Health technology assessment
Antimicrobial Wound Dressings (AWDs)
in Chronic Wounds
Protocol
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1. Glossary

- **Acute wound**: An injury to the skin that occurs suddenly rather than over time. It heals in a predictable and expected rate according to the normal wound healing process.

- **Antibacterial**: Active against bacteria.

- **Antibiotics**: Agents that act selectively against bacteria and are normally administered systemically. They usually have one specific target of disruptive activity in bacterial cells and act against a narrower range of bacteria than antiseptics\(^1\).

- **Antimicrobial**: Any agent that kills or prevents the multiplication of microorganisms eg bacteria or fungi. Antimicrobials may be antibiotics, antiseptics or disinfectants\(^1\).

- **Antimicrobial wound dressing**: A dressing that carries or delivers an antimicrobial agent. Dressings to be included in this HTA are fabric, viscose knitted fabric gauze or tulle, calcium alginate, hydrogel, paste, ointment, low adherent polyester, polyurethane foam, soft polymer, silicone, hydrocolloid, carboxymethylcellulose, low adherent acetate and starch based dressings. Antimicrobial agents to be included are honey, iodine, silver, polihexanide (PHMB), enzyme (eg glucose oxidase and lactoperoxidase) alginogels, octenidine, chlorhexadine and dialkylcarbamoyl chloride (DACC). This encompasses all products listed as AWDs in section A5.3 of BNF 67. There are some topical agents not listed in section A5.3 of BNF 67 that would still be eligible for inclusion (provided they contain one of the antimicrobials listed above) eg silver sulfadiazine creams and povidone-iodine powder.

- **Antiseptics**: Chemical agents that can be applied topically to the skin or wounds. They are relatively non-selective agents that inhibit multiplication of, or kill, microorganisms\(^1\).

- **Bioburden**: The extent of microbial contamination.

- **Biofilm**: Complex polymicrobial communities that attach to a surface.

- **Chronic wound**: A chronic wound develops when an acute wound fails to heal within the expected period for that type of wound, which might be anything from a couple of weeks to several weeks. For the purpose of this HTA, the wounds of interest are foot ulcers in people with diabetes, pressure ulcers, and venous/arterial ulcers. Other wounds may be included if time and resources allow (eg dehisced surgical wounds).
• Critical colonisation or localised infection: Microbes multiply and the wound moves from benign colonisation to an infected state with impaired healing but without tissue invasion or host immunological response. There is currently no consensus on how to define or identify critical colonisation.

• Debridement: The process of cleaning an open wound by removal of foreign material and dead tissue, so that healing may occur without hindrance\(^2\).

• Diabetic neuropathy: Damage to the nerves seen in some people with long-standing diabetes. It most commonly affects the legs, causing pain or numbness working up from the feet\(^2\).

• Disinfectant: Relatively non-selective agents often with multiple sites of action that kill a wide range of microorganisms including bacteria and fungi. Disinfectants are generally not suitable for use on body tissue because they are toxic to human cells.

• Excoriation: The destruction and removal of the surface of the skin or the covering of an organ by scraping, the application of a chemical, or other means\(^2\).

• Induration: Abnormal hardening of a tissue or organ\(^2\).

• Maceration: The softening of a solid by leaving it immersed in a liquid\(^2\).

• Pressure ulcer: Localised injury to skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear. A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated\(^3\).

• Protease: Any enzyme that catalyses the splitting of a protein\(^2\).

• Venous ulcer: Venous ulcers arise from venous valve incompetence and calf muscle pump insufficiency which leads to venous stasis and hypertension. This results in microcirculatory changes and localised tissue ischaemia\(^4\).
2. Research questions

What is the clinical and cost effectiveness of different antimicrobial dressings, compared to other dressings and techniques, for treating localised wound infection in chronic wounds?

What are the patient and organisational issues associated with the use of different antimicrobial dressings in patients with chronic wounds?

2.1. Clarification of scope

Using the EUNETHTA core model as a basis (http://meka.thl.fi/htacore/model/AE-tables_intervention.pdf), the following questions were highlighted as needing to be addressed in this HTA. These are intended to help structure the HTA, rather than to act as specific research questions that each require primary or secondary research to address. The methods used to address each of these questions will vary. Furthermore, if additional questions that need to be addressed become apparent during the work, these will be added to the scope, and the reason for their addition documented.

Health Problem

1. Which types of chronic wounds are antimicrobial wound dressing currently used for?
2. Which chronic conditions are associated with chronic wounds?
3. What is the ICD 10 code for the chronic wounds?
4. What are the known risk factors for this type of chronic wound?
5. What are the symptoms to indicate the chronic wound is infected?
6. What are the consequences of the chronic wound with localised infection if untreated?
7. What is the prevalence of these types of chronic wound?

Description and technical characteristics of the technology

8. What outcomes are expected to be impacted by the AWDs e.g. reduced infection?
9. How are the dressings currently used in people with chronic wounds ie at what stage in the clinical pathway, and for how long?
10. How are chronic wounds with localised infection currently being managed ie are AWDs dressings being used appropriately?
11. What are the alternatives to AWDs?
12. Who manufactures the AWDs?
13. Which AWDs are currently procured for NHS Scotland?
14. Which health care staff groups currently use AWDs, and why?
15. What kind of training is currently offered in the use of these types of dressing?
16. What kind of training and information is required for patients and their families?

Safety

17. What harms are associated with different AWDs?
18. Are there any occupational harms associated with AWDs?
19. What are the consequences of using AWDs in wounds without increased bioburden?

Clinical effectiveness

20. How does the AWD modify the severity of the symptoms?
21. How does the AWD modify the progression (including improvement of localised infection, as well as wound healing) of a chronic wound?
22. How does the AWD modify the need for hospitalisation?
23. How does the AWD modify the need of other intervention or resource?
24. What is the effect of the AWD on quality of life?
25. How does the AWD affect activities of daily living?
26. Under which conditions is it more important to use a bactericidal (ie kills bacteria) rather than a bacteriostatic (ie stops growth of bacteria) dressing?
27. What type of dressing is most effective for the delivery of different types of antimicrobials?

Costs and economic evaluation

28. What types of resources are used when using AWDs and their alternatives?
29. What quantities of these resources are used when using AWDs and their alternatives?
30. What are the unit costs of these resources?
31. What is the impact of AWDs on indirect costs?
32. Overall, what are the incremental costs of the AWD relative to its comparator? i.e. resource impact assessment.
33. What are the incremental benefits of the AWD relative to its comparator?
34. What is the cost-effectiveness of the AWDs?

Organisational aspects

35. What kind of staff training is currently given, and by whom?
36. Who decides which patients have AWDs and on what basis?
37. What volume and types of AWDs are used in NHSScotland at national and health board level?
38. How are decisions currently being made by healthcare professionals about which dressings to use? What decision aids are there, and are they being used?
39. What AWDs do local formularies list?
40. Do staff use different AWDs for different types of wound? How is this decision made?
41. Are AWDs being purchased nationally or locally, and is there any overlap?
42. In what clinical settings are AWDs being used?
43. How confident do healthcare professionals feel about their decision making around prescribing AWDs?

Patient issues

44. What is the burden of the wound on the daily life of patients?
45. What is patients’ current experience of wound dressings?
46. What would patients like to see in the future with regards to the use of AWDs?
47. What information on dressings is being communicated and shared by health professionals to patients and their family/carers?
48. What are the views of patients and their carers on these dressings?
49. What factors affect access to AWDs?
3. HTA process

The HTA process comprises four elements: clinical effectiveness, cost effectiveness, patient issues and organisational issues. The clinical effectiveness section mainly uses published literature to establish the clinical benefits and harms associated with the technology. This focuses on outcome measures of importance to patients evaluated in standard clinical settings. The cost-effectiveness element seeks to assess the relative costs and consequences associated with the use of the technology compared with standard alternative treatments. The patient issues section will include a review of the literature, and may entail primary research to understand patients’ experience of the technology, and their needs and preferences. The organisational issues element may also use primary research to assess the infrastructure requirements of NHSScotland, and any issues arising in service delivery in different settings and areas. It could also include review of local policy documents and other relevant literature.

An HTA topic group will be convened comprising different specialities and a mix of NHS board areas, to give advice during the project. Patient representatives will also be invited to be on the topic group. Manufacturers of the technology will be contacted to help researchers understand particular systems and how they are being used in NHSScotland.
4. Background and summary of the technology

4.1. Chronic Wounds

The healing of a skin wound normally involves four sequential phases: haemostasis (stopping of blood flow), inflammation, repair and remodelling (scar tissue formation)\(^5\). Sometimes, an acute wound will become ‘stuck’ at one of these four stages, and this can cause a wound to become chronic\(^5\). All wounds have the potential to become chronic\(^6\). There is no clearly defined length of time after which an acute wound becomes chronic. Typically, a chronic wound develops when an acute wound fails to heal within the expected period for that type of wound, which might be anything from a couple of weeks to several weeks\(^7\).

For the purpose of this HTA, the main wounds of interest are foot ulcers in people with diabetes, pressure ulcers, and venous/arterial ulcers. These were chosen as clinical experts advised us that these were the most important groups. However, there are other chronic wound types (eg dehisced surgical wounds) that may be of interest, and will be included if time and resources allow.

The healing process is complex, as it is dependent on numerous patient-related and wound-related factors, and on the treatment received\(^8\). Healing may be impaired by a number of local and systemic factors, including: poor nutrition, reduced blood supply, circulatory disorders, medication, chemotherapy, radiotherapy, psychological stress, lack of sleep, obesity, infection, reduced wound temperature, underlying disease, maceration, inappropriate wound management, patient compliance, unrelieved pressure, immobility, substance abuse (including alcohol and tobacco), and older age\(^8,9\). Furthermore, healing can be impacted by wound size, wound duration, or wounds in particular anatomical locations\(^8,10\).

The chronic wound environment is different to the acute wound environment. The clinical signs of a chronic wound includes: non-viable wound tissue (slough and/or necrosis); lack of healthy granulation tissue; no reduction in wound size over time; and recurrent wound breakdown\(^9\).

More than 90% of chronic wounds can be classified into three major types: foot ulcers in people with diabetes, pressure ulcers, and venous/arterial ulcers\(^11\). Each of these are described in more detail below:

*Foot ulcers in people with diabetes*: People with diabetes are at increased risk of peripheral vascular disease and neuropathy, as well as having a higher risk of developing infections and decreased immune response. People with diabetes can develop ulcers on their feet because of neuropathy, ischaemia or both. The initial injury may be from acute or thermal trauma, or from repetitively or continuously applied mechanical stress\(^12\).
Pressure ulcers: These occur most commonly around bony prominences (e.g., the coccyx, heels, and ankles), and are the consequence of prolonged, unrelieved pressure. This constant pressure causes damage to the skin by decreasing blood supply, which is made worse by other factors such as friction and excess moisture. Anyone with limited mobility is at risk of developing a pressure ulcer. Poor nutrition and incontinence may also increase risk.

Venous and arterial ulcers: These wounds normally occur in older people, and can be lymphovenous, venous, arterial, or both venous and arterial in origin. Approximately 1% of the population will suffer from leg ulceration at some point in their lives. Venous ulcers account for the majority of leg ulcer cases. They are the consequence of dysfunctional valves in the veins, which causes blood and fluid to pool in the lower extremities. This results in poor circulation, congestion, and chronic inflammation at the site, with the tissue eventually breaking down and forming an ulcer. The application of graduated compression in the form of stockings or bandages is a proven treatment for healing venous leg ulceration. Arterial insufficiency ulcers are the direct result of blocked blood flow to small vascular beds in the body (e.g., the dorsum (top) of the foot). If a wound occurs in this area, it is unable to heal itself due to lack of blood flow.

These three types of wounds are especially prone to recurrence. This may often be because the patients’ underlying and wound-provoking factors have not been remedied. Reported recurrence rates range from 23% to 40% for pressure ulcers, 24% to 57% for venous ulcers, and upward of 60% for foot ulcers in people with diabetes.

4.2. Local Wound Management

As already described, the factors that contribute to wound formation and their chronicity are multifactorial. Therefore, ongoing wound and patient assessment is important, in order to identify and address the compounding factors that may impede wound healing:

‘Identifying and treating the underlying aetiology of a chronic wound such as venous insufficiency, arterial perfusion, diabetes, or unrelieved pressure as well as systemic factors such as nutritional status, immunosuppression, and infection that may contribute to poor wound healing are key to successful wound treatment.’

However, regardless of the wound type, general local wound management principles exist for a wide variety of chronic wounds. In 2003, the Wound Bed Preparation and TIME acronym was developed to help in the treatment of chronic wounds. The aim was to help clinicians to identify the key barriers to healing, taking into account comorbidity, patient centered issues and wound bed diagnosis (TIME) to design a wound management plan. The individual elements of TIME are:
**T**issue: This relates to the debridement or removal of devitalized or non-functional tissue, which is not optimal repair tissue. Debridement also plays an important role in reducing the levels of bacterial biofilms. Debridement (mechanical or surgical) of devitalised tissues and bacterial biofilms has become a 'must-do' component of wound bed preparation.\(^5\)\(^,\)\(^15\).

**I**nfection/Inflammation: Infection and inflammation may impair wound healing.

**M**oisture balance: This relates to achieving the optimal balance of moisture in the wound bed, which can impact considerably on the healing of wounds.\(^5\) Exudate needs to be controlled to create the optimal moist environment for wound healing, and also to protect the surrounding skin from the risks of maceration and excoriation.\(^15\)

High levels of exudate are associated with a number of factors, including bacterial colonisation of a wound.\(^15\) However, a wound can still be infected even in the absence of thick or discoloured exudate.\(^15\) Low levels of exudate may delay epithelialisation.

**E**dge of the wound/epithelial migration: An indicator that the three other components of the TIME acronym have been adequately addressed is if there is a healthy sheet of epithelial cells migrating from the edge of a chronic wound.\(^5\) Lack of improvement in wound dimensions and non-progression of the wound edge indicate failure to heal.\(^15\)

4.2.1. Bacterial Biofilms

Most chronic wounds (approximately 60%) contain bacterial biofilms.\(^16\) This compares to approximately 6% of acute wounds.\(^16\) Biofilms are complex microbial communities that develop on or near wound surfaces.\(^15\) They are usually invisible to the naked eye, and cannot be detected by routine cultures (but can be detected using more sophisticated approaches eg electron microscopy and confocal scanning laser microscopy).\(^15\),\(^17\) They form quickly (within 2-4 hours) and evolve into a fully mature biofilm community within 2-4 days.\(^15\) They can consist of a single bacterial or fungal species, but are most commonly polymicrobial.\(^15\)

Mature biofilms are extremely tolerant to most systemic antibiotics and topical antimicrobial agents, and also to the body’s own defences (ie antibodies and reactive oxygen species generated by inflammatory cells). Thus debridement is normally the best option for rapidly reducing biofilms in chronic wounds. However, biofilms can fully reform within 48-72 hours after debridement if effective bacterial barrier dressings are not applied straightaway.\(^5\) Topical antimicrobial interventions are potentially more effective at this post-cleaning/post-debridement stage.\(^15\) Use of topical antimicrobial agents in the presence of biofilms should only occur after biofilm disruption.\(^15\)
Although biofilms might be an important contributor to wound chronicity, not all wounds with delayed healing can be assumed to contain a biofilm. In addition, it is not known whether the presence of a biofilm in a wound will always lead to problems.

4.2.2. Infection/inflammation

All open wounds are colonized with microorganisms, but this usually has no clinical consequences. The World Union of Wound Healing Societies (WUWHS) state that the presence of microbes in a wound can result in:

- Contamination: the microbial burden does not increase or cause clinical problems (no host response).
- Colonisation: the microbes multiply, but wound tissues are not damaged (no host response).
- Critical colonisation or localised infection: microbes multiply and the wound moves from benign colonisation to an infected state with impaired healing but without tissue invasion or host immunological response. There is currently no consensus on how to define or identify critical colonisation.
- Infection (spreading or systemic): bacteria multiply, healing is disrupted and deep tissues are damaged. Bacteria might produce localised problems or cause systemic illness (host response).

It has been suggested that infection and excessive inflammation impair wound healing. One mechanism by which healing might be impaired is that inflammation and infection lead to elevated levels of proteases in chronic wounds. These proteases are part of the inflammatory response of the host to fight the infection. However, persistently elevated levels of proteolytic activity in chronic wound fluids are linked to the destruction of essential growth factors, their receptors and extracellular matrix proteins.

Opinions differ on which clinical signs define wound infection. There is no hard scientific test to diagnose wound infection, so clinical judgement and sound clinical assessment skills are needed to interpret signs and symptoms. Some wounds are clearly infected, with purulent secretions or some of the manifestations associated with inflammation (erythema, warmth, pain or tenderness, or induration). When wounds occur in people with neuropathy (which can obscure or cause pain), ischaemia (which may reduce erythema, warmth or induration), or venous insufficiency (which can mask warmth or cause induration), the expression of inflammation can be limited. In such cases, some define infection by ‘secondary’ signs of local infection eg nonpurulent exudate, discoloured or friable (easily bleeding) granulation tissue, breakdown or pocketing at the wound base, or an abnormally foul odour. For more criteria for identifying wound infection, refer to the European Wound Management Association (EWMA) position document.
In the literature, infection is sometimes defined microbiologically, suggesting that apparently uninfected but non-healing wounds may demonstrate either ‘critical colonisation’ with certain virulent species or a heavy bacterial bioburden. However, other research suggests it is not the density of organisms, but the presence of specific bacterial species, the diversity of bacteria, or patients individual response to the colonisation, that might delay wound healing in apparently uninfected but non-healing wounds\textsuperscript{18}. There appears to be uncertainty in this area in the literature.

Clinically infected wounds normally require systemic antibiotic therapy, whereas clinically uninfected wounds that are healing as expected do not require antimicrobials. There is controversy surrounding how to treat poorly healing wounds with ‘secondary’ signs of infection, and whether these would benefit from any topical antimicrobial agent\textsuperscript{18}.

4.3. Antimicrobial wound dressings (AWDs)

An antimicrobial is any agent that kills or prevents the multiplication of microorganisms, eg bacteria or fungi. For the purpose of this HTA, studies will be eligible for inclusion if the intervention involves an antimicrobial being in contact with a wound for a period of time. This would include dressings that are impregnated with the antimicrobials of interest; and also topical application of antimicrobials that are held in place with a non-impregnated dressing.

Antimicrobials may be antibiotics, antiseptics or disinfectants:

- **Antibiotics**: agents that act selectively against bacteria and may be administered systemically or sometimes topically. They usually have one specific target or disruptive activity in bacterial cells and act against a narrower range of bacteria than antiseptics. The development of resistance to antibiotics is an increasing problem\textsuperscript{1}.

- **Antiseptics**: chemical agents that can be applied topically to skin or wounds. They are relatively non-selective agents that inhibit multiplication of, or kill, microorganisms. They have multiple sites of antimicrobial action on cells and, therefore, are not as at risk of bacterial resistance as antibiotics\textsuperscript{20}. They may also have toxic effects on tissue cells, which has led to controversy and reduced their widespread use. Antiseptics are often referred to as ‘topical antimicrobials’ even though the term also applies to topical antibiotics\textsuperscript{1}.

- **Disinfectants** – relatively non-selective agents often with multiple sites of action that kill a wide range of microorganisms including bacteria and fungi. Disinfectants are generally not suitable for use on body tissues because they are toxic to human cells\textsuperscript{1}.

According to the literature, clinically infected wounds would usually be treated with systemic antibiotic therapy\textsuperscript{18}. A guideline produced by SIGN.
(Scottish Intercollegiate Guidelines Network) on venous leg ulcers gives a C-grade recommendation (evidence from case-control and cohort studies) that:

‘In patients with chronic venous leg ulcers, systemic antibiotics should not be used unless there is evidence of clinical infection’\(^4\).

For wounds that are uninfected, and healing as expected, topical antimicrobial therapy is not normally indicated. There may be a role for topical antimicrobial therapy for wounds that are failing to heal and have some secondary signs of infection\(^18\). However, it is not immediately obvious from the literature what the evidence is to direct usage of these products.

Topical antimicrobial therapy may have a role in reducing bioburden in chronic wounds, preventing systemic infection and ultimately in allowing the wound to heal. Some advantages and disadvantages of topical antimicrobial therapy in infected chronic wounds have been proposed by Lipsky et al\(^18\). These include:

- **Advantages:** concentrated antimicrobial action at the site of the infection; can use novel agents not suitable for systemic use; may avoid the use of systemic antibiotics, thereby helping reduce antibiotic resistance.

- **Disadvantages:** Systemic absorption of agents on larger wounds; lack of clinical effectiveness evidence; local hypersensitivity or contact dermatitis reactions; may interfere with normal wound healing.

Antimicrobials have traditionally been applied topically in mediums like creams and ointments. More recently, antimicrobials have been impregnated into dressings such as alginates, foams and sponges. This allows controlled release at the wound surface. Different AWDs have different antibacterial and fluid-handling properties. These different characteristics make them more or less suitable for different types of wounds: “choice of an appropriate antibacterial dressing should be based on the wound type and condition and on clinically applicable measures, such as antibacterial, healing, and exudate handling effects, and not on any single laboratory parameter”\(^21\).

The most commonly used topical antimicrobials used in the UK are: silver; iodine (povidone iodine and cadexomer iodine); honey; enzyme alginogel; octenidine and polyhexamethylbiguanide (PHMB).

Guidelines, which are based on expert opinion\(^15\), suggest that once the decision has been made to use an AWD, the effect on the wound should be closely monitored. This means assessing it at every dressing change, and fully at 2 weeks.

According to the BNF67 (antimicrobial dressings section; appendix 5.3), spreading infection at the wound site requires treatment with systemic antibacterials. However, it states that for local wound infection, an AWD might be
used to reduce the level of bacteria at the wound surface (but it will not eliminate spreading infection).

The BNF goes on to list various AWDs. For more details, please refer to appendix A5.3 (https://www.medicinescomplete.com/mc/bnf/current/PHP9654-antimicrobial-dressings.htm). These are all eligible for inclusion in the HTA. Even though these are all listed in the BNF, this does not imply that they are all available or recommended for use in NHSScotland.

The information from appendix 5.3 of the BNF(67), mostly relates to dressings that are impregnated with an antimicrobial. There are also other topical agents elsewhere in the BNF that would be eligible for inclusion in this HTA, if they were held in contact with the wound for a period of time. These include silver sulfadiazine creams and povidone-iodine powder.

### 4.4. Clinically relevant endpoints

Most studies evaluating the use of AWDs in chronic wounds have endpoints relating to healing. However, there is some disagreement in the literature about how appropriate this is, given that chronic wounds are difficult to heal\(^1\). The argument being that the purpose of AWDs is to reduce wound bioburden and treat local infection. It is argued by some that AWDs main purpose is not to promote wound healing. Therefore, more appropriate endpoints might relate to measurement of wound bioburden and assessment of the clinical indicators of infection\(^1,15\). However, there is no exact definition of wound infection given in the literature, which makes it a challenging endpoint to use.

Many clinical experts consulted for this HTA supported the argument that the purpose of AWDs is to reduce bioburden. Therefore, for this HTA, the primary outcomes of interest relate to wound infection: resolution of localised wound infection, improvement in signs and symptoms of wound infection, and reduction of bioburden.

Secondary outcomes will be ulcer healing, ulcer size and depth, time to healing, rate of healing, use of systemic antibiotics, health-related quality of life, adverse events, ease of use, patient acceptability and comfort, and any other relevant outcomes identified from the literature.
5. Scottish context

The use of AWDs has increased rapidly in recent years and accounts for a quarter of wound dressings spend. The community spend on honey and silver dressings in NHSScotland in 2012 was approximately £3.2 million (Personal Communication; Paul Hornby; National Services Scotland).

At present, due to the lack of robust evidence to support the use of antimicrobial dressings, there is a reliance on best practice statements and consensus documents. These are widely available electronically\(^8,^9,^{15,23}\). Many documents are based on work supported by commercial company education grants. (Personal Communication; Margaret Ryan, Lead Clinician Prescribing Services & Lynne Watret, Non Medical Prescribing Services; November 2013).

At a national level the use of antimicrobial dressing products is one of ten National Therapeutic Indicators (the remaining being in relation to prescribing of medicines). These indicators have been developed as part of the Scottish Government prescribing Efficiency and Productivity work-stream (2011-2014). The aim is to continue to improve the quality of prescribing in Primary Care whilst optimising efficiencies\(^24\).

Chronic wounds are an important health problem, affecting many patients. They cause considerable morbidity, are detrimental to quality of life, and consume significant healthcare resources in terms of both the costs of the products used for treatment and also staff (particularly nursing) time. One study from 2013 estimated that the mean annual cost of treating a venous leg ulcer was £1,493 for participants receiving two-layer compression hosiery, and £1,795 for patients treated with a four-layer bandage\(^25\). Furthermore:

- Pressure ulcers can cost an average of £1,214 (category 1 – early stage, when the skin is still intact) to £14,108 (category IV – most severe stage, with full tissue loss) each\(^15\), and
- Venous leg ulcers cost the NHS (for the whole of the UK) nearly £200 million a year, and foot ulcers in people with diabetes £300 million a year\(^15\).

Figure 1 shows the prescription of AWDs, in each NHS board in Scotland, as a percentage of total wound products (taken from National Therapeutic Indicators; 2012 Baseline Data\(^24\)). The number of dispensed prescriptions (items) is used to measure the frequency of prescribing. The total items of antimicrobial wound products are divided by total items of wound management products. It is not clear what AWDs are included, but it is likely that most of the cost comes from silver dressings. Prescribing of AWDs in often nurse led\(^24\).
Figure 1

Antimicrobial wound products as percentage of total wound products (items)
Report Period: Jan-12 to Mar-12
6. Existing evidence

A high level scoping search was done in order to assess the size and quality of the evidence base in this topic area. Only secondary literature was searched for, and the search was limited to a handful of websites/databases (eg The Cochrane Library, the GIN website, NICE and SIGN). For full details of the search, please refer to: Literature\20131015 ERC referral scoping v2.docx

Most of the information identified related to silver dressings, and this has been summarised in the following section. Very little was identified relating to other AWDs, but this perhaps reflects the limited search undertaken at this stage of the project.

6.1. Silver Dressings

The Healthcare Improvement Scotland (HIS) scoping report (published in January 2013)\textsuperscript{26} addressed the questions:

- ‘Are silver dressings clinically effective for the healing of infected wounds, compared with other types of dressing?’ and;

- ‘If clinical effectiveness has been established, are silver dressings cost effective for the healing of infected wounds, relative to other types of dressing?’

The report included the following evidence:

- A Cochrane systematic review\textsuperscript{27} (Vermeulen et al 2007) containing three randomised controlled trials (RCTs). The review authors concluded that silver-containing foam dressings did not significantly increase complete ulcer healing after 4 weeks of follow up, compared with standard foam dressings or best local practice; although a greater reduction in ulcer size was observed with silver-containing foam compared with standard foam or best local practice. Insufficient evidence was available to recommend the use of silver-containing dressings for the treatment of infected or contaminated chronic wounds.

- The Scottish Intercollegiate Guidelines Network (SIGN) produced a guideline in 2010 on the management of chronic venous leg ulcers\textsuperscript{4}, in which silver dressings were not recommended in the routine treatment of patients with venous leg ulcers. This was based on the Cochrane review previously described, and an RCT by Michaels et al (the VULCAN trial)\textsuperscript{28, 29}.

- A Cochrane systematic review\textsuperscript{30} (Bergin and Wraight 2006) on silver-based wound dressings and topical agents for treating foot ulcers in
people with diabetes identified no RCTs or controlled trials meeting the inclusion criteria. The review authors concluded that trials were needed to determine clinical and cost effectiveness and long-term outcomes including adverse events.

- Other synthesised information was found, including from the Canadian Agency for Drugs and Technology in Health (CADTH) health technology inquiry service\textsuperscript{31} and the Drugs and Therapeutics Bulletin\textsuperscript{32}, covering broadly the same evidence base and concurring with the conclusion of insufficient evidence of effectiveness of silver dressings for the healing of infected wounds.

- The VULCAN trial examined the cost effectiveness of silver dressings for the healing of venous leg ulcers without reference to infection\textsuperscript{28, 29}. The authors concluded that there was no evidence to support the routine use of silver dressings beneath compression for venous leg ulcers.

The high level scope for this protocol highlighted a further four systematic reviews\textsuperscript{33-36} (with meta-analyses), an evidence summary\textsuperscript{23}, an RCT\textsuperscript{37} and a health-economic analysis\textsuperscript{38} on AWDs containing silver. The reviews and evidence summary all support the conclusions of the HIS scoping report; there is a need for good-quality RCTs, with adequate follow-up, before the clinical effectiveness of silver AWDs can be established.

6.2. Other AWDs

One of the systematic reviews (a Cochrane review) examined hydrocolloid dressings for healing foot ulcers in people with diabetes\textsuperscript{34}. This included five studies (535 participants). These compared hydrocolloids with basic wound contact dressings, foam dressings, alginate dressings and a topical treatment. One of the main results reported was that ‘there was no statistically significant difference in healing between an antimicrobial (silver) fibrous-hydrocolloid dressing and standard alginate dressing; an antimicrobial dressing (iodine-impregnated) and a standard fibrous hydrocolloid dressing or a standard fibrous hydrocolloid dressing and a topical cream containing plant extracts’\textsuperscript{34}. 
7. Literature searching

Sections 7, 8 and 9 of this protocol refer just to the clinical and cost effectiveness parts of the HTA. The methods for the patient and organisational issues parts of the HTA are outlined in sections 10 and 11.

The search strategy will involve systematically searching electronic databases and relevant professional and manufacturers’ websites. Electronic searches will be conducted to identify reports of published and ongoing studies. Studies published in languages other than English will not be included in the review. The details of the sources that will be searched are listed in Appendix 1.

For the clinical effectiveness chapter, the literature search will follow an iterative process, with initial searches focusing on the highest levels of evidence (ie systematic reviews and meta-analyses of clinical trials). In topic areas where insufficient evidence is found, lower levels of evidence will be retrieved, starting with randomised clinical trials, and working through observational (case-control and cohort) studies, and case series if necessary.
8. Selection of the literature

Sections 7, 8 and 9 of this protocol refer just to the clinical and cost effectiveness parts of the HTA. The methods for the patient and organisational issues parts of the HTA are outlined in sections 10 and 11.

8.1. Inclusion criteria

Literature will be selected using the PICO framework (population, intervention, comparator, outcome) as follows:

Population

Adults (aged ≥18) with chronic wounds. The chronic wounds to be included are:

- foot ulcers in people with diabetes
- pressure ulcers
- venous and/or arterial ulcers (including ulcers of lymphovenous origin)

In studies which include mixed wound types – the data relating to the wounds of interest will be extracted if possible. If the data is not presented separately for the different wound types, the study will not be eligible for inclusion. If necessary, the authors will be contacted for more details.

Although the primary outcome of this HTA relates to wound infection, the population eligible for inclusion will not be limited to those defined as having a chronic wound with localised infection. Studies reporting on the secondary outcomes of this HTA (eg time to healing) might be missed if the population is limited to those defined as having infected chronic wounds.

Other chronic wound types may be included if resources allow (see last paragraph of section 8.1 – ‘Other chronic wounds)

Intervention

Wound dressings, produced by any manufacturer, containing any of the following antimicrobial agents:

Antimicrobial agents to be included are honey, iodine, silver, polihexanide (PHMB), enzyme (eg glucose oxidase and lactoperoxidase) alginogels, octenidine, chlorhexadine and dialkylcarbamoyl chloride (DACC). This encompasses all products listed as AWDs in section A5.3 of BNF 67.

A dressing is defined as anything that carries or delivers an active ingredient, which can be bactericidal (ie kills bacteria) or bacteriostatic (ie stops growth of bacteria). Dressings to be included are:
• fabric, viscose knitted fabric gauze or tulle, calcium alginate, hydrogel, paste, ointment, low adherent polyester, polyurethane foam, soft polymer, silicone, hydrocolloid, carboxymethylcellulose, low adherent acetate and starch based.

Studies will be eligible for inclusion if the intervention involves an antimicrobial being in contact with a wound for a period of time. This would include dressings that are impregnated with the antimicrobials of interest; and also topical application of antimicrobials that are held in place with a non-impregnated dressing (e.g. cadexomer iodine or honey being applied to a wound, and then held in place using a dry dressing).

There are some topical agents not listed in section A5.3 of BNF 67 that would still be eligible for inclusion (provided they contain one of the antimicrobials listed above) e.g. silver sulfadiazine creams and povidone-iodine powder.

**Comparator**

- Dressings that do not contain any antimicrobial agent.
- Studies will also be included if they compare AWDs to other AWDs.
- Other wound management products/techniques that propose to reduce bioburden (debrisoft, larval therapy, and debridement).

**Outcome**

Resolution of localised wound infection, improvement in signs and symptoms of wound infection, and reduction of bioburden.

All studies that report on wound infection will be eligible for inclusion. As discussed in section 4.2.2, there is no hard scientific test to diagnose wound infection, or to measure bioburden, which makes them challenging to use as outcome measures. Therefore, the way in which infection is measured (e.g. by clinical signs and symptoms, or by swabs) may differ in the literature, but all will be included. Signs and symptoms of localised infection include odour, friable tissue and periwound oedema,

Secondary outcomes are: ulcer healing, ulcer size and depth, time to healing, rate of healing, use of systemic antibiotics, health-related quality of life (using any measure, the appropriateness of which will be discussed in the final HTA), adverse events, ease of use, and patient acceptability and comfort. The HTA will also include any other relevant outcomes identified from the literature, or highlighted by patients or clinical experts as important. The reason for including any additional outcomes, that are not listed here, will be documented.
Information on how long AWDs should be used for will also be extracted from the studies when available.

**Study types**

The search will initially focus on secondary research (ie systematic reviews and meta-analyses). Systematic reviews of any study type will be eligible for inclusion. A search for primary literature will be done to update the results of any secondary literature, and to answer any questions that remain unanswered. The primary literature search will work through the hierarchy of evidence, from randomised controlled trials, then non-randomised trials, observational studies (cohort and case-control), and case-series/studies if required (or deemed necessary).

**Other chronic wounds**

In order to keep the project manageable, the review will be limited to the three wound types detailed above. These were chosen as clinical experts advised us that these were the most important groups. However, there are other chronic wound types (eg dehisced surgical wounds) that may be of interest.

In order to be as inclusive as possible, the literature search will be broad enough to include all chronic wounds. Based on the quality and quantity of the literature, and if resources allow it, a decision will be made to include other wound types. Any decisions to add in additional sections will be recorded and the rationale given in the final HTA report.

### 8.2. Exclusion criteria

The HTA will exclude:

- animal studies, *in-vitro* studies, discussion articles, non-systematic reviews, editorials, meeting abstracts, letters to the editor and opinion papers
- any study that does not report patient-related outcomes
- studies in which the population of interest is people aged under 18 with chronic wounds

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1 The exclusion of *in-vitro* studies and animal studies has been challenged by some external experts. However, the decision was made to focus on studies based in the clinical setting with patient related outcomes. This will enable us to make recommendations on patient care. Also, the extra resource it would take to search for and review these studies would mean that less resource was available for the other sections (notably organisational and patient issues).
• articles published in languages other than English (unless a translation is available)

• studies in which the intervention of interest is AWD dressings containing larvae

• studies that are concerned with the prevention of local wound infection in apparently uninfected wounds, and

• studies on patients with infected acute wounds or abscesses (including burns). For clarification, an acute wound is an injury to the skin that occurs suddenly rather than over time. It heals at a predictable and expected rate according to the normal wound healing process.

8.3. Clinical effectiveness

Two health service researchers will independently screen all titles and abstracts to ensure relevancy and consistency of paper selection. Full text English papers thought to be relevant based on title and abstract will be obtained where possible. The relevance of each study will be assessed according to the inclusion and exclusion criteria outlined in section 8.1 and 8.2. Studies which do not fulfil all of the criteria will be excluded with reasons for this documented, together with their biographic details. Any discrepancies in the relevancy of papers based on title and abstract will be resolved by consensus. If necessary, a third reviewer will be included.

8.4. Cost effectiveness

Cost effectiveness studies often make reference to an incremental cost effectiveness ratio, which takes into account the differences in costs and outcomes between two competing interventions. Key economic search terms include the various types of economic evaluation; cost-effectiveness analysis, cost-utility analysis, cost-minimisation analysis, cost-consequence analysis, and cost-benefit analysis.

Regarding the selection of cost effectiveness literature, the relevance of each identified study will be assessed according to, not only the inclusion and exclusion criteria in section 8.1 and 8.2, but also whether the studies report both costs and outcomes. In some instances such as for a cost-minimisation analysis, it is worth noting that the outcomes may be equal rather than incremental.

There may be some studies that only report the respective costs of the various interventions. Although these studies will not be included in the summary of cost effectiveness literature, these studies may help inform further analysis (see 10.2). It is also worth noting that, in terms of outcomes, such further analysis will be based upon clinical outcomes indentified following the clinical effectiveness literature search.
Two health economists will independently screen all titles and abstracts to ensure relevancy and consistency of paper selection. As for the clinical effectiveness papers, studies which do not fulfil the required criteria will be excluded with the reasons for this documented.
9. The selection and reviewing process

Sections 7, 8 and 9 of this protocol refer just to the clinical and cost effectiveness parts of the HTA. The methods for the patient and organisational issues parts of the HTA are outlined in sections 10 and 11.

9.1. Data extraction strategy

Initially, the literature search will be limited to secondary evidence. Therefore, most of the data extracted will not be coming straight from the primary studies. However, if the reviews are deemed to be of sufficient quality, the assumption will be made that the data presented is accurate and complete. Where more than one review reports on the same study, the data will be cross-checked, to ensure consistency. The fulltext of primary papers reported in reviews will only be obtained if there is any reason to suspect that the data presented in the reviews is incorrect or incomplete.

It is expected that the following information, if available, will be extracted from the secondary information:

- Study details
  - Year of publication
  - Study objectives
  - Selection criteria (main inclusions and exclusions)

- Quality (assessed using the SIGN checklist for systematic reviews/meta-analyses)

- Results
  - Number of included studies, and total number of participants
  - Main characteristics of included studies (including quality)
  - Main results (pooled results; narrative summary)

Other data that is deemed to be of relevance and importance will be extracted, and the reason noted and justified.

It is expected that there will be some instances where primary studies are searched to supplement the secondary evidence. Primary studies which match the inclusion criteria will have the following clinical or cost-effectiveness related information recorded (where available):

- Study Details
  - Year of publication
  - Funding source
  - Country
- Study objectives
- Type of study
- Setting

- Study population
  - Number and characteristics of participants
  - Inclusion and exclusion criteria

- Baseline Characteristics
  - Mean / SD age (years)
  - Gender (% male / % female)
  - Health condition(s) under investigation (including underlying disease)
  - Comorbidities
  - Control
    - Duration and size of ulcers

- Methodology

- Intervention details
  - Unit of treatment (person/wound)
  - Length and frequency of follow up
  - Number of participants
  - Comparator (details)
  - Treatment protocol adherence?
  - Concomitant treatment (systemic antibiotics, compression bandaging etc)

- Withdrawals
  - Number recruited / attrition
  - Reason for attrition

- Results
  - Outcome measures
  - Adverse effects

- Quality (assessed using the appropriate SIGN checklist)
  - Statistical power
  - Randomisation procedure
  - Allocation concealment
  - Baseline comparability of groups
  - Withdrawals
  - Intention to treat analysis
Cost effectiveness measures
- Direct costs disaggregated to resource quantities and unit process
- Indirect costs
- Costing methods
- Measure of health benefits
- Valuation of health states
- Discounting approach and rates
- Outcomes
- Sensitivity analysis
- Source of clinical effectiveness data

External validity – how generalisable are the results of the study to NHSScotland.

One researcher will perform data extraction, recording the results in evidence tables. A second researcher will quality check all the data in the evidence tables. Any disagreement on an element of a study will be resolved through consensus or through consultation with a third reviewer. Reviewers will not be blinded to authors, institutes or publication details. Where there is insufficient information in the published text, contact will be made with the authors for clarification, if time constraints allow.

9.2. Quality assessment strategy

The quality of clinical papers will be assessed independently by two reviewers. Again, disagreement will be resolved through consensus, and if necessary, a third reviewer will be consulted. The quality of the different types of studies reviewed will be assessed using the appropriate SIGN methodology checklist tool.

Cost effectiveness will be assessed using an internationally recognised quality assessment tool. The quality of the evidence base for economic evaluations will be considered and summarised.

9.3. Multiple publications of the same data

For studies with multiple publications, only the most up-to-date or complete data will be included in this review. However, if the publications report on different elements of the trial (ie different outcomes, different analyses etc), they will be included.

9.4. Evidence tables

Data extraction will be recorded in evidence tables in word. A different evidence table will be produced for each type of wound and category of antimicrobial.
10. **Data synthesis**

10.1. **Clinical effectiveness**

For each of the different wound types, a narrative review of the evidence will be written, separately for each category of antimicrobial. If two or more primary studies are considered comparable, the data will be pooled in a meta-analysis (the full methodology of which will be described in the final HTA).

Rather than reappraising the same primary studies included in existing synthesized reports on AWDs, the narrative review will focus initially on good quality systematic reviews and HTAs. Any additional studies not incorporated into these reviews will also be included. If there are no good quality systematic reviews or HTAs for particular types of AWD, the narrative review will focus on the primary evidence (starting with randomised and then non-randomised clinical trials, then working through cohort and case-control studies, and then case series if required).

The narrative review will be written by one researcher, and quality-assured by a second.

10.2. **Cost effectiveness**

A narrative review of the cost effectiveness evidence will be written, separately for each type of AWD, including a summary table incorporating key items of extracted data.

The narrative review will include a summary description of each economic evaluation, and each summary description will follow the general format presented below. However, it is acknowledged that the format will need to be flexible to allow for variability of available data.

1. **Overview**
   1. Study objective
   2. Patient group/comparators
   3. Type of economic evaluation

2. **Methods**
   1. Description of model/analysis
   2. Perspective
   3. Time horizon/discounting
   4. Effectiveness data (relative efficacy, quality of life [QoL])
   5. Cost data (resource use/medicine costs)

3. **Results**
   1. Base case
   2. Sensitivity analysis
4. Uncertainty/limitations with the evaluation
   1. Key uncertainties
   2. Other uncertainties

5. Summary

The narrative review will be written by one health economist, and quality-assured by a second.

Where there are no economic studies that are generalisable to NHS Scotland, or where those identified are of poor quality, consideration may be given to the development of a de novo economic analysis.

Separate to any cost effectiveness assessment, a resource impact analysis (RIA) may be carried out to inform NHSScotland surrounding the resource impact of any changes in clinical practice. Data for the RIA will primarily be drawn from the information collected as part of the cost effectiveness assessment; resource use, resource unit costs, indirect costs (see key questions in Section 1.1).
11. Patient Issues

A review of studies relevant to the patient experience of AWDs will set the context for the patient issues section. Data is expected to come from qualitative research and case studies, therefore no restrictions are placed on study design.

An expert in the incorporation of patient issues in HTAs will also be consulted.

In the absence of an evidence base, following ethical approval, we will interview a group of NHSScotland patients (together or individually) who have received, or are currently receiving, AWDs. Interviews/focus groups will be recorded and transcribed and a thematic analysis undertaken.
12. Organisational Issues

The extent and range of AWD use in Scotland will be determined. It is anticipated that a multi-faceted approach will be required, involving making contact with NHS Boards and asking for assistance from other national NHS organisations (e.g. National Procurement, Scottish Antimicrobial Prescribing Group) to determine the current level of use across the acute and primary care sectors. A cohesive approach to data collection will be used, to ensure that any data gathered regarding use in the different NHS Boards is comparable. Users of the technology (i.e. clinical experts) will be contacted to determine: any issues of safety; how they assess patients to determine suitability for the technology; the professional groups involved in the prescribing and provision of AWDs; the processes and procedures to include AWDs in the patient pathway; any guidelines these groups use and any issues relating to the practical use by NHS staff; training issues; maintenance of the technology; support and resources patients in the community may require to use the technology effectively; and any unintended effects of the use of AWDs. The views and perspectives of NHS staff groups on their prescribing practices will also be sought.
13. **SIGN consensus guidelines**

For areas lacking clinical effectiveness evidence, a consensus guideline will be produced in collaboration with SIGN.

The Scottish Intercollegiate Guidelines Network uses a modified online Delphi method to develop consensus guidelines. This involves identifying a group of experts using the existing method of engagement with SIGN Council to identify suitable clinicians, health professionals and patient representatives. The group then follows a modified Delphi process which consists of a series of online surveys or questionnaires. The results from each round of survey are analysed and then fed back to participants before the next round. Participants can then modify their answers based on previous results, results can be ranked by their mean score and low scoring options can be eliminated.

Guidelines can be formed by ranking and voting on inclusion or exclusion criteria and statements over a set number of rounds. Consensus can be formed quickly or the process ended if consensus cannot be reached.

The resultant document then follows an editorial process to finalise the wording before publication. This process will be managed by a Health Services Researcher working within the Evidence directorate in Healthcare Improvement Scotland.
14. **Timetable**

The key milestones for this project are summarised in the table below.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection</td>
<td>May-December 2014</td>
</tr>
<tr>
<td>Draft report production</td>
<td>Winter 2014/2015</td>
</tr>
<tr>
<td>Final report production</td>
<td>Spring 2015</td>
</tr>
<tr>
<td>Distribution/publication</td>
<td>Spring 2015</td>
</tr>
</tbody>
</table>
15. Dissemination

The results of this project will be disseminated to the following groups:

AWD project team
Chairs and Chief Executives of NHS boards in Scotland
Directors of Planning
Scottish Government Health Directorates
Directors of Nursing
Directors of Public Health
Directors of Pharmacy
Medical Directors
Health and Community Care Committee
Secretary of State for Health, UK Parliament
Minister for Health and Social Services, National Assembly for Wales
Minister for Health, Social Services and Public Safety, Northern Ireland Assembly
Community Health Partnerships
Manufacturers, voluntary organisations, patient groups and others who have contributed to the report.

Healthcare Improvement Scotland
16. The Team

16.1. Project team

Jenny Harbour (Information Scientist)
Stephen Heller-Murphy (Health Services Researcher)
Joanna Kelly (Health Services Researcher)
Naomi Fearns (Health Services Researcher)
Karen Macpherson (Lead Health Services Researcher/Project Lead)
Susan Myles (Lead Health Economist/Project Lead)
Doreen Pedlar (Project Co-ordinator)
Marina Tudor (Project Officer)

16.2. Topic proposer

Margaret Ryan, Lead Clinician Prescribing Services, NHS Greater Glasgow and Clyde
Lynne Watret, Non Medical Prescribing Advisor, NHS Greater Glasgow and Clyde

16.3. Topic Group Membership (as of May 2014)

Margaret Ryan, Lead Clinician Prescribing Services, NHS Greater Glasgow and Clyde
Lynne Watret, Non Medical Prescribing Advisor, NHS Greater Glasgow and Clyde
Glynis Billimore, Vascular Nurse Specialist, Chair of Leg Ulcer Forum Scotland
Professor Julie Brittenden, Senior lecturer in Vascular Surgery, University of Aberdeen
Lorna Brown, Lead for Prescribing and Clinical Pharmacy, NHS Greater Glasgow and Clyde
Jo Dumville, Senior Lecturer in Applied Health Research, University of Manchester
Gavin Gorman, Non Medical Prescribing Lead, NHS Greater Glasgow and Clyde

David Gray, Honorary Professor/Tissue Viability Nurse Specialist, NHS Grampian, Scottish Tissue Viability Nurses representative

Dr Teresa Inkster, Consultant Microbiologist, NHS Greater Glasgow and Clyde

Alison Johnstone, Tissue Viability Nurse, NHS Greater Glasgow and Clyde, Scottish Tissue Viability Nurses representative

Professor Alistair Leanord, HAI Medical Adviser, Scottish Government

May Loney, Dermatology nurse specialist, Leg Ulcer Forum Scotland

Celia Macaskill, Dermatology nurse specialist, Leg Ulcer Forum Scotland

Joanne McCardle, Diabetic Podiatrist, NHS Lothian

Graeme McIntosh, Commodity Manager, National Procurement, NHS National Services Scotland

Nils Michael, Economist, Scottish Government

Abigail Mullings, Deputy Chief Nursing Officer – Safe Care, Scottish Government

Jill Nowell, Lead Pharmacist for Medicines Utilisation, NHS Forth Valley, Directors of Pharmacy Group representative

Linda Primmer, Community Tissue Viability Nurse, NHS Lothian, Scottish Tissue Viability Nurses representative

Thomas Ross, Lead Pharmacist (South & Mid), NHS Highland, Directors of Pharmacy Group representative

Ailsa Sharp, Lecturer in Adult Nursing/ Tissue Viability, Napier University, Scottish Tissue Viability Nurses representative

Jacqueline Sneddon, Project Lead for Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland

Professor Richard White, Professor of Tissue Viability, University of Worcester

SHTG Working Group
17. Appendices

17.1. Appendix 1: Literature search checklists

17.1.1. Checklist – HTA: Scottish context and service organisation

**Scottish context**
Chief Scientist Office
Healthcare Improvement Scotland
HSRU
ISD
National Procurement
NES
Scottish Government publications
Scottish Public Health Observatory (ScotPHO)
SHOW
*If applicable and agreed with HSR also search:*
Health Facilities Scotland
Health Protection Scotland
Health Scotland
SMC (drugs only)

**Health Service Delivery**
Health Foundation
King’s Fund
NHS Improving Quality
NHS Service Delivery and Organisation Programme

17.1.2. Checklist – HTA: secondary evidence

**Guidelines**
AHRQ National Guideline Clearing House
Australian NHMRC
CMA Infobase
e-guidelines (use as a check against other sources – possible to view titles, but not to access e-guidelines summaries)
GAIN: Guidelines and Audit Implementation Network (Northern Ireland)
Guidelines International Network
New Zealand Guidelines Group
NHS Evidence (use guidelines filter on search results)
NICE (guidelines)
RCN Clinical Guidelines
SIGN
TRIP Database (Guidelines)
Secondary evidence
Adelaide Health Technology Assessment
AHRQ
Alberta Heritage Foundation for Medical Research
Aggressive Research Intelligence Facility (ARIF)
Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S)
Bandolier
BMJ Clinical Evidence
CADTH
Canadian Medical Association
Centers for Medicare and Medicaid Services
Centre for Clinical Effectiveness (Monash)
Clinical Evidence
Clinical Knowledge Summaries
Cochrane Database of Systematic Reviews
Commissioning body summaries (Delicious KMU login)
Database of Abstracts of Reviews of Effects (DARE) (CRD and Cochrane)
Dynamed
ECRI (HTAIS)
Euroscan
EVIDENT database (Evidence Database on New Technologies)
EVIP Net
Health Evidence Network
Health Quality Ontario
Health Services Assessment Collaboration (HSAC)
Health Systems Evidence
HIQA - Health Information and Quality Authority
HTA database (via CRD and Cochrane)
Institute for Clinical Evaluative Sciences, Canada
KCE (English language full text or summary)
Liverpool Reviews and Implementation Group
Madox Horizon Scanning Reports
Medical Research Council (MRC)
MSAC
MUHC, Technology Assessment Unit McGill University
National Health and Medical Research Council (NHMRC)
National Horizon Scanning Centre
US National Institutes of Health
NHS Evidence (Filter search results by the following Types of Information: commissioning guides, evidence summaries, HTA, systematic reviews)
NHS HTA Programme
NICE (technology appraisals, public health guidance, diagnostics guidance, interventional procedures, medical technologies, cancer service guidance)
PenTAG, Peninsula College of Medicine and Dentistry
PubMed Clinical Queries (Systematic Reviews section)
ScHARR TAG
SHTAC, University of Southampton

TRIP
UpToDate
VA Technology Assessment Program (VATAP)
West Midlands Health Technology Assessment Collaboration (WMHTAC)

**Web Search (focused)**
Google

*Bibliographic databases (limit to systematic reviews)*
MEDLINE
MEDLINE In-Process
EMBASE
CINAHL (or other topic related database e.g. Psychinfo)
Web of Knowledge

17.1.3. Checklist – HTA: health economics

Health Economic Evaluations Database (HEED)
NHS EED (CRD and Cochrane Library)

*Health Economics Centres*
CEA registry, Tufts University
Centre for Health Economics, University of York
CHEPA, McMaster University
CHERE, University of Sydney
CHPPE, University of Melbourne, Australia
ESHER, University of Newcastle
Health Economics Research Group, Brunel University
HEDS, ScHARR, University of Sheffield
HEG, University of East Anglia
HERC, University of Oxford
Institute of Health Economics, Alberta, Canada
London school of economics and political science
Southampton University Economics Dept
York Health Economics Consortium

*Other web-sites of potential interest*
Audit Scotland
CODECS
EconLIT
European Network of Health Economics Evaluation Databases
Health and Social Care Information Centre
Health Economics core library recommendations by NLM
Health Economics.com  
International Health Economics Association  
NHS Finance Manual  
Paediatric Economic Database Evaluation (PEDE) database  
Prescription Services, NHS Business Services Authority  
RePEc (large database of economics papers)  
WHO (Statistics and data)  
WHO-CHOICE: choosing health interventions that are cost effective

**Economic Publications**  
Hospital Episode Statistics (for free data)  
NHS Reference costs  
OHE guide to UK health and health care statistics  
Scottish Health Service Costs  
Unit Costs of Health and Social Care

17.1.4. Checklist – HTA: patient issues

Better Together (Scottish Patient Experience Programme)  
Campbell Collaboration  
Centre for Qualitative Research  
Cochrane Consumer Network (CCNet)  
Community Health Exchange (CHEX)  
Developing Patient Partnerships  
DIPEX  
Health Talk Online  
Youth Talk Online  
International Alliance of Patients’ Organizations  
Involve  
National Association for Patient Participation  
National Voices  
NHS Centre for Involvement  
NHS Improving Quality  
NHS Surveys  
Patient Opinion  
Patient UK Discussion Forums  
Patient Views  
Patients Accelerating Change  
Patients Association  
Picker Institute  
The James Lind Alliance

**Equalities**  
Equality Evidence Finder  
Equality in Health MKN
17.1.5. Checklist – HTA: safety

Australian Commission on Safety and Quality in Health Care
Australian Patient Safety Foundation
Canadian Patient Safety Institute
Centre for Research Excellence in Patient Safety
FDA
Institute for safe medication practices
Institute of Medicine
King’s Patient Safety and Service Quality Research Centre
MedlinePlus: Patient Safety
MHRA
National Coordinating Council for Medication Error Reporting and Correction
National Patient Safety Foundation
NPSA
Patient safety board (RCS – Edinburgh)
Patient Safety Research Group
RCN: patient safety
Scottish Patient Safety Alliance
Scottish Patient Safety Research Network
The Joint Commission: Patient Safety
VA National Center for Patient Safety
World Alliance for Patient Safety

17.1.6. Checklist – HTA: topic specific resources

Societies/Colleges
American Academy of Dermatology
American Academy of Family Physicians
American College of Certified Wound Specialists
American College of Physicians
American Medical Association
American Professional Wound Care Association
American Society of Dermatology
Association for the Advancement of Wound Care
Association of Physicians
Australasian College of Dermatologists
Australasian Wound and Tissue Repair Society
Australian Wound Management Association
British Association of Dermatologists
British Medical Association
British Society for Paediatric Dermatology
Canadian Association of Wound Care
Canadian Dermatology Association
Dermatology Nurses Association
Diabetes UK
European Pressure Ulcer Advisory Panel
European Tissue Repair Society
European Wound Management Association
Global Wound Academy
International Society of Dermatology
Japanese Society for Wound Healing
Leg Ulcer Forum
Medical Dermatology Society
New Zealand Dermatological Society
New Zealand Wound Care Society
Primary Care Dermatology Society
RCN
Royal College of GPs
Royal College of Physicians (London and Edinburgh)
Scottish Dermatological Society
Society of Vascular Nurses
Tissue Viability Nurses Association
Tissue Viability Nurses Association of Ireland
Tissue Viability Online
Tissue Viability Society
World Union of Wound Healing Societies
Wound Care Association of NSW
Wound Care Society
Wound Healing Society
Wound Management Academy
Wound Management Association of Ireland
Wound Ostomy and Continence Nurses Society

Manufacturers
Molnlycke Healthcare
Smith & Nephew
Convatec
Johnson & Johnson Medical
Systagenix Wound Management Ltd
Unomedical Ltd
Coloplast
Urgo Ltd
Hartmann, Paul
3M Healthcare
Braun Medical
Crawford Pharm
Derma Sciences Europe Ltd
Activa Healthcare
Aspen Medical
BSN Medical
Covidien
17.1.7. Checklist – HTA: primary literature

*Bibliographic databases (limit to systematic reviews first)*
- MEDLINE
- MEDLINE In-Process
- EMBASE
- CINAHL (or other topic related database e.g. Psychinfo)
- Web of Knowledge
- CENTRAL
- Biomed Central

*Others as appropriate to topic e.g.*
- ASSIA
- ERIC (via OVID)
- HMIC (via OVID)
- HSTAT
- LILACS

17.1.8. Checklist – HTA: ongoing trials and conference proceedings

*Ongoing research*
- Clinical trials service unit & epidemiology studies unit
- Cochrane Library (protocols and ongoing HTAs)
- DUETS
- MRC (funded research projects)
- Public Library of Science Clinical Trials Hub
- Research Summaries Register
- UK Clinical Research Network Portfolio Database

*International trial registers (Always search resources marked *)
- Clinicaltrials.gov (refine with care, results may be missed)
- Current Controlled Trials – active register & archive
- International Clinical Trials Registry Platform Portal - WHO Centerwatch
- Clinical Research Studies Protocol database (SEARCH)
- Clinical Trial Results
- Cordis (European R&D)
- EU-CTR
- European Medicines Agency (EMEA)
- NHMRC Clinical Trials Centre - Sydney
- RePORTER (previously CRISP)
- Trials Central
Conference Proceedings (if required – see HSR)
Zetoc
NLM Gateway
The Conference Website
Directory of published proceedings
References


