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Norman G, Dumville JC, Westby MJ, Stubbs N, Soares MO

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T A B L E   O F   C O N T E N T S

[Intervention Protocol]

Dressings and topical agents for treating venous leg ulcers

Gill Norman[1], Jo C Dumville[1], Maggie J Westby[1], Nikki Stubbs[2], Marta O Soares[3]

[1]Division of Nursing, Midwifery & Social Work, School of Health Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [2]Wound Prevention and Management Service, Leeds Community Healthcare NHS Trust, St Mary's Hospital, Leeds, UK. [3]Centre for Health Economics, University of York, York, UK

Contact address: Gill Norman, Division of Nursing, Midwifery & Social Work, School of Health Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester Academic Health Science Centre, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL, UK. gill.norman@manchester.ac.uk.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of (1) dressings and (2) topical agents for healing venous leg ulcers in any care setting and to rank treatments in order of effectiveness, with assessment of uncertainty and evidence quality.

BACKGROUND

Description of the condition

Venous leg ulcers are a common and recurring type of complex wound that heal by secondary intention (that is by the growth of new tissue rather than by primary closure). Problems with the leg veins (such as damage to the valves, or blockages) reduce the efficient return of blood to the heart and increase the pressure in the veins (Ghauri 2010), which may result in venous leg ulcers. The precise chain of events that links the high venous pressures (chronic venous hypertension) with skin breakdown and a chronic wound is not fully understood (Coleridge Smith 1988; Valencia 2001).

Venous leg ulcers commonly occur on the gaiter region of the lower leg (from just below the ankle up to mid-calf). A venous leg ulcer is defined as any break in the skin that has either been present for longer than six weeks or occurs in a person with a history of venous leg ulceration. Differential diagnosis of the type of leg ulcer (i.e. the underlying cause) is made by taking a clinical history, physical examination, laboratory tests and haemodynamic assessment (RCN 2013; SIGN 2010). The latter typically includes an assessment of arterial supply to the leg using the ankle brachial pressure index (ABPI), measured using a hand-held Doppler ultrasound probe or scanner. Clinically significant arterial disease as a cause of ulceration is usually ruled out by an ABPI of at least 0.8 (Ashby 2014; NICE 2016a; SIGN 2015). True venous ulcers are moist, shallow and irregularly shaped and lie wholly or partly within the gaiter area of the leg. Leg ulcers can be associated with venous disease in combination with vascular disease, which impairs arterial blood supply; in these instances they are said to have a 'mixed' aetiology (to have more than one cause). Open skin ulceration due solely to limb ischaemia from vascular disease is less common. Accurate, current estimates of leg ulcer prevalence are hard to identify because most surveys do not differentiate between causes of leg ulceration, or do so per limb but not per person (Moffatt 2004;

Srinivasaiah 2007; Vowden 2009b). Estimates of the prevalence of open leg ulceration (any cause) range from 4 to 48 cases per 10,000 (Graham 2003; Johnson 1995; Walker 2002), with the point prevalence of venous leg ulceration in Australian and European studies being between 10 per 10,000 and 30 per 10,000 (Nelzen 2008). A recent estimate suggests that venous ulceration has a point prevalence of 2.9 cases per 10,000 in the United Kingdom (UK), whilst mixed arterial/venous leg ulceration has a point prevalence of 1.1 per 10,000 (Hall 2014).

Venous disease is a chronic condition that is characterised by periods of ulceration (i.e. an open wound) followed by healing and then recurrence. An early cross-sectional survey reported that half of current or recent ulcers had been open for up to nine months and that 35% of people with leg ulcers had experienced four or more episodes (Callam 1987). This picture was supported by a subsequent cross-sectional study (Nelzen 1994). More recent analysis of almost 1200 people with venous leg ulcers documented a 24-week healing rate of 76% and a recurrence at one year of 17% (Gohel 2005).

Cohort data from 20,000 people have shown that initial wound area and duration accurately predict healing in venous leg ulcers (Margolis 2004). In this study, ulcers smaller than 10 cm² with durations of less than 12 months at first visit had a 29% chance of not healing by the 24th week of care, whilst ulcers larger than 10 cm² with duration longer than 12 months had a 78% chance of not healing by 24 weeks (Margolis 2004). A small cohort study has suggested that percentage change in area over the first four weeks of treatment may be an indicator of whether a wound will heal within 24 weeks (Kantor 2000). Older age has been identified as an independent risk factor for delayed healing (Gohel 2005), while slow healing is also a risk factor for recurrence, possibly because it reflects the extent of underlying venous insufficiency (Gohel 2005). Regression modelling based on a small retrospective cohort study supported the importance of initial total ulcer area and age and also identified male gender and history of previous leg ulceration as risks for longer healing times (Taylor 2002).

Venous ulcers are painful, can be malodorous and prone to infection, and may severely affect patients' mobility and quality of life. The presence of leg ulceration has been associated with pain, restriction of work and leisure activities, impaired mobility, sleep disturbance, reduced psychological well-being and social isolation (Herber 2007; Maddox 2012; Persoon 2004). In severe cases, ulceration can lead to limb amputation, although this may be more common in people with comorbid arterial insufficiency (Dumville 2009; Nelzen 1997; Valencia 2001). Recent research suggests that people with complex wounds, including those with venous leg ulcers, commonly see complete wound healing as the most important outcome to them (Cullum 2016; Madden 2014).

The financial cost of treating an unhealed leg ulcer in the UK has most recently been estimated at around GBP 1700 per year (price year 2012) (Ashby 2014). An earlier evaluation estimated the average cost of treating a venous leg ulcer in the UK (based on costs for material for dressing changes) as between EUR 814 and EUR 1994 and, in Sweden as lying between EUR 1332 and EUR 2585 (price year 2002), with higher costs associated with larger and more chronic wounds (Ragnarson 2005). In Bradford, UK, GBP 1.69 million was spent on dressings and compression bandages, and GBP 3.08 million on nursing time (estimates derived from resource use data for all wound types) during the financial year 2006 to 2007 (Vowden 2009a). Data from a German study, which estimated total costs including those classified as indirect or intangible costs, estimated mean annual costs of leg ulcers as EUR 9060 per patient (price year 2006). This figure is higher than other estimates because it includes non-health service costs to the patient and to society (Augustin 2012). These data are all derived from high-income countries and thus may not be a true reflection of costs elsewhere, which may be higher or lower.

Description of the intervention

The review will include all dressings and topical agents applied directly onto or into wounds and left *in situ*. This contrasts with products used to irrigate, wash or cleanse wounds and that are only in contact with wounds for a short period. Dressings are widely used in wound care with the aim of protecting the wound and promoting healing by influencing the local wound environment (Bradley 1999), typically by physical means, such as thermal insulation, absorption of exudate and physical protection. Dressings may also have pharmacological, immunological or metabolic actions. In addition, this review will include studies of topical agents such as hydrogel gels, ointments and creams that are placed in contact with the wound and left in situ, that is, topical agents and dressings that remain in contact with the wound and may be covered with a secondary dressing.

First-line treatment for venous leg ulcers is compression therapy in the form of bandages, stockings or mechanical devices (Nelson 2014; O'Meara 2012). This application of external pressure around the lower leg assists venous return and reduces venous reflux (Woo 2013). We therefore anticipate that wound dressings will commonly be used in combination with compression therapy.

Dressings

The classification of dressings usually depends on the key material used in their construction, and whether additional substances are added to the dressing. Several attributes of an ideal wound dressing have been described (BNF 2016), including the ability of the dressing to:
- absorb and contain exudate without leakage or strike-through, in order to maintain a wound that is moist but not macerated;
- achieve freedom from particulate contaminants or toxic chemicals left in the wound;

- provide thermal insulation, in order to maintain the optimum temperature for healing;
  - allow permeability to water, but not bacteria;
  - optimise the pH of the wound;
  - minimise wound infection and avoid excessive slough;
  - avoid wound trauma on dressing removal;
  - accommodate the need for frequent dressing changes;
  - provide pain relief; and
  - be comfortable.

There are a wide range of types of dressings available which may be used for treating wounds including venous leg ulcers; some of these and their properties are described below (BNF 2016). Impregnated dressings may have a range of bases, such as foams or alginates.

Absorbent dressings are applied directly to the wound and may be used as secondary absorbent layers in the management of heavily exuding wounds. Examples include Primapore (Smith & Nephew); this can be lifted off at dressing removal, or removed by irrigation. Bonding to a secondary viscose pad increases absorbency. Examples include: Curasorb (Covidien), SeaSorb (Coloplast) and Sorbsan (Unomedical).

Capillary-action dressings consist of an absorbent core of hydrophilic fibres held between two low-adherent contact layers. Examples include: Advadraw (Advancis) and Vacutex (Protex).

Films, that is, permeable film and membrane dressings are permeable to water vapour and oxygen, but not to water or micro-organisms. Examples include Tegaderm (3M) transparent film and OpSite (Smith & Nephew).

Foam dressings contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface. There are a variety of versions and some include additional absorbent materials, such as viscose and acrylate fibres, or particles of superabsorbent polyacrylate, which are silicone-coated for nontraumatic removal. Examples include: Allevyn (Smith & Nephew), Biatain (Coloplast) and Tegaderm (3M) foam adhesive and non-adhesive dressings.

Honey-impregnated dressings contain medical-grade honey that is purported to have antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Examples include: Medihoney (Medihoney) and Activon Tulle (Advancis).

Hydrocolloid dressings are usually composed of an absorbent hydrocolloid matrix on a vapour-permeable film or foam backing. Examples include: Granuflex (ConvaTec) and NU DERM (Systagenix). Fibrous alternatives that resemble alginates and are not occlusive have also been developed: Aquacel (ConvaTec).

Iodine-impregnated dressings release free iodine, which is thought to act as a wound antiseptic when exposed to wound exudate. Examples include Iodoflex (Smith & Nephew) and Iodozyme (Insense).

Low-adherence dressings and **wound contact materials** usually consist of cotton pads that are placed directly in contact with the wound. They can be non-medicated (e.g. paraffin gauze dressing, saline gauze dressing) or medicated (e.g. containing povidone iodine or chlorhexidine). Examples include paraffin gauze dressing, BP 1993 and Xeroform (Covidien) dressing - a non-adherent petrolatum blend with 3% bismuth tribromophenate on fine mesh gauze.

Odour-absorbent dressings contain charcoal and are used to absorb wound odour. Often this type of wound dressing is used in conjunction with a secondary dressing to improve absorbency. An example is CarboFLEX (ConvaTec).

Other antimicrobial dressings are composed of a gauze or low-adherent dressing impregnated with an ointment thought to have antimicrobial properties (e.g. chlorhexidine gauze dressing (Smith & Nephew)). Alternatively a dressing such as Cutimed Sorbact (BSN Medical) uses a hydrophobic layer to bind micro-organisms to the dressing surface, allowing them to be removed from the wound when the dressing is changed.

Protease-modulating matrix dressings alter the activity of proteolytic enzymes in chronic wounds. Examples include: Promogran (Systagenix).

Silver-impregnated dressings are used to treat infected wounds, as silver ions are thought to have antimicrobial properties. Silver versions of most dressing types are available, including silver impregnated dressings (e.g. silver hydrocolloid etc). Examples include: Acticoat (Smith & Nephew) and Urgosorb Silver (Urgo).

Soft polymer dressings are composed of a soft silicone polymer held in a non-adherent layer; these are moderately absorbent. Examples include: Mepitel (Mölnlycke) and Urgotul (Urgo).

Topical agents

The following types of topical agents are considered as interventions in this review:

Cadexomer-iodine paste consists of a water-soluble, modified starch polymer containing iodine. It releases free iodine when exposed to wound exudate. The free iodine acts as an antiseptic on the wound surface, and the cadexomer absorbs wound exudate and encourages de-sloughing. Examples include: Iodosorb (Smith & Nephew) ointment and powder.

Collagenase-containing ointment is an enzymatic debriding ointment. Collagenase is thought to digest collagen in necrotic tissue and to contribute to granulation and epithelialisation (the final stage of wound healing).

Hydrogels consist of a starch polymer and up to 96% water. They can absorb wound exudate or rehydrate a wound depending on the wound moisture levels. Hydrogels are often considered to be dressings, but are also topical in nature. They are supplied in either flat sheets, an amorphous hydrogel or as beads. Examples include: ActiformCool (Activa) and Aquaflo (Covidien).

Phenytoin topical is thought to promote wound healing by a number of mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition and antibacterial activity.

Silver sulfadiazine cream is a topical antimicrobial cream that is used to treat and prevent infection in wounds by damaging bacterial cell membranes. Examples include Flamazine (Smith & Nephew) and Silvadene (Pfizer).

We will not consider studies evaluating any products containing growth factors, platelet rich plasma or other platelet-derived products and colony-stimulating factors.

How the intervention might work

Animal experiments conducted over 40 years ago suggested that acute wounds heal more quickly when their surfaces are kept moist rather than left to dry and scab (Winter 1962; Winter 1963a; Winter 1963b). A moist environment is thought to provide optimal conditions for the cells involved in the healing process with faster revascularisation (Dyson 1992) and development of granulation tissue (Svensjö 2000), as well as allowing autolytic debridement (removal of dead tissue by natural processes), which is thought to be an important part of the healing pathway (Cardinal 2009).

The desire to maintain a moist wound environment is a key driver for the use of wound dressings and related topical agents. Whilst a moist environment at the wound site has been shown to aid the rate of epithelialisation in superficial wounds, excess moisture at the wound site can cause maceration (breakdown) of the surrounding skin (Cutting 2002), and it has also been suggested that dressings that permit fluid to accumulate might predispose wounds to infection (Hutchinson 1991). Wound treatments vary in their level of absorbency, so that a very wet wound can be treated with an absorbent dressing (such as a foam dressing) to draw excess moisture away and avoid skin damage, whilst a drier wound can be treated with a more occlusive dressing or a hydrogel to maintain a moist environment.

Some dressings are now also formulated with an 'active' ingredient (e.g. silver, honey or protease modulators).

Why it is important to do this review

Venous leg ulcers are a relatively common type of complex wound that have a negative impact on people's lives and incur high costs for health services and society. Leg ulcers are painful, sometimes malodorous, prone to infection, and may severely affect patients' mobility and quality of life, and in severe cases, there is a risk of limb amputation. There are a number of treatments for venous leg ulcers, but many ulcers prove hard to heal, although healing is a key outcome for patients.

We conducted an open consultation with consumers who self-selected through their response to questions posted on the Cochrane Wounds website and Facebook page to ask them which treatments for treating venous leg ulcers they would like to see considered. Although some identified compression as the main consideration,

others mentioned specific types of dressings. These included many of the dressing types listed in Description of the intervention, including charcoal-containing (odour-absorbing) dressings, dressings designed to reduce formation and presence of biofilms (bacteria which grow on a surface to form a film of cells) and dressings with antimicrobial properties and debriding actions. Also specifically identified as being of interest was Unna's boot; a specialised dressing which consists of gauze wraps impregnated with zinc oxide and calamine, sometimes in combination with other agents. Although it provides an degree of compression, it is applied primarily as a dressing with adjunctive compression; we will appraise comparisons involving Unna's boot against inclusion criteria, including the requirement that a dressing/topical treatment should be the only systematic difference between groups.

The diversity of dressings and related materials available to health professionals for treating venous leg ulcers makes evidence-based decision-making difficult when determining the optimum treatment regimen for a particular patient (NICE 2016a). With increasingly sophisticated technology being applied to wound care, practitioners need to know the relative effectiveness and cost-effectiveness of these sometimes expensive dressings. Even where cost is not an issue, the most effective treatment may not be available (e.g. in some developing countries) or may be difficult or to use, so that information on the second and third best treatments is important too (Salanti 2011).

There are a number of existing or ongoing evidence syntheses on venous leg ulcer treatment available including Cochrane reviews of different types of dressings and topical treatments (Briggs 2012; O'Meara 2013; O'Meara 2014; O'Meara 2015; Ribeiro 2013; Ribeiro 2014; Westby 2015a). There are also wider reviews of particular types of treatment for all wound types which include data on venous leg ulcers for treatments such as honey, silver, aloe Vera, and phenytoin (Dat 2012; Jull 2015; Shaw 2007; Vermuelen 2007). Other reviews focused on non-healing or chronic ulcers have also included a substantial number of relevant trials (Greer 2013; AHRQ 2013) and there are also older general reviews (e.g. Bouza 2005; O'Donnell 2006).

Guidance drawing on reviews available at the time has also been published (Robson 2006; SIGN 2010). The SIGN 2010 guideline recommended that low-adherent dressings be used routinely but that alternative dressings (hydrocolloids, alginates or hydrogels) may be considered to assist with pain, exudate and slough respectively. Earlier guidance (Robson 2006) recommended that maintaining a moist wound environment be prioritised in dressing choice. Most recently the UK National Institute for Health and Care Excellence (NICE) issued advice on the use of advanced and antimicrobial dressings for chronic wounds including venous leg ulcers (NICE 2016b). This updated the SIGN 2010 guidance to include the findings of the most recent systematic reviews.

However, despite the existence of high-quality recent systematic reviews, there is insufficient evidence to support the use of any particular type of advanced or antimicrobial dressing or treatment

as the direct evidence is of low certainty and no network meta-analysis has previously been undertaken in this area. Decision-makers currently have to consider the findings of a plethora of pairwise randomised controlled trials (RCTs) simultaneously and to make qualitative judgements across these in the face of uncertainty, when considering the evidence on dressing use.

Network meta-analysis (NMA) is the simultaneous comparison of linked, multiple, competing treatments in a single statistical regression model (Caldwell 2005; Lu 2004; Salanti 2008). NMA utilises evidence from both 'direct' (head-to-head or 'pairwise') comparisons (e.g. trials directly comparing treatments A and B) and 'indirect' comparisons (e.g. the combination of trials comparing A with C and trials comparing B with C). If both direct and indirect estimates are available, they can be meta-analysed, preserving within-trial randomisation (Grant 2013; Thorlund 2012; Tu 2012).

Where there are relevant common comparators, NMA produces a set of effect estimates for each treatment linked into the network, relative to every other, whether or not they have been compared in head-to-head trials: thus, NMA is a method of obtaining estimates for comparisons for which there is no (direct) trial evidence. Even when direct evidence is available there may not be much of it, so pooling it with data from indirect comparisons generally gives more robust evidence and reduces uncertainty in the estimates of effect (Higgins 1996; Thorlund 2012). It is also possible to calculate the probability of one treatment being the best for a specific outcome, reflecting the precision surrounding the estimates (Caldwell 2014; Salanti 2011).

A glossary of NMA terms is given in Appendix 1.

This review will comprise a network meta-analysis (NMA) for the outcome of venous leg ulcer healing, for alternative dressings and topical agents for the treatment of venous leg ulcers. We will draw on methods previously used in related work (Soares 2014; Westby 2015b). The NMA will enable us to determine which (if any) dressing or topical agent is the most effective for healing venous leg ulcers, taking into account direct and indirect evidence simultaneously. We will also present uncertainty around treatment estimates, and we will explore assumptions being made in the analysis.

O B J E C T I V E S

To assess the effects of (1) dressings and (2) topical agents for healing venous leg ulcers in any care setting and to rank treatments in order of effectiveness, with assessment of uncertainty and evidence quality.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomised controlled trials (RCTs), irrespective of language of report. We will only include cross-over trials that report outcome data at the end of the first treatment period and prior to cross-over. We will exclude studies using quasi-random methods of allocation (such as alternation). We will highlight trials in which three or more interventions are randomised and include all relevant arms.

Types of participants

We will include trials recruiting adults (aged at least 18 years) described as having venous leg ulcers, managed in any setting. We will accept study authors' definitions of venous leg ulcers. Where wounds are described only as "leg ulcers" without information as to aetiology we will assume that they are venous in origin. Trials in which a minority of leg ulcers are described as having a mixed or arterial pathology will be included provided that these are fewer than 25% of participants. Trials including other types of mixed wound populations will not be included. We will include participants at any stage of their treatment process - for example participants with or without ulcers described as being hard to heal or clinically infected.

Types of interventions

Interventions of direct interest

The interventions in this section are all those that can be directly applied as dressings or topical agents to open venous leg ulcers. We will present results for these interventions and include them in summary tables. In the context of a network of competing treatments, there are no 'comparators'. We will use the term "comparison" to mean two interventions compared in a single study and the term "contrast" to mean two interventions compared across all studies with that comparison. A contrast may be represented by a single study, a simple direct meta-analysis or by the NMA.

We will consider trials for which at least one of the interventions is (1) any dressing, including impregnated dressings or saline-moistened dressings or combination dressings*, or (2) any topical agent applied directly to an open venous leg ulcer and left *in situ*. The treatment of interest should be the only systematic difference between treatment groups. We will not take into account secondary dressings. We will also consider 'no dressing' as a valid intervention, where the wound is left open/covered only by compression bandaging.

* 'combination dressings' means two or more dressings applied sequentially over time (e.g. hydrocolloid for 4 weeks followed by

alginate for 4 weeks), or a product containing two or more types of dressing material (e.g. a multilayer product comprising silicone polymer and hydrocolloid).

Some of the interventions we will consider are as follows; we will use the categories listed below as the basis for grouping the treatments used in individual studies.

- Basic wound contact dressings (includes low-adherence (including paraffin gauze) or absorbent dressings (of any absorbency))
- Saline-moistened gauze (all degrees of moistness)
- Hydrogel dressing (includes hydrogel sheet or hydrogel application (amorphous) or sodium hyaluronate)
- Vapour-permeable films and membranes (includes adhesive film (semi-permeable) or adhesive film with absorbent pad)
- Soft polymer dressings (with/without absorbent pad or cellulose)
- Hydrocolloid dressing (with/without adhesive border or matrix hydrocolloid)
- Fibrous (spun) hydrocolloid
- Foam dressings (all absorbencies)
- Alginate dressings
- Capillary action dressings
- Alginate dressing with charcoal
- Other charcoal-containing dressing
- Honey sheet dressing or topical honey
- Cadexomer Iodine ointments
- Iodine-containing dressings
- Soft polymer dressing (with silver)
- Hydrocolloid (with silver)
- Foam dressings (with silver)
- Alginate dressings (with silver)
- Silver sulfadiazine cream
- Protease-modulating matrix dressings
- Collagenase-containing ointment
- Topical phenytoin
- Topical zinc oxide
- No dressing (wound left exposed)
- Other treatments considered by the review team (with additional clinical advice where required) to be dressings or topical agents applied directly to the wound and left in situ.

The following interventions are excluded from the set of interventions of direct interest: treatments in which dressings are attached to external devices such as negative pressure wound therapies, skin grafts, growth factor treatments, platelet gels and larval therapy. We will also exclude interventions which, although topical, are not delivered as a physical presence (liquid or solid) on the wound surface such as oxygen, ultrasound, laser or radiant heat therapies. Where studies compare an eligible with an ineligible intervention we will include them but will only fully extract data if they contribute to the network by enabling a comparison of two eligible interventions through indirect evidence. Studies that assess one eligible intervention and that do not contribute to the network will

be listed separately. Where studies use a placebo comparator for an eligible intervention we will include them and treat the placebo as representing no additional active treatment. For example a comparison of a cream containing an antibiotic with a placebo would be treated as a comparison of topical antibiotic with an emollient cream without active properties.

We will group together dressings in the same class, for example, all hydrocolloid dressings will be grouped together regardless of whether they are adhesive or non-adhesive (BNF 2016). This grouping will be regardless of a particular brand's stated absorbency, size, concentration of active component or the degree of moistness. Thus, where studies have only compared two dressings from the same class (for example, two alginates or two foam dressings), we will exclude them from the review as they will contribute no information about the effectiveness of the class. We will consider an impregnated dressing to be in a different class from a non-impregnated dressing. In all instances we will seek clinical advice to determine whether dressings should be considered to belong to the same or different classes. Judgements about whether particular dressings belong to the same class will be made on the basis of BNF classifications (BNF 2016) and clinical expert advice where there is remaining uncertainty. Evidence from comparisons between dressings of the same class can be found in the individual Cochrane reviews of particular types of dressings. Trials of this type will also be clearly identifiable in the list of excluded studies. We anticipate that the great majority of participants will be treated with concurrent compression therapy and will note the type of compression therapy used. We will also include any RCT in which other concurrent therapies are given (e.g. antibiotics, debridement), provided that these treatments were delivered in a standardised way across the trial arms of the individual trial (such that the treatment of interest is the only systematic difference). We will not treat separately comparisons with and without concurrent therapies, that is, we will consider intervention 1 + concurrent therapy versus intervention 2 + concurrent therapy to be the same as intervention 1 versus intervention 2.

We assume that the interventions are exchangeable, that is, participants in the network could, in principle, be randomised to any of the treatments being compared. For example, that a person with a venous leg ulcer could be equally likely to be randomised to a silver dressing, a polyurethane foam dressing, honey or saline gauze. Depending on the wound requirements for the dressing (e.g. highly absorbent), this may not always be a good assumption for individual wounds, but may be reasonable across the population in the trials.

Types of outcome measures

We will report outcome measures at the last time point available (assumed to be at the end of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this is different from latest time point available). Initially, we will

note when studies report results at other time points, or whether they include Kaplan-Meier plots, or both.

Primary outcomes

The primary outcome for this review is complete wound healing. We will regard the following as providing the most relevant measures of outcome for the analyses:

- the proportion of wounds healed (frequency of complete healing: arm-level data);
- time to complete healing (survival data: study-level data reported as a hazard ratio (HR) with standard error (SE)).

We will accept authors' definitions of what constitutes a healed wound.

Secondary outcomes

We will not consider any secondary outcomes here, however they are considered in other relevant reviews (Briggs 2012; O'Meara 2013; O'Meara 2014; O'Meara 2015) and ongoing reviews (Ribeiro 2013; Ribeiro 2014; Westby 2015a).

Search methods for identification of studies

Electronic searches

We will search the following electronic databases to identify reports of relevant randomised clinical trials:

- the Cochrane Wounds Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL, latest issue);
- Ovid MEDLINE (1946 to date);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, to date);
- Ovid Embase (1974 to date);
- EBSCO CINAHL (1982 to date).

The draft search strategy for CENTRAL is shown in Appendix 2. We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). There will be no restrictions with respect to language, date of publication or study setting. We will also search the following clinical trials registries:

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organisation International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx);

- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included studies as well as relevant systematic reviews, meta-analyses, guidelines and health technology assessment reports. We will also contact review groups that are working on relevant ongoing reviews. We will use any additional unpublished data for included studies obtained by previous reviews, and will undertake cross-checking to ensure that all relevant studies with evaluable outcome data are included.

Data collection and analysis

Selection of studies

Two review authors will independently assess the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we will obtain full-text copies of all studies considered to be potentially relevant. Two review authors will independently check the full papers for eligibility; disagreements will be resolved by discussion and, where required, the input of a third review author. Where required and possible, we will contact study authors where the eligibility of a study is unclear. We will record all reasons for exclusion of studies for which we had obtained full copies. We will complete a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies have been reported in multiple publications/reports we will obtain all publications. Whilst the study will be included only once in the review, we will extract data from all reports to ensure maximal relevant data are obtained.

Data extraction and management

We will extract the following information from each included study:

- interventions being compared, including any ineligible interventions randomised to additional trial groups;
- duration of the intervention;
- details of any co-interventions;
- the unit of randomisation (e.g. participant or ulcer);
- the number of ulcers per person;
- the unit of analysis (including any selection methods for people with multiple ulcers);
- the number of participants in each arm;
- the hazard ratio and its 95% confidence interval (or any data that will allow its calculation (Parmar 1998; Tierney 2007)) for comparisons between arms;

- the number of participants who healed in each arm, both at the latest time point and (if different) at another time specified as of primary interest in the study's methods section;
  - all other follow-up times reported;
  - we will note if a Kaplan Meier plot is displayed;
  - missing data rates per arm, and reasons for 'missingness', including the number of people dying.

Data on potential effect modifiers

We are not aware of any population-specific effect modifiers for this research question: there is no existing evidence to suggest that one type of dressing works better than another for certain subgroups, such as different baseline ulcer characteristics (e.g. size and duration of ulcer) although it may the case that some dressings are evaluated only in particular groups (e.g. those classed as having 'hard-to-heal' ulcers).

However, we will extract from each included study data that may act as effect modifiers (in this context):
  - type of funding (e.g. industry, academic, government); this will be dichotomised into not-for-profit and other;
  - risk of bias.

Other data

We will also extract the following baseline and study data, reporting separately for each intervention arm if possible:
  - care setting;
  - age of participants;
  - duration of leg ulcer(s);
  - size of venous leg ulcer(s) (area/volume);
  - nature of leg ulcer wound(s) (e.g. sloughy, necrotic, infected, 'hard-to-heal'.

Assessment of risk of bias in included studies

We will assess risk of bias for each included study, and will report separately the overall risk of bias for each direct pairwise comparison meta-analysis for complete healing data. For the network meta-analysis, we will interpret the overall risk of bias for each comparison, drawing on both indirect and direct data (see the section on Quality Assessment of Evidence (GRADE 2013), below). Two review authors will independently assess included studies using the Cochrane tool for assessing risk of bias (Higgins 2011a); a third review author will be consulted where consensus cannot be reached. This tool addresses six specific domains: sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other issues. We will then summarise data for the key biases these domains reflect - selection bias, detection bias, attrition bias, reporting bias and other bias. We will also record in the notes the comparability of participant characteristics at baseline across the two groups, including whether an adjusted analysis was conducted. We will use

these data to help inform decisions on the risk of selection bias. In terms of other bias, an issue particularly relevant to wounds is unit of analysis. We will record all issues with unit of analysis, for example, where participants are randomised but (where they have multiple wounds) all wounds have outcome data presented, or one wound is selected.

Overall risk of bias and linking to GRADE assessment

In order to link these Cochrane ratings to the GRADE assessment for risk of bias of the evidence (downgrading 0, 1 or 2 times), we will use a two-stage process. Firstly, we will obtain an all-domain risk of bias for each study and then we will use this to produce an overall risk of bias for each comparison.

All-domain risk of bias for each study

We will summarise data for each of the key domains of selection bias, detection bias, attrition bias, reporting bias and other bias, assigning one of four ratings: low, unclear, high and very high. For example, selection bias will be informed by sequence generation, allocation concealment and comparability of baseline characteristics.

In an adaption of the GRADE approach (Guyatt 2011), we will produce an all-domain risk of bias, with four ratings defined as:
  - 'very high' - two or more key domains with a high risk of bias or a single domain with very high levels of uncertainty (e.g. very high degree of differential missing data)
  - 'high' - high risk of bias for any one domain or there was judged to be 'almost high' risk of bias across more than one domain
  - 'low' - low risk of bias for each of the key domains
  - 'unclear' - insufficient information for at least one key domain (with the other domains being at low risk of bias).

We will include this all-domain risk of bias in the summary risk of bias figure, by adding additional columns to the risk of bias figure for each study. For the purposes of the GRADE assessment we will then group together studies with low and unclear all-domain risks of bias.

Overall risk of bias for a direct contrast

Where a single study contributes to a contrast the overall risk of bias will be that of the all-domain risk of bias assigned to that study. Where more than one study contributes to a contrast we will assign an overall risk of bias for the contrast by calculating a weighted average based on the inverse variance-derived weights from the meta-analysis and using this in conjunction with the overall (all-domain) risk of bias; numerical values will be assigned to the all-domain ratings for each study: low/unclear (1), high (2) and very high (3) and the weighted average calculated. We will align this with the GRADE categories of no limitations (not downgraded for

risk of bias), serious limitations (downgraded once), and very serious limitations (downgraded twice) (Guyatt 2011; Salanti 2014). We will report the overall risks of bias for these direct contrasts. Two review authors will undertake the all-domain 'Risk of bias' assessments with the involvement of a third if consensus cannot be reached; they will also both assess the overall risk of bias for each direct contrast. We will present the overall risk of bias associated with each direct estimate in a network diagram using colours to represent different ratings.

Overall risk of bias in the network

Each direct contrast in the network will contribute differently to the estimation of each NMA summary effect (each NMA comparison). The contribution will depend on a combination of the variance of the direct treatment effect and the network structure (Chaimani 2013). Contrasts with a great deal of direct information are highly influential on 'neighbouring' contrasts. Conversely, contrasts with little direct evidence (i.e. based on a single small trial) tend to have less influence on the rest of the network. The variance of the direct estimates can also affect their relative contribution to other contrasts. A recently published tool, Krahn 2013, allows the contribution of each direct estimate to be determined for each contrast in the network informed by mixed evidence (direct and indirect), or when multiple loops of indirect evidence inform the same link. The percentage contribution of each direct contrast to each network estimate will be summarised using the STATA routine *netweight* (STATA 2011). The overall risk of bias for each NMA comparison estimate is a composite measure of the risks of bias for all the direct contrasts contributing to that NMA comparison and will be determined by calculating a weighted average risk of bias using the percentage contributions and the all-domain risks of bias for all the direct contrasts.

Measures of treatment effect

Relative treatment effects

We do not anticipate being able to calculate the hazard ratio (HR) for the majority of studies. We therefore anticipate presenting the risk ratio (RR) (95% CI) for the proportion of people healed. We will present the mean value with 2.5% and 97.5% confidence intervals. In order to conduct these analyses (see Data synthesis), we will use outcome data reported in individual studies, as raw data at the latest time point, unless otherwise stated. Where there are sufficient data we will calculate HR with 95% CI and model time-to-event data.

Unit of analysis issues

We expect the main unit of analysis issues to occur when participants have more than one wound per person. We will treat the participant as the unit of analysis when the number of wounds assessed appears equal to the number of participants (e.g. one wound per person). This will include studies in which participants were randomised to treatments and there was more than one wound per person, but results were reported for one selected wound; we will consider whether there is risk of bias in the selection process. Where studies randomise at the participant level, use the allocated treatment on multiple wounds per participant, and measure and analyse outcomes at the wound level, (e.g. wound healing), there will be unit of analysis issues if the data are not correctly analysed. In these cases we will try to approximate the correct analyses if possible and appropriate, in accordance with Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using information adapted from Higgins 2011b. Where this is not possible we will make a decision about inclusion of data in the analysis, and will record these studies as being at high risk of bias if the number of participants and the mean number of wounds per person is judged to warrant this.

If cluster-randomised trials are identified, we will decide the analytical approach based on the type and volume of cluster data. We will account for the correlation between the effect sizes from multi-arm studies in the analysis.

Dealing with missing data

It is common to have data missing from trial reports. Excluding participants post-randomisation, or ignoring those participants who withdraw from the trial or are lost to follow-up, compromises the randomisation and potentially introduces bias into the trial. Where there are missing data for the primary outcome of proportion of ulcers healed, we will assume participants did not have the outcome (i.e. they will be considered in the denominator but not the numerator). We will consider examining this assumption in a sensitivity analysis.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

We will assess the presence of clinical heterogeneity within each pairwise comparison (i.e. the degree to which studies vary in terms of participant, intervention and outcome characteristics) by comparing data extracted for included studies. We will focus on key variables which are potential effect modifiers, such as whether studies were at high risk of bias in key domains and the source of funding for the study. We will also consider the generalisability of our findings with reference to participant characteristics such as ulcer size and duration.

Assessment of transitivity across treatment comparisons

'Transitivity' refers to the situation in which an intervention effect measured using an indirect comparison is valid and equivalent to the intervention effect measured using a direct comparison; where there are differences in effect modifiers across comparisons, the transitivity assumption may not be met and there will be inconsistency in the network (Grant 2013; Jansen 2013). We have not identified any potential effect modifiers from the literature, and therefore have to assume that there is transitivity with respect to known effect modifiers across the pairwise comparisons. There are also limited underlying theoretical reasons to consider effect modification for these treatments - however, in preparing the network we will explore the effect of the funding source and differences in risk of bias as possible effect modifiers across the network. We will investigate inconsistency in the network (see Data synthesis).

Assessment of reporting biases

If possible we will assess for the presence of reporting bias using a contour-enhanced funnel plot, provided there are at least 10 included studies for a comparison (Peters 2008; Salanti 2014).

Data synthesis

General methods

We will perform pairwise meta-analyses in a frequentist framework using the statistical software STATA 2011 (Salanti 2014). Experience (Westby 2015a) suggests that there are likely to be insufficient data for us to model the impact of follow-up duration on estimates of effect. We therefore plan to conduct analyses based on binary data and to analyse using the risk ratios. We will extract or calculate HRs where possible using established methods (Parmar 1998; Tierney 2007), Should there be sufficient data we will consider modelling the hazard function (Dias 2014; Soares 2014) using WINBUGS (WinBUGS 2016). We will use STATA 2011 to calculate the contributions matrix for the network and use the results of this together with the evaluation of risk of bias (see Assessment of risk of bias in included studies) to inform a GRADE evaluation for the entire network (Salanti 2014). We will summarise the findings according to GRADE principles (GRADE 2013; Schünemann 2011a; Schünemann 2011b). Where there are zero events in any trial arm we will follow the general approach taken by STATA and add 0.5 to the numerator and 1 to the denominator for each arm in the trial.

Methods for standard meta-analysis

We will perform pairwise meta-analyses in a frequentist framework using RevMan 2014 or STATA 2011 as appropriate, using inverse variance weighting and a random-effects model, and only analysing trials reporting that pairwise comparison. We will also present the data for these direct comparisons from the network in forest plots (Schünemann 2011a); for reasons of space we do not plan to present all possible comparisons. While we will report treatment effects for all data in an appendix table (or additional forest plots in an appendix) we will focus on presenting the results for all comparisons versus a reference comparator, which is likely to be basic non-adherent dressings or saline gauze. Other comparisons may be presented as appropriate.

Methods for network meta-analysis

We will use STATA to produce a network diagram based on all included studies in order to inform the analysis plan (Chaimani 2013). We will then exclude from the analysis of individual treatment, two-arm studies in which one of the interventions can be described as 'standard care' or 'mixed care'. These are treatment arms where the 'intervention' involves the choice of more than one treatment: they are unlikely to be consistently applied. However, we anticipate that such interventions may be acceptable for a grouped sensitivity analysis (see section on Sensitivity analysis). We will also exclude from the main analysis studies that have one intervention of direct interest (e.g. hydrocolloid) compared with one ineligible intervention (e.g. radiant heat), unless we find, after examining the network diagram, that the ineligible intervention links two or more interventions of direct interest.

We will perform multivariable network meta-analysis using the STATA 2011 software. We will use the 'mvmeta' command and adopt a random-effects approach and a consistency model. We will use per-arm data (see Data extraction and management) throughout. The STATA routine will take into account correlations between the effect sizes from multi-arm studies. The NMA results will be reported for 'mixed treatment contrasts', which means the meta-analysis involves both direct evidence and indirect evidence from across the whole network. The output will be reported as pooled RRs, with their 95% CIs. If there are sufficient data we will also perform an analysis of time-to-event data using the log HR with standard error (SE).

We will undertake analyses for network comparisons (where indirect evidence or both direct and indirect evidence contributes) in a frequentist framework as above. Where required, we will account for correlations induced by multi-arm studies. We will also present the data in forest plots.

We will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks (Salanti 2011) for each treatment. Both these measures are based on an assessment of the probability of each treatment being best, second best, etc. in terms of being the most likely to heal venous leg ulcers (when compared with all other evaluated treatments). We will use the STATA methods described by Chaimani 2013.

We plan to present two networks: one for individual treatments and one in which interventions are grouped in broader categories,

with clinical guidance; this latter network will include comparisons with standard care as described above. We plan to use the following pre-specified categories: no dressing, basic wound dressings, advanced dressings and antimicrobial dressings (as described in the BNF 2016); we will keep the different types of specialist dressings (e.g. protease-modulating matrix dressings) and the different topical agents as separate categories.

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

We will assess statistically the presence of heterogeneity within each pairwise comparison using the I² statistic that measures the percentage of variability that cannot be attributed to random error (Higgins 2003). We will also take into account the overlap of confidence intervals and the variability in the point estimates. We will regard effect estimates where I² is less than 50% as having low levels of heterogeneity, given the potential for wide confidence intervals in pairwise comparisons within a network, which we anticipate may be sparse.

Assessment of statistical inconsistency

We will assess inconsistency in two main ways: determining local inconsistencies (around particular contrasts in the network) and assessing inconsistency for the network as a whole. These tests are often underpowered so we will carry out the assessment using the 90% significance level.

Contributions of direct evidence in the network

The contribution of a particular direct estimate to each of the pairwise estimates in a network of evidence, and to the network as a whole, depends on the statistical precision of the direct estimate and its relative position in the network. A recently published tool, Krahn 2013, allows the contribution of each direct estimate to be determined for each link in a network informed by mixed evidence (direct and indirect), or when multiple loops of indirect evidence inform the same link. Where possible we will apply these methods to the evidence loops in our network, and will use this information to help assess inconsistency in the network and to inform considerations of risk of bias. We acknowledge that this approach returns approximate weights.

Local approaches to evaluating inconsistency

To evaluate the presence of inconsistency locally we may use two main approaches. Firstly we will consider a loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct

and indirect estimates for a specific comparison in the loop (inconsistency factor, IF). Then, the magnitude of the inconsistency factors and their 90% CIs can be used to make inferences about the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using the 'ifplot' command in STATA 2011.

Secondly, we will consider a "node splitting" approach (Dias 2010; Salanti 2014). This method will be applied, singly, to each direct contrast (called a "node" by Dias 2010). A STATA 2011 routine will be used to calculate an indirect estimate using the rest of the network, by running the NMA after excluding the direct evidence for that contrast. The indirect estimates will then be compared with the respective direct estimates.

For both approaches a ratio of risk ratios with its 90% CI is calculated for each contrast. If the CI excludes 1, statistically there is significant inconsistency. We will also consider whether the CI includes 2 or more (or 0.5 or less). This would mean that the direct estimate could be twice as large (or half as big) as the indirect estimate, which is an indication of potential inconsistency (Chaimani 2013).

Global approaches to evaluating inconsistency

We will evaluate consistency in the entire network simultaneously, by extending the analysis to include an inconsistency model that omits consistency equations (Dias 2013). This uses a design-by-treatment interaction model, which allows for different trial designs (Higgins 2012; White 2012). This approach will produce a set of inconsistency parameters. After fitting the inconsistency model we will test the null hypothesis of consistency by globally testing the set of inconsistency parameters using a global Wald test. This test may lack power and we will consider a significance level of P < 0.1.

Investigation of heterogeneity and inconsistency

If sufficient studies are available, we will perform network meta-regression (data permitting) or subgroup analyses using funding source and risk of bias as possible sources of inconsistency or heterogeneity, or both.

Sensitivity analysis

If possible, we will re-analyse the network with studies removed if they are considered to be at high risk of bias for any one or more of selection, attrition or detection bias (Appendix 3).

We will consider a sensitivity analysis to assess the possible impact of missing outcome data on the network estimates, via assessment of risk of attrition bias (as defined in Appendix 3), testing the assumption of imputation of no event for missing data.

Where one or more studies are clearly outliers (i.e. in terms of direction or size of relative treatment effect, both, or as flagged in

inconsistency testing) we will conduct a sensitivity analysis where the study is removed from the network, as long as the network is still analysable.

Quality assessment of evidence (GRADE) generated from the network meta-analysis

We will summarise the findings according to GRADE principles (Schünemann 2011a; Schünemann 2011b). The quality and certainty of the data included in any synthesis model is key to determining the validity of the results and of inferences made. We will explore the application of GRADE methodology to network meta-analysis, focusing on the approach of Salanti 2014. We will assess evidence quality in two main ways, firstly, for each contrast and secondly, for the network as a whole, in order to assess the quality of the ranking order. We will assess individual GRADE factors as follows:

• Risk of bias: contributions for each particular contrast will be considered, and used to assess the overall risk of bias for that contrast. We will assess overall risk of bias per contrast and also for the network as a whole (see Assessment of risk of bias in included studies).

• Indirectness: this is likely to be assessed as without limitations because we have not identified any effect modifiers.

• Inconsistency: at the level of the contrast, we will take into consideration both heterogeneity in the direct evidence for that comparison and inconsistency related to different routes of analysis for the comparison (e.g. direct versus indirect evidence and two-arm versus three-arm trials). The latter will be conducted using a node splitting approach (Dias 2013). As well as assessing the meta-analyses of the direct evidence for inconsistency, we will consider the NMA predictive intervals for that comparison in relation to GRADE 'default' minimum important differences (0.75 and 1.25) (Guyatt 2011). We note that inconsistency can only be assessed where there is both direct and indirect evidence. GRADE inconsistency will be assessed as serious limitations if there is heterogeneity in the direct estimate or inconsistency in the network with respect to that comparison. Very serious limitations will be attributed to the comparison if there is severe heterogeneity or severe inconsistency or limitations with both heterogeneity and inconsistency. We cannot at this stage pre specify exact thresholds for determination of severe limitations for this domain, as we will consider both methodological and statistical factors and we anticipate a sparse network; we intend to use reviewer judgements and discussion to reach consensus. Rationales will be described transparently in the review report. At the level of the network, we will consider the global Wald test for inconsistency (see Data synthesis; Assessment of heterogeneity). Tests of this nature are typically underpowered, so a P value less than 0.1 will be considered significant. Additionally, if several contrasts show direct and indirect results that would have led to different clinical decisions, we will consider inconsistency to be present.

• Imprecision: at the level of the contrast, we will assess inconsistency for each pairwise comparison using the GRADE default minimally important difference values of 1.25 and 0.75 for the RR. We will also take into account the sample size for the direct evidence informing this contrast and consider it in relation to the optimal information size. At the level of the network we will assess the overlap of the rankograms and the magnitude of the SUCRA estimates.

• Publication bias: will also be assessed for each pairwise comparison using standard GRADE; we will use contour-enhanced funnel plots where appropriate (where there are 10 or more studies). We will use the contributions matrix to translate these judgements to the network as a whole.

'Summary of Findings' tables

We plan to present the main results of the review in 'Summary of findings' tables, reporting the results for a representative set of contrasts, with one row for each intervention versus the reference comparator, which is likely to be basic non-adherent dressings or saline gauze, for both the individual and grouped interventions networks. These tables will present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data (Schünemann 2011a). 'Summary of findings' tables also include an overall grading of the evidence using the GRADE approach. For calculating absolute risk differences for the probability of healing we plan to use a 'control group risk', calculated as the median of the risks for the reference comparator across all studies with these interventions.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary of NMA terms

Arm-specific outcomes/arm-level data: raw outcome data (e.g. mean (SD) or risk) for each arm of the trial (see also **treatment contrast**).

Assumptions for NMA: in common with all meta-analysis, the true treatment effect across trials is assumed to be described by a **fixed-effect** or **random-effects** model. Additionally, **transitivity** is assumed and, concurrently, **exchangeability** and **consistency**.

Baseline risk: the absolute risk of the outcome in the 'control' group. This is affected by the presence of **prognostic factors**. Some authors have used the baseline risk as a proxy **effect modifier**, but in general the effect estimate (RR/OR/HR) is independent of the baseline risk; on the other hand, the absolute risk difference depends on baseline risk.

Bayesian approach: the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation of a health-care evaluation. In the Bayesian paradigm, **prior** beliefs about parameters in the models are specified and factored into the estimation. **Posterior distributions** of model parameters are then derived from the prior information and the observed data. In NMA, it is common to use **non-informative priors** for effect estimates.

Coherence/consistency: the direct effect estimate (e.g. mean difference or log odds ratio) is the same as the sum of the indirect effect estimates.

Connected network: a group of linked interventions, such that every trial in the network has at least one intervention in common with at least one other trial. Sometimes individual comparisons are not connected to the rest of the network (disconnected network) and can sometimes be joined in by extending the network to include **supplementary** interventions.

Contour-enhanced funnel plot: contour-enhanced funnel plots show areas of statistical significance, and they can help in distinguishing publication bias from other possible reasons for asymmetry. In a network of interventions, each study estimates the relative effect of *different* interventions, so asymmetry in the funnel plot cannot be judged. To account for this, an adaptation of the funnel plot can be used, in which the standard error is plotted against an adjusted effect size for each study: the adjusted effect size for a comparison is the study-specific effect size minus the mean for the meta-analysis for that comparison.

Contrast/study-level data: outcome data for the comparison (e.g. mean difference, odds ratio).

Decision space/decision set: the interventions in the decision set are the focal treatments of interest to systematic review authors.

Deviance Information Criterion (DIC): the DIC is a measure of the balance between model fit (the posterior mean deviance) and model complexity (the **leverage**) and calculated as the sum of these two; the smaller the DIC, the better the model. DIC is often used to compare models, for example, comparing fixed-effect and random-effects models. If there is an important difference in DIC between models, there is evidence of heterogeneity.

Direct evidence/direct comparison: head-to-head comparison of two treatments, for example, A versus B (see also **indirect evidence**).

Edge: line representing a direct comparison on a **network diagram**.

Effect modifier: effect modification occurs when the effect of A versus B (as the RR/OR/HR for binary outcomes) is significantly different in two or more subgroups, and this leads to **heterogeneity**, either within trials or between trials, or both. Factors that give rise to subgroup effects are called effect modifiers, and it is important to identify potential effect modifiers and allow for them in the analysis. The identification of significant effect modifiers may lead to stratification (separate analyses for each subgroup) or to a decision not to combine data from different trials in a meta-analysis. In general, trials have different distributions of effect modifiers (e.g. proportion of people with and without diabetes), leading to **inconsistency** between trials in the treatment effect. This is often magnified when there is a network of different comparisons.

Exchangeability: it is assumed that treatments in a NMA are exchangeable, so, if treatment B had been given to patients in the indirect A versus C trials and if A had been given in the B versus C indirect trials, then the true AB differences in these indirect studies would be identical to the true AB difference in direct A versus B trials, or at least from the same common distribution. Furthermore, if patients in other trials within the wider linked network (e.g. D versus E trials) were given A and B, the AB differences would also be the same or from the same distribution. This assumption breaks down when there are **effect modifiers**.

Fixed-effect: the true treatment effect is assumed to be constant across trials (fixed-effect) - see also **random-effects** and **transitivity**.

Global inconsistency: inconsistency across a network is described as global inconsistency. It can be evaluated statistically by fitting models that allow and do not allow for inconsistency. A 'leave-one comparison-out' approach, often called 'node splitting,' can also be applied, with each direct comparison being excluded from the network and then estimating the difference between this direct evidence and the indirect evidence from the network.

Heterogeneity in a NMA: patients are not randomised to different trials. Therefore, there may be systematic differences in study characteristics or the distribution of patient characteristics across trials. If these characteristics influence the treatment effects (i.e. are **effect modifiers**), then there are systematic differences in treatment effects across trials, which is called between-trial heterogeneity. There may also be within-trial heterogeneity if there are subgroups of an effect modifier for which results are reported separately. In a NMA, the term, '**heterogeneity**' applies to variation in effect modifiers *within* a single comparison (e.g. A versus B); the term, '**inconsistency**' refers to the imbalance in effect modifiers *between* comparisons.

Heterogeneity variance parameter (τ^2): in a **random-effects** model we assume there is heterogeneity for each pairwise comparison (e.g. A versus B) with variance (τ^2_{AB}), but in a NMA we often assume that there is a common heterogeneity amongst all the comparisons in the network; this common heterogeneity has a variance (τ^2), which is called the 'heterogeneity variance parameter'. It can be compared with empirical distributions of heterogeneity values typically found in meta-analyses (Salanti 2014; Turner 2012).

Inconsistency/incoherence: this occurs when the effect estimate derived from an indirect comparison is not the same as the effect estimate derived from a direct comparison. For example, in a network of three interventions, there is inconsistency if d_{AB}(direct) $\neq$ d_{AB}(indirect), where d_{AB}(indirect) = d_{AC}(direct) - d_{BC}(direct); the effect estimates are given as mean differences or log (odds ratios/ risk ratios/hazard ratios). Note that in order to investigate inconsistency there must be both indirect and direct evidence (loops in the network). See also **global inconsistency**.

Inconsistency factor: this is the absolute difference between the direct and indirect estimates on the log scale (or the logarithm of the ratio of the two odds/hazard ratios) for one of the comparisons in a **loop**. A statistically low-powered z-test and a 95% CI of the inconsistency is computed to determine whether this difference is significant.

Indirect evidence/indirect comparison: comparison of two treatments, for example, A versus B, obtained from combinations of other comparisons (e.g. trials comparing A versus C and trials comparing B with C) (see also **direct evidence**).

Indirect comparison meta-analysis: meta-analysis of a set of treatments that are linked via common comparator(s), but none are compared directly; evidence is combined in a single internally consistent model.

Leverage: this is the effective number of parameters of the model, which is calculated differently for fixed-effect and random-effects models, with the latter having greater complexity.

Likelihood (function): the likelihood function is a tool for inferring the underlying distribution of the observed data. To do this, we propose a **model** to represent the data - often a parametric distribution is assumed (e.g. binomial) - and unknown parameters of that distribution are determined, given the data, by maximising the likelihood (the larger the likelihood, the closer the model fit).

Loop (of evidence): combination of direct and indirect evidence, such that the interventions in the network diagram can be linked to form a closed loop.

Meta-analysis: a statistical synthesis of the results from two or more separate studies. Methods involve calculating a weighted average of effect estimates from the separate studies.

Mixed treatment comparison meta-analysis: another name for **network meta-analysis**.

Model: a statistical model is a (simplified) mathematical representation of the system we wish to learn about, and which generates our observed data. The model will usually depend on some known factors, such as other variables measured alongside the data, and some unknown parameters that we wish to determine. Then having determined the unknown parameters, the model should be able to simulate data that are an approximation of the real data, allowing us to make inferences from the data.

Multi-arm trial: individual trial that compares more than two interventions. It is important to take into account correlations within these trials in the analysis.

Network: trials must be linked in a network of interventions, such that every trial in the network has at least one intervention in common with at least one other trial.

Network diagram: graphical representation of the interventions in the network. It consists of **nodes** representing the interventions and **edges** representing the comparisons. The amount of available information can be presented by 'weighting' the nodes and edges using different node sizes and line thicknesses according to the number of studies reporting that treatment or comparison respectively. Other types of weighting are discussed in Chaimani 2013.

Network meta-analysis (NMA): NMA is the simultaneous combination of data from randomised comparisons of multiple competing treatments (A versus B, A versus C, A versus D, B versus D, and so on), to deliver an internally consistent set of estimates while respecting the randomisation in the evidence. The use of indirect estimates can provide information on comparisons for which no trials exist. It can also improve the precision of the direct estimate by reducing the width of the CIs compared with the direct evidence alone.

Node: intervention represented on a network diagram, usually by a circle of weighted size.

Pairwise meta-analysis: meta-analysis of one or more trials of direct comparisons (e.g. A versus B) - see **direct evidence**.

Prognostic factors: population or study characteristics that affect the risk of the outcome. In a sufficiently large randomised trial that is free from bias, prognostic factors are distributed evenly between intervention groups and do not affect the effect estimate (RR/OR/HR for binary outcomes) unless they are **effect modifiers**, but they do affect the **baseline risk** and absolute risk difference.

Random-effects: trial-specific treatment differences are assumed to be from a common distribution - see also **fixed-effect** and **transitivity**.

Ranking: ordering of treatments according to their relative effectiveness.

Sparse data: data with wide confidence intervals because of few events as a consequence of small studies or short follow-up periods.

Study-level data: see **contrast**.

SUCRA: Surface Under the Cumulative RAnking. This is a measure of the probability that the given treatment is the best. Thus, a SUCRA would be 1 (or 100%) when a treatment was certain to be the best and 0 (0%) when a treatment was certain to be the worst.

Supplementary set (of interventions): interventions added to the network to provide additional evidence on relative treatment effects of the **decision set**. This may be to connect an otherwise unconnected network of treatments, to increase the precision of the treatment effect estimates or to help address between-trial heterogeneity.

Transitivity: NMA requires a transitivity assumption, such that there is no imbalance in the distribution of **effect modifiers** across the different types of treatment comparisons (see also **exchangeability**).

'Unadjusted' meta-analysis: meta-analysis of all the treatment arms for a particular treatment (e.g. all A arms). This breaks the randomisation and should not be done.

References include: Caldwell 2005; Caldwell 2014; Chaimani 2013; Cipriani 2013; Dias 2013; Dias 2014; Grant 2013; Jansen 2013; Lu 2004; Salanti 2008; Salanti 2011; Salanti 2014; Soares 2014; Spiegelhalter 2003; Thorlund 2012; Tu 2012; WinBUGS 2016.

Appendix 2. Draft search strategy for CENTRAL

#1 MeSH descriptor: [Bandages] explode all trees

#2 MeSH descriptor: [Alginates] explode all trees

#3 MeSH descriptor: [Hydrogels] explode all trees

#4 MeSH descriptor: [Honey] explode all trees

#5 MeSH descriptor: [Silver] explode all trees

#6 MeSH descriptor: [Silver Sulfadiazine] explode all trees

#7 MeSH descriptor: [Charcoal] explode all trees

#8 MeSH descriptor: [Silicones] explode all trees

#9 MeSH descriptor: [Colloids] explode all trees

#10 MeSH descriptor: [Polyurethanes] explode all trees

#11 (dressing* or pad or pads or gauze or tulle or film or bead or foam* or non-adherent or "non adherent" or hydrocolloid* or "sodium hyaluronate" or alginat* or hydrogel* or silver* or honey* or matrix or iodine* or "protease modulat*" or "capillary action" or charcoal or silicon* or polymer* or polyurethane* or hydrocellular or hydropolymer* or carboxymethylcellulose or carboxymethyl-cellulose or gelatin* or NaCMC or "gel forming" or gel-forming):ti,ab,kw

#12 ((odour or odor) near/3 absorb*):ti,ab,kw

#13 (primapore or curasorb or seasorb or sorbsan or advadraw or vacutex or tegaderm or opsite or allevyn or biatain or medihoney or activon tulle or granuflex or "nu derm" or aquacel or iodoflex or iodozyme or xeroform or carboflex or cutimed or sorbact or promogran or acticoat or "urgosorb silver" or mepitel or urgotul or activheal or alione or askina or comfeel or duoderm or flexigran or hydrocoll or nu-derm or "ultec pro" or mepilex or versiva or urgoclean or cutinova or tegasorb or dermafilm or replicare or signadress or algoplaque or varihesive or advasorb or copa or lyofoam or permafoam or polymem or suprasorb or transorbent or trufoam or urgocell or kendall or kerraboot or cavi-care):ti,ab,kw

#14 {or #1-#13}

#15 MeSH descriptor: [Metronidazole] explode all trees

#16 metronidazole:ti,ab,kw

#17 MeSH descriptor: [Anti-Bacterial Agents] explode all trees

#18 MeSH descriptor: [Administration, Topical] explode all trees

#19 {and #17-#18}

#20 (topical near/2 (antibiotic* or antimicrobial* or antibacterial*)):ti,ab,kw

#21 MeSH descriptor: [Iodophors] explode all trees

#22 {and #18, #21}

#23 ((topical near/2 iodin*) or ("cadexomer iodine")):ti,ab,kw

#24 MeSH descriptor: [Collagenases] explode all trees

#25 {and #18, #24}

#26 (topical near/2 collagen*):ti,ab,kw

#27 MeSH descriptor: [Phenytoin] explode all trees

#28 {and #18, #27}

#29 (topical near/2 phenytoin):ti,ab,kw

#30 MeSH descriptor: [Zinc Oxide] explode all trees

#31 {and #18, #30}

#32 (topical near/2 zinc):ti,ab,kw

#33 (iodosorb or actiformcool or aquaflo or flamazine or silvadene):ti,ab,kw

#34 MeSH descriptor: [Ointments] explode all trees

#35 (ointment* or lotion* or cream* or powder* or gel or gels):ti,ab,kw

#36 (topical next (agent* or preparation* or therap* or treatment*)):ti,ab,kw

#37 {or #15-#16, #19-#20, #22-#23, #25-#26, #28-#29, #31-#36}

#38 {or #14, #37}

#39 MeSH descriptor: [Leg Ulcer] this term only

#40 MeSH descriptor: [Varicose Ulcer] explode all trees

#41 (varicose next ulcer* or venous next ulcer* or leg next ulcer* or stasis next ulcer* or crural next ulcer* or ulcus next cruris or ulcer next cruris):ti,ab,kw

#42 {or #39-#41}

#43{and #38, #42}

Appendix 3. Assessing risk of bias

1. Was the allocation sequence randomly generated? (Part of 'Selection bias')

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random-number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process provided to permit a judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed? (Part of 'Selection bias')

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study? (Performance bias for blinding of participants and caregivers; detection bias for outcome assessors)

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Either participants or some key study personnel were not blinded, and the non-blinding was likely to introduce bias.

Unclear

Either of the following.

- Insufficient information provided to permit a judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed? (Attrition bias)

Low risk of bias

Any one of the following.

- No missing outcome data.

- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
  - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
  - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.
  - For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size.
  - Missing data have been imputed using appropriate methods.

High risk of bias
Any one of the following.
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was enough to induce clinically relevant bias in observed effect size.
  - 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
  - Potentially inappropriate application of simple imputation.

Unclear
Either of the following.
- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
  - The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting? (Outcome reporting bias)
Low risk of bias
Either of the following.
- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias
Any one of the following.
- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes of the study were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear
Insufficient information provided to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias
Low risk of bias
The study appears to be free of other sources of bias.
High risk of bias
There is at least one important additional risk of bias. For example, the study:
- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Gill Norman: developed the protocol; coordinated the protocol development; produced the first draft of the protocol; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; approved the final version of the protocol prior to submission; and is a guarantor of the protocol.

Jo Dumville: conceived the review question; developed the protocol; secured funding; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; approved the final version of the protocol prior to submission; and is a guarantor of the protocol.

Maggie Westby: developed the protocol; contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Nicki Stubbs: contributed to writing or editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Marta Soares: contributed to writing or editing the protocol; made an intellectual contribution to the protocol; and advised on the protocol.

Contributions of editorial base

Nicky Cullum (Co-ordinating Editor): edited the protocol; advised on methodology, interpretation and content; approved the final review prior to submission.
Gill Rizzello (Managing Editor): co-ordinated the editorial process, advised on content; edited the protocol.
Reetu Child and Naomi Shaw: (Information Specialists) designed the search strategy and edited the search methods section.
Ursula Gonthier (Editorial Assistant): edited the references.

DECLARATIONS OF INTEREST

Gill Norman: my employment at the University of Manchester is funded by NIHR and focuses on high priority Cochrane reviews in the prevention and treatment of wounds.

Jo Dumville: I receive research funding from the NIHR for the production of systematic reviews focusing on high priority Cochrane reviews in the prevention and treatment of wounds.

Maggie Westby: my employment at the University of Manchester is funded by NIHR and focuses on high priority Cochrane reviews in the prevention and treatment of wounds.

Nikki Stubbs: funding from pharmaceutical companies supports training and education events in the service and payments have been received by the author for non product related educational sessions. These have been unrelated to the subject matter of the systematic review and have never been in support or in pursuit of the promotion of products.

Marta Soares: none known.

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