or absence of signs of bacteraemia or fungaemia
			Confirmation of CVC as the only source of infection
	Laboratory diagnosis		Catheter in situ or catheter removed at the time of diagnosis
			Source of blood cultures (paired blood samples - 1 peripheral and 1 from catheter lumen or ≥ 2

			blood samples from different catheter lumens)
			Source of catheter culture(s) (catheter tip/ hub/segment)
			Method used to obtaining culture (roll/ vortexing/sonication)
			Culture medium (type, CHG inhibitors - present or absent)
			Assessment method(s) used (semi-quantitative/ quantitative/ differential time to positivity)
	Intervention group		Unit of analysis
			Number of patients included
			Number of patients analysed
			Number of catheters included
			Number of catheters analysed
			Number of catheter days
	Control group		Unit of analysis
			Number of patients included
			Number of patients analysed
			Number of catheters included
			Number of catheters analysed
			Number of catheter days
Incidence of CRBSI		Diagnostic criteria	
		Intervention	Events
			Total
		Control	Events
			Total
Incidence of other catheter-related infection		Diagnostic criteria	
		Intervention	Events
			Total
		Control	Events
			Total
Incidence of skin colonisation		Diagnostic criteria	
		Intervention	Events
			Total
		Control	Events
			Total
Incidence of catheter colonisation		Diagnostic criteria	
		Intervention	Events
			Total
		Control	Events
			Total
ADVERSE EVENTS	Incidence of adverse events (1)	Diagnostic criteria	
		Intervention	Events
			Total

		Control	Events
			Total
	Incidence of adverse events (2)	Diagnostic criteria	
		Intervention	Events
			Total
		Control	Events
			Total
	Incidence of adverse events (3)	Diagnostic criteria	
		Intervention	Events
			Total
		Control	Events
			Total
PERFORMANCE METRICS	Frequency of dressing change due to dislodgement, soiling etc (state reason for dressing change)	Intervention	Events
			Total
		Control	Events
			Total
	Reported measures of catheter dislodgement, movement or security	Intervention	Events
			Total
		Control	Events
			Total
QUALITY ASSESSMENT			Was the method used to assign participants to the treatment groups really random?
			What method of assignment was used?
			Was the allocation of treatment concealed?
			What method was used to conceal treatment allocation?
			Were details of baseline comparability presented?
			Was baseline comparability achieved for the most important prognostic indicators?
			Were the outcome assessors / data analysts (microbiologists)blinded to the treatment allocations?
			Was there information on likely contamination of samples or missing samples?
			Was follow-up of patients adequate? (at least 80% of study population)
			Were the reasons for withdrawal stated?
			Was an intention-to-treat analysis included?
			Was the study powered to detect differences in outcomes?
			Description of power calculations (brief)
			Notes

Search Strategy Report for Tegaderm CHG Dressing

1. IDENTIFICATION OF PUBLISHED LITERATURE

(A)TEGADERM SEARCHES

Medline and Medline in Process: Ovid. 1946 to Present

1. tegaderm.mp.
2. (chlorhexidine gluconate or chg).mp.
3. Chlorhexidine/
4. 3M.mp.
5. or/2-4
6. dressing$.mp.
7. 5 and 6
8. 1 or 7

Embase: Ovid. 1974 to 2013 July 17

1. tegaderm.mp.
2. (chlorhexidine gluconate or chg).mp.
3. chlorhexidine gluconate/
4. 3M.mp.
5. or/2-4
6. dressing$.mp.
7. 5 and 6

Cochrane Library
Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
Cochrane Central Register of Controlled Trials (CCRT): Wiley Interscience. 1898-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	tegaderm:ti,ab,kw
#2	(chlorhexidine gluconate or chg):ti,ab,kw
#3	MeSH descriptor: [Chlorhexidine] this term only
#4	3M:ti,ab,kw
#5	#2 or #3 or #4
#6	dressing*:ti,ab,kw
#7	#5 and #6
#8	#1 or #7

EconLit: Ovid. 1961 to June 2013

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

Web of Science Conference Proceedings index: Web of Science. 1990-present

#7	#6 OR #1
#6	#5 AND #4
#5	Topic=(dressing*)
#4	#3 OR #2
#3	Topic=(3M)
#2	Topic=((chlorhexidine gluconate or chg))
#1	Topic=(tegaderm)

(B) COMPARATORS SEARCHES

i. Searches for comparators and central venous catheters

a. Medline and Medline in Process: Ovid. 1946 to Present

1. Catheterization, Central Venous/
2. (central adj3 (venous$ or line or pressure)).tw.
3. ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw.
4. exp catheterization, peripheral/
5. Catheters, Indwelling/
6. ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw.
7. ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw.
8. exp Vascular Access Devices/
9. ((cva or cvad or vad or access) adj3 device$).tw.
10. (cvc$ or picc).tw.
11. or/1-10

12. dressing$.mp.
13. exp Bandages/
14. bandage$.mp.
15. adhesive$.mp.
16. gel$.mp.
17. gauze$.mp.
18. tape.mp.
19. film.mp.
20. (permeable or impermeable or non-permeable).mp.
21. ethicon.tw.
22. (smith adj2 nephew).tw.
23. or/12-22
24. 11 and 23
25. opsite$.tw.
26. biopatch$.tw.
27. or/24-26

Embase: Ovid. 1974 to 2013 July 17

1. central venous catheterization/
2. central venous catheter/
3. (central adj3 (venous$ or line or pressure)).tw.
4. ((venous or vein$ or intravenous) adj3 (catheter$ or cannulat$ or access$)).tw.
5. catheterization/
6. indwelling catheter/
7. ((catheter$ or cannulat$ or access$) adj5 (peripher$ or indwell$ or neck or jugular or chest or subclav$ or axillary or groin or femor$)).tw.
8. ((catheter$ or cannulat$ or access$) adj5 (hickman or broviac or cook)).tw.
9. ((cva or cvad or vad or access) adj3 device$).tw.
10. (cvc$ or picc).tw.
11. or/1-10
12. dressing$.mp.
13. exp silver dressing/ or exp foam dressing/ or exp hydrogel dressing/ or exp biological dressing/ or exp hydrocolloid dressing/ or exp wound dressing/ or exp gauze dressing/ or exp occlusive dressing/
14. exp bandage/
15. bandage$.mp.
16. adhesive$.mp.
17. gel$.mp.
18. gauze$.mp.
19. tape.mp.
20. film.mp.
21. (permeable or impermeable or non-permeable).mp.
22. ethicon.tw.
23. (smith adj2 nephew).tw.
24. or/12-23
25. 11 and 24

26. opsite$.tw.
27. biopatch$.tw.
28. or/25-27

b. Cochrane Library

Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
Cochrane Central Register of Controlled Trials (CCRT): Wiley Interscience. 1898-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#1	MeSH descriptor: [Catheterization, Central Venous] this term only
#2	(central next/3 (venous* or line or pressure)):ti,ab,kw
#3	((venous or vein* or intravenous) next/3 (catheter* or cannulation or access*)):ti,ab,kw
#4	MeSH descriptor: [Catheterization, Peripheral] explode all trees
#5	MeSH descriptor: [Catheters, Indwelling] this term only
#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
#7	((catheter* or cannulation or access*) next/5 (hickman or broviac or cook)):ti,ab,kw
#8	((cva or cvad or vad or access) next/3 device*):ti,ab,kw
#9	(cvc* or picc):ti,ab,kw
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	dressing*:ti,ab,kw
#12	MeSH descriptor: [Bandages] explode all trees
#13	bandage*:ti,ab,kw
#14	adhesive*:ti,ab,kw
#15	gel*:ti,ab,kw
#16	gauze*:ti,ab,kw
#17	tape:ti,ab,kw
#18	film:ti,ab,kw
#19	(permeable or impermeable or non-permeable):ti,ab,kw
#20	ethicon:ti,ab,kw
#21	(smith next/2 nephew):ti,ab,kw
#22	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23	#10 and #22
#24	opsite*:ti,ab,kw
#25	biopatch*:ti,ab,kw
#26	#24 or #25

c. *EconLit: Ovid. 1961 to June 2013*

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

d. *Web of Science Conference Proceedings index: Thomson Scientific.*

#22	#21 OR #20 OR #19
#21	Topic=(biopatch*)
#20	Topic=(opsite*)
#19	#18 AND #7
#18	#17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8
#17	Topic=((smith NEAR/2 nephew))
#16	Topic=(ethicon)
#15	Topic=((permeable or impermeable or non-permeable))
#14	Topic=(film)
#13	Topic=(tape)
#12	Topic=(gauze*)
#11	Topic=(gel*)
#10	Topic=(adhesive*)
#9	Topic=(bandage*)
#8	Topic=(dressing*)
#7	#6 OR #5 OR #4 OR #3 OR #2 OR #1
#6	Topic=((cvc* or picc))
#5	Topic=(((cva or cvad or vad or access) NEAR/3 device*))
#4	Topic=(((catheter* or cannulat* or access*) NEAR/5 (hickman or broviac or

#3	cook)))
#2	Topic=(((catheter* or cannulat* or access*) NEAR/5 (peripher* or indwell* or neck or jugular or chest or subclav* or axillary or groin or femor*)))
#1	Topic=(((venous or vein* or intravenous) NEAR/3 (catheter* or cannulat* or access*)))
	Topic=((central NEAR/3 (venous* or line or pressure)))

e. Summary of search results of comparators and central venous catheters

Database	Tegaderm ($$tegaderm)	Date searched	Comparators ($$comparators)	Date searched
Medline ($$medline)	389	23/07/13	1919	23/07/13
Embase ($$embase)	822	23/07/13	3154	23/07/13
CCRCT ($$ccrct)	96	23/07/13	246	23/07/13
HTA ($$hta)	0	23/07/13	1	23/07/13
DARE ($$dare)	2	23/07/13	5	23/07/13
CDSR ($$cdsr)	1	23/07/13	6	23/07/13
NHS EED ($$nhseed)	4	23/07/13	11	23/07/13
EconLit ($$econlit)	0	23/07/13	0	23/07/13
Web of Science Conference Proceedings index ($$wos-cpi)	145	23/07/13	267	23/07/13
Total	1459	-	5609	-
Total unique in database	914	-	3751	-
MAUDE	109	29/07/13	69	29/07/13 & 30/08/13
EuroScan	0	29/07/13	0	29/07/13
EMEA	0	29/07/13	0	29/07/13
MHRA	1	29/07/13	1	29/07/13
Clinicaltrial.gov ($$clinicaltrials.gov)	311 (with comparator search)	30/07/13	454	30/08/13

ii. Searches for comparators and arterial catheters

a. Medline and Medline in Process: Ovid. 1946 to Present

28. ((arterial or artery or arteries or intra arterial) adj3 line).tw.
29. (art line or a line).tw.
30. ((arterial or artery or arteries or intra arterial) adj3 (catheter$ or cannulat$ or access$)).tw.
31. ((catheter$ or cannulat$ or access$) adj5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)).tw.
32. ((catheter$ or cannulat$ or access$) adj5 (seldinger or punktion)).tw.
33. ((arterial or artery or arteries or intra arterial) adj3 device$).tw.
34. IAC.tw.
35. 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 23 (from medline comparator searches) and 35
37. 36 not 27

b. Embase: Ovid. 1974 to 2013 October 28

29. artery catheterization/
30. artery catheter/
31. ((arterial or artery or arteries or intra arterial) adj3 line).tw.
32. (art line or a line).tw.
33. ((arterial or artery or arteries or intra arterial) adj3 (catheter$ or cannulat$ or access$)).tw.
34. ((catheter$ or cannulat$ or access$) adj5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)).tw.
35. ((catheter$ or cannulat$ or access$) adj5 (seldinger or punktion)).tw.
36. IAC.tw.
37. or/29-36
38. 24 (from Embase comparator searches) and 37
39. 38 not 28

c. Cochrane Library

Cochrane Database of Systematic Reviews (CDR): Wiley Interscience. 1996-present
Cochrane Central Register of Controlled Trials (CCRT): Wiley Interscience. 1898-present
Health Technology Assessment Database (HTA): Wiley Interscience. 1995-present
Database of Abstracts of Reviews of Effects (DARE)): Wiley Interscience. 1995-present
NHS Economic Evaluation Database (NHS EED): Wiley Interscience. 1995-present

#27	((arterial or artery or arteries or intra arterial) next/3 line):ti,ab,kw
#28	(art line or a line):ti,ab,kw
#29	((arterial or artery or arteries or intra arterial) next/3 (catheter* or cannulat* or access*)):ti,ab,kw
#30	((catheter* or cannulat* or access*) next/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)):ti,ab,kw
#31	((catheter* or cannulat* or access*) next/5 (seldinger or punktion)):ti,ab,kw
#32	IAC:ti,ab,kw
#33	#27 or #28 or #29 or #30 or #31 or #32
#34	#23 (from Cochrane comparator searches) and #33
#35	#34 not #26

d. EconLit: Ovid. 1961 to September 2013

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

e. Web of Science Conference Proceedings index: Web of Science. 1990-present

#31	#30 not #22
#30	#29 AND #18 (from WoS CPI comparator searches)
#29	#28 OR #27 OR #26 OR #25 OR #24 OR #23
#28	Topic=(IAC)
#27	Topic=(((catheter* or cannulat* or access*) NEAR/5 (seldinger or punktion)))
#26	Topic=(((catheter* or cannulat* or access*) NEAR/5 (wrist or radial or ulnar or foot or brachial or elbow or dosalis)))
#25	Topic=(((arterial or artery or arteries or "intra arterial") NEAR/3 (catheter* or cannulat* or access*)))
#24	TS=((art-line or a-line))
#23	Topic=((arterial or artery or arteries or "intra arterial") NEAR/3 line)

f. Summary of results for comparator and arterial catheters database searches

Database	Comparators ($$comparators)	Date searched
Medline ($$medline)	603	29/10/13
Embase ($$embase)	903	29/10/13

CCRCT ($$ccrct)	356	29/10/13
HTA ($$hta)	0	29/10/13
DARE ($$dare)	0	29/10/13
CDSR ($$cdsr)	21	29/10/13
NHS EED ($$nhseed)	0	29/10/13
EconLit ($$econlit)	0	29/10/13
Web of Science Conference Proceedings index ($$wos-cpi)	291	29/10/13
Total	2174	-
Total unique in database[3]	1625	-

[3]Only records that have not been retrieved in the initial search strategies for central venous catheterisations were downloaded and imported.

12.2 Appendix 2: Search strategy for unpublished clinical evidence (and adverse events) (section 7.1.1)

The following information should be provided.

12.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See 10.1 Appendix 1

12.2.2 The date on which the search was conducted

See 10.1 Appendix 1

12.2.3 The date span of the search.

See 10.1 Appendix 1

12.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See 10.1 Appendix 1

12.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Appendix 10.2

12.2.6 The inclusion and exclusion criteria.

See Table B1 Selection criteria used for published and unpublished studies

12.2.7 The data abstraction strategy.

Data extraction

Data extraction was undertaken by one reviewer and checked by a second reviewer. Discrepancies will be resolved by discussion between two reviewers. If required, a designated member of the 3M team (or the project team) was consulted. Details of eligible studies were extracted into a piloted data extraction. The following data was extracted from the eligible study:

9. Author, year of publication
10. Country, funding source
11. Setting (medical ICU/ surgical ICU etc)
12. Baseline characteristics (including diagnosis/ age/sex/medications)
13. Details relating to CVC
14. CVC type [short-term or long-term; tunnelled or non-tunnelled etc]
    (v) Insertion: site [subclavian; internal jugular; femoral etc]
    (vi) Insertion procedure: [use of maximal sterile barrier procedures; performed by trained staff; method of skin preparation]
    (vii) Length of catheter insertion (days)
    (viii) Use of antibiotic lock solution
15. Details relating to dressing [type of dressing; dressing change protocol]
16. Details relating to outcomes
17. Primary outcome (CR-BSI)

(iii) Clinical diagnosis –
- Confirmation of the presence or absence of signs of bacteraemia or fungaemia
- Evidence of systemic infection (fever, chills +/- hypotension)
- Catheter in situ or catheter removed

(iv) Laboratory diagnosis –
- Relating to peripheral blood culture
- Presence or absence of positive culture
- Relating catheter culture
- Source of culture (catheter tip/ hub/segment)
- Method for obtaining culture (Roll/ vortexing/sonication)
- Culture medium (type/ presence of absence of CHG inhibitors)
- Diagnostic method (semi-quantitative/ quantitative/ differential time to positivity)
- Rates per treatment arm

18. Secondary outcomes

(i) Skin colonisation
- Assessment methods used
- Rates per treatment arm

(v) Catheter colonisation
- Assessment methods used
- Rates per treatment arm

(vi) Adverse events
- Assessment methods used

- Rates per treatment arm

(vii) Additional outcomes
- Assessment methods used
- Rates per treatment arm
-

Details for [4] to [10] will be extracted per treatment arm to enable pair-wise comparison.

Quality assessment

The methodological quality of the included study was assessed using the criteria proposed by Centre for Reviews and Dissemination. Items of quality assessment will be incorporated into the data extraction form. Items evaluated included the following:

1. Random sequence generation
2. Allocation concealment
3. Baseline comparability
4. Pre-specified eligibility criteria
5. Blinding (outcome assessors [blinding of care-givers/patients may be difficult to achieve in most studies])
8. Reporting of the primary outcome (as a point estimate with a measure of variability)
9. Inclusion of an intention-to-treat analysis

Disagreements were resolved through discussion with or without referral to a third party.

No formal quality assessment was undertaken for non-RCT evidence or unpublished evidence relating to adverse events.

2. IDENTIFICATION OF UNPUBLISHED LITERATURE- Clinical Evidence and Adverse Events (section 7.7.1)

Trials register and website searching

a. Clinicaltrials.gov (searched 30th July 2013)

36 studies found for: tegaderm

b. FDA (http://www.fda.gov/) Manufacturer and User Facility Device (MAUDE) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm (searched 29th July 2013)

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

c. EuroScan http://euroscan.org.uk/

29th July 2013

Tegaderm: no search results were found

d. MHRA http://www.mhra.gov.uk/#page=DynamicListMedicines

1 result for tegaderm: http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033763.pdf (29th July 2013)

1 result for tegaderm: www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON197918(23rd October 2013)

e. EMEA (searched 29th July 2013)

Tegaderm - did not match any documents

12.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

12.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

a) Electronic databases

Studies were identified by searching the following electronic databases and research registers:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (OvidSP) 1948 to August 2013
- EMBASE (OvidSP) 1980 to August 2013
- Cumulative Index to Nursing and Allied Health Literature (EBSCO host) 1982 to August 2013
- Cochrane Database of Systematic Reviews (Wiley Online) 1996 to August 2013
- Cochrane Central Register of Controlled Trials (Wiley Online) 1898 to August 2013
- Health Technology Assessment Database (Wiley Online) 1995 to August 2013

- Database of Abstracts of Review of Effects (Wiley Online) 1995 to August 2013
- NHS Economic Evaluation Database (Wiley Online) 1995 to August 2013
- BIOSIS Previews (ISI Web of Knowledge) 1969 to August 2013
- Science Citation Index Expanded (Web of Science) 1899 to August 2013
- Conference Proceedings Index-Science (Web of Science) 1990 to August 2013
- EconLit (OvidSP) 1961 to August 2013
- UK Clinical Research Network (CRN) Portfolio Database (NIHR) 2001 to October 2012
- National Research Register (NRR) Archive (NIHR) 2000 to September 2007.
- Current controlled trials 2000 to October 2012
- ClinicalTrials.gov (US NIH) 2000 to October 2012

12.3.2 The date on which the search was conducted.

23 July 2013

12.3.3 The date span of the search.

All resources were initially searched from inception to October 2012. With the exception of the four research registers, updated searches to August 2013 were conducted on the remaining electronic databases.

12.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

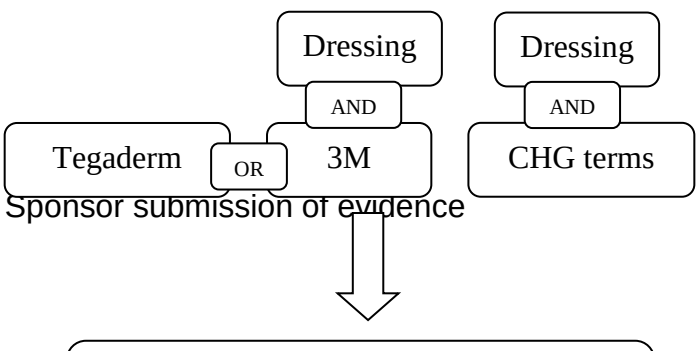
The keyword strategies developed in the review of clinical effectiveness (section 7.1.1) were used with a sensitive economic evaluation (where applicable) or quality of life search filter aimed at restricting search results to economic and cost-related studies (used in the searches of MEDLINE, CINAHL and EMBASE). All resources were initially searched from inception to October 2012. With the exception of the four research registers, updated searches to August 2013 were conducted on the remaining electronic databases.

12.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

To identify additional published, unpublished and ongoing studies, the reference lists of all relevant studies (including existing systematic reviews) were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify articles that cite the relevant articles. In addition, systematic keyword searches of the World Wide Web were undertaken using the Google search engine and key experts in the field were contacted.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

Framework for the search strategy



No limits in terms of date, language or study design were applied to the searches. Studies were also identified from reference tracking of included studies, identified reviews and relevant guidelines. Key investigators were also contacted for information about completed studies.

12.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

12.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The resources searches took place at the same time as the search for economic evidence see 10.3.1

12.4.2 The date on which the search was conducted.

The resources searches took place at the same time as the search for economic evidence see 10.3.2

12.4.3 The date span of the search.

The resources searches took place at the same time as the search for economic evidence see 10.3.3

12.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The resources searches took place at the same time as the search for economic evidence see 10.3.4

12.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The resources searches took place at the same time as the search for economic evidence see 10.3.5

12.4.6 The inclusion and exclusion criteria.

Studies were selected for inclusion according to pre-determined inclusion and exclusion criteria. Studies were included if they reported an economic evaluation of interventions for reducing catheter related infections for patients in acute setting.

Studies that performed economic evaluations alongside trials were excluded if they did not extrapolate the outcomes beyond the trial duration as these economic analyses are only valid for the trials under consideration. Studies that were considered to be methodologically unsound, that were not reported in sufficient detail to extract costs and outcome estimates (including abstracts) or did not report an estimate of cost-effectiveness (e.g. costing studies) were

also excluded. Papers not published in the English language were also excluded.

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer. Any citations that clearly do not meet the inclusion criteria were excluded. Second, and all abstracts and full text articles were examined independently by two reviewers and any disagreements in the selection process were resolved through discussion.

12.4.7 The data abstraction strategy.

Response

13 Related procedures for evidence submission

13.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

13.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

13.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).