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System-wide assessment of wound care interventions: A scoping review

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For:

The Wound Care Steering Committee
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Executive Summary

What are effective interventions for wound care across the healthcare system?

- Numerous interventions are available for patients, healthcare providers, and health policy-makers to choose from for treating patients with wounds.
- Optimal wound care management for patients with wounds is unclear.

How was the study conducted?

- Rigorous scoping review methods were used.
- Included studies were systematic reviews and economic analyses.
- All studies had to include adults who experienced a wound and report at least one of the following outcomes: healing, admission to hospital, resources, cost or cost-effectiveness. All interventions and comparators were included.
- The included studies were appraised to assess their methodological quality.

What did the study find?

Based on evidence from the highest quality systematic reviews for which a meta-analysis was conducted, the following interventions are likely effective:

Wound type	Effective intervention versus comparator
Venous/arterial leg ulcers	High compression stockings versus compression bandage
	Elastic bandage versus inelastic bandage
	Cadexomer iodine plus compression therapy versus usual care plus compression therapy
	Multi-layer high compression versus single-layer compression
	Pentoxifylline with or without compression versus placebo or all other treatments
	2-layer stocking versus short-stretch bandage
	Elastic high compression versus multi-layer inelastic compression
	Tissue engineered skin versus dressings

Wound type	Effective intervention versus comparator
	4-layer bandage versus short-stretch bandage or versus multi-layer short-stretch bandage
	Cadexomer iodine versus usual care
Pressure ulcers	Hydrocolloid versus usual care
	Air-fluidized beds versus usual care
	Alternative foam mattress versus standard foam mattress
	Electrotherapy versus sham therapy
	Nutritional support versus usual care
Diabetic ulcers	Artificial skin graft with usual care versus usual care alone
	Hydrogel dressing versus basic wound dressing
	Hydrogel versus gauze with usual care
	Hyaluronic acid derivatives versus usual care
	Low-frequency low-intensity noncontact ultrasound versus sharp debridement
	Low-frequency high-intensity contact ultrasound versus sharp debridement
	Granulocyte-colony stimulating factor versus control (unspecified)
Mixed chronic wounds	Apligraf skin graft versus usual care
	Dermagraft skin graft versus usual care
	Any artificial skin graft plus standard wound care versus usual care
	Silver dressings versus non-silver dressings
Burns	Honey versus silver sulfadizine or conventional dressings

Based on evidence from the highest quality cost-effectiveness/cost-utility analyses, the following interventions are likely cost-effective:

Wound type	Cost-effective intervention versus comparator
Venous ulcers	Pentoxifylline plus usual care versus standard compression with external treatment
	4-layer high compression bandages versus standard compression with external treatment
	4-layer high compression bandages versus short-stretch high compression

Wound type	Cost-effective intervention versus comparator
	bandages
Pressure ulcers	Multi-disciplinary community wound care teams versus usual nursing care
Diabetic ulcers	Hyperbaric oxygen therapy plus standard care versus standard care alone
	Becaplermin gel containing recombinant human platelet derived growth factor plus standard care versus usual wound care alone
Diabetic foot infections	Ertapenem versus piperacillin/tazobactam

What are the next steps?

- TC LHIN's Wound Care Steering Committee may wish to use the above findings to map what is currently being practiced within the LHIN to ensure evidence-based and effective practices are in place,
- TC LHIN's Wound Care Steering Committee may wish to conduct a Delphi process with committee members and wound care content experts to determine the area of focus for the LHIN's Wound Care Program,
- TC LHIN may wish to fund a network meta-analysis, which is a statistical technique that can be used to rank all of the treatment options available, and
- The *breakthrough* team will prepare two manuscripts for publication based on the work of this report.

Introduction

There are many different types of wounds, which can be broadly classified as acute and chronic wounds [1-3]. Acute wounds can be defined as wounds that heal in "an orderly and timely reparative process", while chronic wounds are those that have not progressed through the ordered process of healing to yield a functional result [3]. The main types of acute wounds include burns, lacerations, surgical wounds, and traumatic wounds [1-3]. In contrast, the main types of chronic wounds include wounds due to chronic disease (e.g., venous ulcers, arterial ulcers, and diabetic ulcers), pressure ulcers, and infected surgical wounds [1-3].

Burns are the most common type of acute wound, with over two million people experiencing a burn each year and 80,000 people hospitalized as a result of a burn per year in the United States alone [4]. The main types of burns include superficial (or a first-degree burn), partial thickness (or a second-degree burn), and full-thickness (or a third-degree burn) [5]. Post-surgical incisions are another form of an acute wound, which often heal in a timely manner [6]. Deep tissue wounds, such as complicated sternal wounds for cardiac surgery patients, can develop in 1-5% of patients, and often result in an increased length of hospital stay [7].

It has been estimated that chronic wounds cost the healthcare system $10 billion annually in North America alone [8]. These estimates often don't capture indirect costs, including the frustration, economic loss, and decreased quality of life experienced by those suffering from chronic wounds. Surgical wounds that become infected are a form of chronic wound [9]. Individuals with chronic conditions, such as diabetes and spinal cord injuries (SCI), immunosuppressed individuals (e.g., patients with cancer or HIV), and older adults often suffer from impaired wound healing for a variety of reasons [3, 8]. These populations are typically at

risk for a chronic wound, as they have a decreased ability to heal appropriately and the potential to be exposed to circumstances where chronic wounds can develop. An example is pressure ulcer development in the SCI population.

Pressure ulcers are a significant burden to the healthcare system. It has been estimated that pressure ulcers consume 4% of the annual National Health Service expenditure (or £1.4–£2.1 billion per year) in the United Kingdom alone [10]. In Canada, the prevalence of pressure ulcers is between 24-26% in acute care hospitals, 28-31% in non-acute care facilities (including long-term care and nursing homes), 21-23% in mixed settings (acute and non-acute care), and 13-17% in community care settings [11].

Numerous interventions are available to treat acute and chronic wounds. Just as the management of spine pain has been compared to a "supermarket" [12], the treatment of wounds can also be described as such and decision-makers, such as patients, clinicians, and policy-makers are forced to choose from a plethora of treatments. Furthermore, a multi-faceted approach to wound care is often employed, so several interventions may be used concurrently. These include wound cleansing (e.g., irrigation, providone-iodine), dressings (e.g., paraffin gauze, honey, silver-impregnated, hydrocolloid, radiant heat dressing, semelil gel, soft silicone), skin replacement therapy (e.g., apligraf, dermagraft, graft jacket, orcel, promogran, hyalograft, laser skin), stockings (e.g., compression socks), Chinese herbal medicine, nutritional supplementation (e.g., vitamin C, collagen protein, zinc sulfate), support surfaces and off-loading devices (e.g., foam mattress, water mattress, low air loss mattress, alternating pressure mattress), biologic agents (e.g., protease-modulating matrix, fibroblast-derived dermal replacement, recombinant platelet-derived growth factor), adjuvant therapies (e.g., topical negative pressure, closed-assisted vacuum therapy, electric current, hyperbaric oxygen therapy, ultrasound, electromagnetic

therapy, laser, light, hydrotherapy), and wound care programs (e.g., case management, patient education, multidisciplinary teams). Some of these interventions have been further elaborated upon in Appendix 1. As the evidence of these interventions is recondite across the literature, we were approached by the Toronto Central Local Health Integrated Network (TC LHIN) to conduct a scoping review to identify optimal and cost-effective treatment of wounds from high quality systematic reviews and economic analyses.

Objectives

1) To conduct a systematic search to identify effective interventions for wound care across the healthcare system.

2) To characterize this literature regarding study characteristics (e.g., costing study/systematic review, number of studies identified, type of study designs included, methodological quality), patient characteristics (e.g., clinical population, mean age), wound care interventions examined, and outcomes examined.

Methods

Our scoping review was conducted using methodologically rigorous methods proposed by previous researchers, Arksey and O'Malley [13]. The overall approach that we use to conduct scoping reviews at *breakthrough* is presented in Appendix 2. A scoping review proposal was submitted to the TC LHIN on September 13, 2012. Feedback was received by the TC LHIN and the proposal was revised, as necessary.

Search Strategy

Comprehensive literature searches were conducted in the following electronic databases from inception onwards: MEDLINE (OVID interface, 1950 until October 26, 2012), EMBASE (OVID interface, 1980 until October 26, 2012), and the Cochrane Library (Issue 10 of 12, 2012). The search terms included both medical sub-headings (MeSH) and free text terms related to wound care interventions. The literature searches were conducted by an experienced librarian (Laure Perrier, Librarian for the University of Toronto, Faculty of Medicine's Continuing Education and Professional Development) on October 26, 2012.The full search strategy for the MEDLINE database is presented in Appendix 3. The search strategy was limited to adults, systematic reviews, and economic studies, using validated search filters.

The search strategy was peer reviewed by another expert librarian on our team (Elise Cogo) using the Peer Review of Electronic Search Strategies (PRESS) checklist [14]. After this exercise, the search strategy was amended, as necessary. The literature search results were exported into RefWorks and then Excel to remove all duplicates from the search results across the three databases. The results were subsequently uploaded to our SysRev Tool, proprietary systematic review software developed by *breaKThrough* team members [15].

Inclusion criteria

The inclusion criteria were framed using the PICOST criteria [16], as follows:

Patients: Adults aged 18 years and older experiencing acute and chronic wounds. Acute wounds included burns, lacerations, surgical wounds, and traumatic wounds, while chronic wounds included those due to chronic disease (e.g., venous ulcers, arterial ulcers, and diabetic ulcers), pressure ulcers, and infected surgical wounds.

Interventions: All wound care interventions were included. Examples include pharmacological agents (e.g., topical agents), non-pharmacological agents (e.g., dressings, vacuum, hyperbaric therapy), and wound care programs.

Comparators: All comparators, such as other wound care interventions; no treatment, placebo, and usual care were eligible for inclusion.

Outcomes: Healing, cost/cost-effectiveness, admission to hospital (including readmissions), and human resources.

Study designs: As the literature-base on wound care is extensive, we focused our review on systematic reviews and economic studies.

Time frame: We did not limit inclusion to year of publication.

Study Selection: Screening

Prior to commencing the screening process, a calibration exercise was conducted to ensure reliability in correctly selecting articles for inclusion. This exercise entailed screening a random sample of 50 of the included titles and abstracts by all team members, independently. The

eligibility criteria were modified, as necessary to optimize clarity. Subsequently, two reviewers independently screened the remainder of the search results for inclusion using a pre-defined relevance criteria form for all levels of screening (e.g., title and abstract, full-text review of potentially relevant articles) in our SysRev Tool. Discrepancies were resolved by discussion or the involvement of a third reviewer. The final screening criteria can be found in Appendix 4 for screening titles and abstracts and Appendix 5 for screening full-text articles.

Data Abstraction:

Data abstraction forms were drafted and pilot-tested by all team members independently on a random sample of 5 articles. The data abstraction forms were revised after this exercise, as necessary. Subsequently, two investigators independently read each article and abstracted the relevant data. Differences in abstraction were resolved by discussion or the involvement of a third reviewer. Separate forms were used for abstracting data from systematic reviews and economic studies.

For systematic reviews, data items included study characteristics (e.g., number of studies identified, type of study designs included, methodological quality, wound interventions examined, comparators), patient characteristics (e.g., clinical population, mean age), and outcome results. The methodological quality of systematic reviews was appraised using the Assessment of Multiple SysTemAtic Reviews (AMSTAR tool), which gives an overall score out of 11 [17]. A score of 8/11 was considered to be a "high quality" systematic review. Data from all systematic reviews that conducted a meta-analysis of the outcomes of interest were abstracted. However, the results of systematic reviews for which a meta-analysis was not conducted were not abstracted if they were assessed as low methodological quality (AMSTAR <8). The final data abstraction form for systematic reviews can be found in Appendix 6.

For economic studies, data items included study characteristics (e.g., type of economic evaluation, horizon, interventions examined, comparators), patient characteristics (e.g., clinical population, cohort used for the economic evaluation), and cost results. Further data abstraction was conducted for cost-utility analyses (CUAs) or cost-effectiveness analyses (CEAs), as these are considered the gold standard of economic evaluations. For example, we abstracted incremental cost effectiveness ratios (ICERs), quality adjusted life years (QALYs), cost per wound healed, and cost per life year from CUAs and CEAs. The methodological quality of CUAs and CEAs was appraised using a 10-item tool developed by Drummond and colleagues [18]. The final data abstraction form for economic studies can be found in Appendix 7.

Synthesis

The literature search results, as well as all of the abstracted data, were summarized descriptively. An in-depth comparison of the literature-base was compiled and depicted in tables. We also identified interventions that might be the most effective and cost-effective for patients experiencing wounds, as well as gaps in the literature to target future research initiatives.

Results

Literature search

The flow of titles and abstracts and full-text articles is presented in Figure 1. As displayed, the literature search resulted in 6,199 titles and abstracts, which were screened in duplicate. Of these, 421 potentially relevant full-text articles were obtained and screened in duplicate. Reasons for exclusion of articles at the full-text level of screening included that it wasn't a systematic review or economic study (n=77), did not describe an intervention to treat wounds (n=35), wasn't written in English (n=25), did not include adults with wounds (n=22), did not examine an outcome of interest (n=14), was a trial protocol or conference abstract (n=10) or was unable to be located (n=6). There were 232 included studies; 110 systematic reviews (comprising 53 systematic reviews without a meta-analysis and 57 systematic reviews with a meta-analysis) plus 15 companion reports and 104 economic studies (comprising 35 CEAs/CUAs and 69 costing studies) plus three companion reports. The references of the included studies can be found in Appendix 8.

Results from included systematic reviews

Systematic reviews –study characteristics

The characteristics of the 110 included systematic reviews are presented in Table 1. The earliest systematic review was published in 1997 and the most recent was published in 2012. The majority of the reviews were published between 2006 and 2010 (46.4%). Most of the systematic reviews were published by authors located in Europe (65.5%) and North America (20.0%). The number of studies included in each systematic review ranged from 0 to 130, with the majority of

reviews including between two and 10 studies (50%). Most of the reviews were limited to RCTs (68.3%).

Systematic reviews – patient characteristics

The types of patients and wounds included in the systematic reviews are presented in Table 1. The five most prevalent types of wounds examined were described as being venous, arterial and unspecified leg ulcers (24.6%), diabetic ulcers or infections (19.1%), mixed chronic wounds (18.2%), pressure ulcers (15.5%), and mixed acute and chronic ulcers (10.9%). Only 31.8% of the included systematic reviews reported on a specific patient population, which included patients with diabetes (15.5%), chronic venous disease (8.2%), or chronic lower limb wounds (1.8%), and patients who were elderly (2.7%), institutionalized (1.8%), ambulatory (0.91%), or had cancer (0.91%). The five most commonly assessed wound care treatments included dressings (29.0%), adjuvant therapies (13.6%), biologic agents (7.7%), wound cleansing (7.7%), and topical negative pressure (7.7%). The five most common comparators were dressings (26.2%), standard care (20.5%), placebo (18.9%), any therapy or unspecified (7.7%), and bandages (5.6%). The duration of treatment ranged from 2 days to 18 months and the duration of follow-up ranged from 2 days to 180 months across the included studies in the systematic reviews.

Systematic reviews – methodological quality

The methodological quality of the 110 included systematic reviews according to the AMSTAR tool is reported in Table 2. Approximately 40% of the included reviews were rated as being high quality, with a score of ≥8 out of a total score of 11. Consistent methodological shortcomings across the systematic reviews included that only 35.5% used a protocol to guide their conduct, 38.2% included a list of excluded studies at level 2 screening, and 26.4% addressed or mentioned

publication bias. Conversely, methodological strengths across the systematic reviews were that 95.5% searched at least two electronic databases, 86.4% provided the characteristics of included studies, 87.3% appraised the quality of the included studies, and 80.9% adequately used the quality appraisal results in formulating conclusions.

Systematic reviews – outcome results

Outcome results from high quality systematic reviews that did not conduct a meta-analysis (or non-meta-analyses) are summarized below, followed by a summary of outcomes by wound type from systematic reviews for which a meta-analysis was conducted. From these summaries, we then highlight the interventions most likely to be effective based on the results of only the highest quality systematic reviews for which a meta-analysis was conducted.

Systematic reviews – outcome results for studies that did not complete a meta-analysis

The results from 16 high quality systematic reviews for which a meta-analysis was not conducted are presented in Table 3. The majority of the systematic reviews found weak/insufficient evidence or no difference between the interventions and comparator groups. One systematic review suggested that revascularization with either open bypass surgery or endovascular revascularization might improve healing of diabetic foot ulcers, yet there was insufficient evidence to recommend one form of revascularization over another [19]. Another systematic review found some evidence that debriding agents have a beneficial effect on healing of surgical wounds compared to traditional gauze dressings, yet the superiority of one type of debriding agent over another could not be established [20]. A third systematic review found that a plaster cast might be effective for healing amputations, as well as for decreasing hospital stay compared with elastic compression [21].

Systematic reviews – outcome results for venous and arterial leg ulcers meta-analyses

Sixty-six meta-analyses reported healing outcomes for patients with venous and arterial leg ulcers, which are presented in Table 4. Of these, 44 meta-analyses reported on the number of ulcers healed. Interventions that were effective for this outcome were high compression stockings versus compression bandage [22], elastic bandage versus inelastic bandage [23], elastic multi-layer high compression bandage versus inelastic compression [24], cadexomer iodine plus compression therapy versus usual care plus compression therapy [25], intermittent pneumatic compression versus compression stockings/Unna's boot [24], multi-layer high compression versus single-layer compression [22, 24], pentoxifylline with or without compression versus placebo [26], 2-layer stocking versus short-stretch bandage [23], ultrasound versus no ultrasound [27], topical negative pressure versus usual care [28], and dermagraft versus standard compression therapy [29].

Eight meta-analyses reported healing or improvement of ulcers for patients with venous or arterial ulcers (Table 4). Interventions that were effective for this outcome included stockings versus bandages [30], elastic high compression versus multi-layer inelastic compression [22], granulocyte-macrophage colony stimulating factor versus placebo [31], tissue engineered skin versus dressings [32], and pentoxifylline versus all other treatments [26]. Four meta-analyses reported the rate of ulcer healing (Table 4). The only intervention that was effective for this outcome was micronized purified flavonoid versus placebo/standard care [33].

Five meta-analyses reported on the time to ulcer healing for patients with venous or arterial ulcers (Table 4). Interventions that were effective for this outcome included bandages versus stockings [30], micronized purified flavonoid versus placebo/standard care [33], 4-layer bandage

versus short-stretch bandage [34] or versus multi-layer short-stretch bandage [23], and topical negative pressure versus usual care [28]. An additional five meta-analyses reported impact on the ulcer size/area reduction (Table 4). Effective interventions included silver treatments versus non-silver therapies [35], micronized purified flavonoid versus control (non-specified) [33], ultrasound versus placebo/standard care [27], and cadexomer iodine versus usual care [25].

Systematic reviews – outcome results for pressure ulcers meta-analyses

Thirty-six meta-analyses reported on healing outcomes for patients with pressure ulcers and sores, which are presented in Table 5. Of these, 25 meta-analyses focused on complete healing of ulcers or sores. Interventions that were effective for this outcome included hydrocolloid versus traditional dressing [36], hydrogel dressing versus hydrocolloid dressing [36], and Nimbus 3 alternating-pressure mattresses versus other alternating-pressure mattresses in the hospital setting [36]. Seven meta-analyses reported on the healing or improvement of ulcers or sores. Interventions that were effective for this outcome included hydrocolloid versus traditional treatment [37], air-fluidized supports versus usual care [38], air-fluidized beds versus usual care [39] or conventional mattresses [36], alternative foam mattress versus standard foam mattress [39], and electrotherapy versus sham therapy [22]. One meta-analysis reported the incidence of ulcers and found that nutritional support was more effective than usual care [40].

Systematic reviews – outcome results for diabetic ulcers meta-analyses

Twenty-five meta-analyses provided data on healing and hospitalization outcomes amongst patients with diabetic ulcers and their results are presented in Table 6. Fifteen meta-analyses provided data on the proportion of diabetic ulcers healed. Effective interventions for this outcome included skin replacement therapy versus usual care [41], artificial skin graft with usual

care versus usual care alone [42], hydrogel dressing versus basic wound dressing [43], hydrogel versus gauze with usual care [44], autologous platelet-rich plasma versus control [45], and Chinese herbal medicine versus usual care [46].

Three meta-analyses provided data on ulcer healing or improvement for patients with diabetic ulcers (Table 6) and the only effective intervention was Chinese herbal medicine versus usual care [46]. Five meta-analyses provided data on non-healing ulcers and effective interventions were Chinese herbal medicine versus usual care [46], hyaluronic acid derivatives versus usual care [47], low-frequency low-intensity noncontact ultrasound versus sharp debridement [47], and low-frequency high-intensity contact ultrasound versus sharp debridement [47]. One meta-analysis provided data on the number of hospital days and granulocyte-colony stimulating factor was more effective than control (unspecified) [48].

Systematic reviews – outcome results for mixed acute and/or chronic wounds meta-analyses

Seventeen meta-analyses reported healing outcomes among patients with mixed acute and/or chronic wounds and their results are presented in Table 7. None of the interventions were effective for patients with acute or mixed acute/chronic wounds. Effective interventions to heal chronic wounds included hydrocolloid dressing versus conventional dressing [49], apligraf skin graft versus usual care [42], dermagraft skin graft versus usual care [42], and any artificial skin graft plus standard wound care versus usual care [42]. An effective intervention to reduce ulcer size was silver dressing versus non-silver dressing [50]. Conflicting results were found for autologous platelet-rich plasma versus usual care with or without placebo [51].

Systematic reviews – outcome results for wound infections meta-analyses

Four meta-analyses reported on treating infection, wound resolution, and length of hospitalization for patients with wound infections and the results are presented in Table 8. Fluoroquinolone treatment (including ciprofloxacin) was more effective than beta-lactam antibiotics in treating infection [52]. Topical negative pressure/vacuum associated closure was more effective than conventional therapy for wound resolution [53]. Finally, vacuum-assisted closure was more effective than conventional therapy [54]. None of these systematic reviews were of high methodological quality.

Systematic reviews – outcome results for burns meta-analyses

Four meta-analyses reported healing outcomes for burns and their results are presented in Table 9. Honey was more effective than silver sulfadizine and conventional dressings in a high quality systematic review that assessed impact on the time to healing of the wound[2].

Summary of effective interventions from the highest quality systematic reviews for which a meta-analysis was conducted

Based on the highest quality systematic reviews for which a meta-analysis was conducted, the following interventions are likely effective:

- Patients with venous or arterial leg ulcers - high compression stockings versus compression bandage [22], elastic bandage versus inelastic bandage [23], cadexomer iodine plus compression therapy versus usual care plus compression therapy [25], multi-layer high compression versus single-layer compression [22], pentoxifylline with or without compression versus placebo or all other treatments [26], 2-layer stocking versus short-stretch bandage [23], elastic high compression versus multi-layer inelastic compression [22], tissue

engineered skin versus dressings [32], 4-layer bandage versus short-stretch bandage [23] or versus multi-layer short-stretch bandage [23], and cadexomer iodine versus usual care [25].

- Patients with pressure ulcers - hydrocolloid versus traditional treatment [37], air-fluidized beds versus usual care [39], alternative foam mattress versus standard foam mattress [39], electrotherapy versus sham therapy [22], and nutritional support versus usual care [40].

- Patients with diabetic ulcers - artificial skin graft with usual care versus usual care alone [42], hydrogel dressing versus basic wound dressing [43], hydrogel versus gauze with usual care [44], hyaluronic acid derivatives versus usual care [47], low-frequency low-intensity noncontact ultrasound versus sharp debridement [47], low-frequency high-intensity contact ultrasound versus sharp debridement [47], and granulocyte-colony stimulating factor versus control (unspecified) [48].

- Patients with mixed chronic wounds - apligraf skin graft versus usual care [42], dermagraft skin graft versus usual care [42], any artificial skin graft plus standard wound care versus usual care [42], and silver dressings versus non-silver dressings [50].

- Patients with burns - honey versus silver sulfadizine or conventional dressings [2].

Results from included economic studies

Economic studies – study characteristics

The characteristics of the 104 included economic studies are presented in Table 10. The earliest economic study was published in 1982 and the most recent was published in 2012. The majority of the economic studies were published between 2006 and 2010 (31.7%). Most of the economic studies were published by authors located in Europe (43.3%) and North America (41.3%). The majority of the studies were costing studies (66.3%), while 11.5% were CUAs/CEAs combined and 22.1% were CEAs alone. Most of the economic studies included a total sample size of 10 to 100 patients.

Economic studies – patient characteristics

Most of the patient populations in the economic studies were elderly (59.6%), followed by patients with chronic venous disease (27.9%) or diabetes (21.2%), and surgical/trauma patients (11.5%; Table 10). The setting ranged from inpatients (including acute and long-term care) (36.6%) to home care (18.3%). The types of wounds examined in these studies included venous ulcers (27.9%), diabetic ulcers or infections (21.2%), pressure ulcers (22.1%), surgical wounds or infections (11.5%), mixed wounds (16.3%), and other wound infections (1.0%). The five most common treatments given to these patients for their wound care included dressings (59.6%), programs/guidelines or systems changes (23.1%), mattresses or pressure off-loading devices (7.7%), surgery (7.7%), oral or intravenous antibiotic treatment (7.7%), and hyperbaric oxygen therapy or use of another device (7.7%). The five most common comparators were dressings (36.5%), standard care (26.9%), programs/guidelines or systems changes (6.7%), mattresses or

pressure off-loading devices (5.8%), topical negative pressure (4.8%), and oral or intravenous antibiotic treatment (4.8%).

Economic studies – outcome results

Outcome results from economic studies regarding resource utilization are summarized below. This section is followed by the methodological quality of the included CEAs/CUAs and their respective outcome results by wound type. Using these summaries, we then highlight the interventions most likely to be cost-effective based on the results of the highest quality CEAs/CUAs.

Economic studies – resource outcome results

Sixty-nine costing studies reported data on resource outcomes, which are presented in Table 11. Numerous interventions and comparators were examined for different types of wounds and a wide variation was observed in the resources required for these interventions. For dressings, personnel time was usually the major cost factor, based on the frequency and number of dressing changes required by nurses. For diabetic patients with severe ulcers, hospitalization was usually the major cost factor due to foot infections and amputations. The mean total cost per patient ranged from $15.6 United States dollars (US) for hydrocolloid dressing [55] to $445,678 Swedish Kronan (SEK) for reamputation (i.e., for patients requiring a second amputation on another limb) [56]. The mean intervention cost per patient ranged from $0.52 Australian dollars (AU) for dry absorbent dressings [57] to $20,845 Spanish pesetas (Pts) for collagenase ointment treatment [58]. Average personnel costs per patient ranged from US$2.26 for hydrocolloid dressings [55] to $57,277.9 Yen (¥) for a hospital incentive system with wound, ostomy, and continence nurses [59]. Finally, average hospital costs per patient ranged from $83 Haitian

Gourdes (HTG) for homemade wound vacuum-dressing system [60] to US$14,410.0 for conventional hospital beds [61].

CEAs/CUAs – methodological quality

The methodological quality of the 35 included CEAs/CUAs according to the Drummond tool [18] is presented in Table 12. Approximately 89% of the CEAs/CUAs had a score of 7 or higher out of a total possible score of 10 indicating they are high quality. The one consistent methodological shortcoming across the CEAs/CUAs was that only 34.3% established the effectiveness of the wound care intervention using data from systematic reviews, RCTs or other types of studies (e.g., observational studies) that had sufficiently large sample sizes. Since effectiveness needs to be established prior to conducting a CEA/CUA, this was considered a major limitation of the majority of the CEAs/CUAs. As such, the 12 analyses that met this criterion were considered higher methodological quality compared with the other analyses. Consistent methodological strengths across the CEAs/CUAs were that all clearly described the question, measured costs and consequences in appropriate physical units, and credibly valued costs and consequences.

CEAs/CUAs – economic results for venous ulcers

The results from 14 of the included CEAs/CUAs examining treatments for venous ulcers are presented in Table 13. Based on these results, cost-effective interventions that were found to be both more effective and less costly were micronized purified flavonoid fraction plus standard therapy versus standard compression with external treatment [62], pentoxifylline plus usual care versus standard compression with external treatment [63], four-layer high compression bandages versus standard compression with external treatment [64] or versus short-stretch high

compression bandages [63]. Additional cost-effective interventions which were considered less costly with similar effectiveness included pinch grafting surgery in primary care versus pinch grafting surgery in the hospital [65] and hydrocolloid dressing versus Vaseline gauze [66]. Furthermore, skin protectant no-sting barrier film plus compression with dressings was more effective and had similar costs compared to standard compression with external treatments [67]. For the three CEAs in which interventions were found to be both more effective yet more costly (one of which was a high quality CEA [68]), incremental cost-effectiveness ratios are presented in Table 13 [68-70]. Four CEAs/CUAs found the other interventions were either more costly with similar effectiveness versus comparators, less effective versus comparators, had a similar cost and effectiveness versus comparators, or the costing analysis was inconclusive.

CEAs/CUAs – economic results for pressure ulcers

The results from 7 of the included CEAs/CUAs examining treatments for pressure ulcers are presented in Table 14. Based on these results, cost-effective interventions which were found to be both more effective and less costly were hydrocolloid wafer dressing versus saline gauze [71], advanced dressings versus conventional simple and saline dressings [72], collagenase-containing ointment plus paraffin gauze and absorbent bandages after saline versus hydrocolloid alone [73], and multi-disciplinary community wound care teams versus usual nursing care [74]. An additional cost-effective intervention was self-adhesive polyurethane foam dressing, which had a similar effectiveness and was less costly compared to moist gauze dressing with saline [75]. One CEA found the intervention to be both more effective yet more costly, and the incremental cost-effectiveness ratio is presented in Table 14 [76]. Finally, type 1 collagen had a similar effectiveness, yet was more costly compared with hydrocolloid [77].

CEAs/CUAs – economic results for surgical wounds

Three CEAs examined treatments for surgical wounds and their results are presented in Table 15. Negative-pressure wound therapy was cost-effective compared to moist wound therapy since it was found to be both more effective and less costly in one CEA [78]. Another CEA found that oral linezolid during hospitalization and after discharge was more cost-effective than IV vancomycin during hospitalization followed by oral linezolid after discharge or compared to IV vancomycin during hospitalization and after discharge [79]. The third CEA, which was the only one that met the effectiveness methodological criterion, found that occlusive moist-environment nongauze-based materials had a similar effectiveness yet were more costly compared with gauze dressings [80].

CEAs/CUAs – economic results for diabetic ulcers

Seven CEAs/CUAs examined treatments for diabetic ulcers and their results are presented in Table 16. Three of these examined interventions were found to be cost-effective based on being both more effective and less costly. Hyperbaric oxygen therapy plus standard care was cost-effective compared to standard care alone in a high quality CUA/CEA [81], this same result was also found in another CUA/CEA which followed patients one year or more after the intervention [82]. Both intensified treatment in a specialized outpatient hospital department [83] and Becaplermin gel containing recombinant human platelet derived growth factor plus standard care were cost-effective compared with usual care [83] or good wound care alone [84]. Additional cost-effective interventions were cadexomer iodine ointment, which was less costly but had a similar effectiveness to standard dressings [85] and the Optima Diab walker compared to the

total contact casting standard off-loading device [86]. The final CUA/CEA found that all interventions had similar effectiveness and different costs [87].

Two CEAs/CUAs examined diabetic foot infections and their results are presented in Table 16. Both of these examined interventions that were found to be cost-effective based on being both more effective and less costly. Ertapenem was cost-effective compared to piperacillin/tazobactam in a high quality CEA/CUA [88]. Furthermore, filgrastim plus antibiotics (i.e., a combination of ceftazidime, amoxicillin, flucloxacillin and metronidazole) was cost-effective versus placebo plus antibiotics (identical combination above) in a CEA that did not establish effectiveness prior to conducting the economic analysis [89].

Two CEAs/CUAs examined mixed wound types and their results are presented in Table 17. Both of these examined interventions that were found to be cost-effective based on being both more effective and less costly. Bio-electric stimulation therapy was cost-effective compared to standard care for chronic non-healing wounds [90]. For chronic wounds, a specialty enterostomal/advanced wound and ostomy skills nursing agency seeing patients exclusively was cost-effective versus a hybrid nursing care model [91]. Neither of these CEAs/CUAs adequately established the effectiveness of the intervention for the economic analysis so were not considered high quality.

Summary of cost-effective interventions from the highest quality cost-effectiveness/cost-utility analyses

Based on the highest quality evidence, the following interventions are likely cost-effective:

- Patients with venous ulcers - pentoxifylline plus usual care versus standard compression with external treatment [92], and four-layer high compression bandages versus standard compression with external treatment [64] or versus short-stretch high compression bandages [63].

- Pressure ulcers - multi-disciplinary community wound care teams versus usual nursing care [74].

- Diabetic ulcers - hyperbaric oxygen therapy plus standard care versus standard care alone [81] and Becaplermin gel containing recombinant human platelet derived growth factor plus standard care versus usual wound care alone [84].

- Diabetic foot infections - Ertapenem versus piperacillin/tazobactam [88].

Discussion

We conducted a comprehensive scoping review to identify optimal and cost-effective wound care interventions. Data from 110 systematic reviews and 104 economic studies were scrutinized and wound care interventions that are likely optimal and cost-effective were identified. These reviews and economic studies examined numerous treatments and comparators and used different outcomes to assess effectiveness and costs. Frequently, the interventions considered in one review or cost-effectiveness analysis comprised the comparator group in another review or cost-effectiveness analysis. This renders the interpretation of our findings difficult and our results cannot be used to rank the effectiveness and respective cost-effectiveness of these interventions.

We included data from 110 systematic reviews, the first of which was published in 1997. This indicates a huge explosion in the number of systematic reviews in this area, with the majority conducted between 2006 and 2010. Based on this, wound care is an area of high priority and it is clear that researchers and clinicians are interested in finding optimal ways to improve quality of care for patients with wounds.

Although numerous reviews and economic studies were included examining a broad range of outcomes, research gaps were apparent. For systematic reviews, the majority of the evidence focused on chronic wounds, including leg ulcers (3 high-quality systematic reviews without a meta-analysis plus 66 meta-analyses), pressure ulcers (4 high-quality systematic reviews without a meta-analysis plus 36 meta-analyses), diabetic foot ulcers (3 high-quality systematic reviews without a meta-analysis plus 25 meta-analyses), and infected wounds (1 high-quality systematic review without a meta-analysis plus 4 meta-analyses). Acute wounds were examined less

frequent and included surgical wounds (3 high-quality systematic reviews without a meta-analysis) and burns (1 high-quality systematic review without a meta-analysis plus 4 meta-analyses). No systematic reviews were identified on other types of acute wounds, such as lacerations or trauma. Only systematic reviews focused on diabetic foot ulcers, surgical wounds, and infected wounds reported on hospitalization outcomes; the rest of the reviews focused on healing outcomes.

Our scoping review identified a large research gap in cost-effectiveness evaluations of wound care interventions. Compared to the large economic burden of wound care in Canada and internationally [8, 10], and the multitude of wound care interventions available, relatively few high quality cost-effectiveness analyses were identified. The 12 high quality CEAs/CUAs that were identified assessed the following types of wounds: venous ulcers (n=7 studies), diabetic ulcers (n=2), pressure ulcers (n=1), surgical wounds (n=1), and diabetic foot infections (n=1). High quality CEAs/CUAs were not identified on burns, lacerations or trauma.

After including data from 110 systematic reviews, we found that some interventions are likely to be more effective than others. For patients with venous or arterial leg ulcers, high compression stockings versus compression bandage [22], elastic bandage versus inelastic bandage [25], cadexomer iodine plus compression therapy versus usual care plus compression therapy [25], multi-layer high compression versus single-layer compression [22], pentoxifylline with or without compression versus placebo or all other treatments [26], 2-layer stocking versus short-stretch bandage [25], elastic high compression versus multi-layer inelastic compression [22], tissue engineered skin versus dressings [32], 4-layer bandage versus short-stretch bandage [25]or versus multi-layer short-stretch bandage [25], and cadexomer iodine versus usual care [25] were found to be effective. For patients with pressure ulcers, hydrocolloid versus traditional treatment

[37], air-fluidized beds versus usual care [39], alternative foam mattress versus standard foam mattress [39], electrotherapy versus sham therapy [22], and nutritional support was more effective versus usual care [40]. For patients with diabetic ulcers, artificial skin graft with usual care versus usual care alone [42], hydrogel dressing versus basic wound dressing [43], hydrogel versus gauze with usual care [44], hyaluronic acid derivatives versus usual care [47], low-frequency low-intensity noncontact ultrasound versus sharp debridement [47], low-frequency high-intensity contact ultrasound versus sharp debridement [47], and granulocyte-colony stimulating factor versus control (unspecified) [48] were effective. For patients with mixed chronic wounds, apligraf skin graft versus usual care [42], dermagraft skin graft versus usual care [42], any artificial skin graft plus standard wound care versus usual care [42], and silver dressings versus non-silver dressings [50] were effective. Finally, for patients with burns, honey was effective versus silver sulfadizine or conventional dressings [2].

Cost-effectiveness studies can have eight possible overall results, which are often represented graphically as quadrants on a cost-effectiveness plane [93], as depicted in Figure 2. The possibilities for the intervention versus comparator are as follows: 1) more effective and less costly; 2) more effective and similar costs; 3) similar effectiveness and less costly; 4) more effective and more costly; 5) similar effectiveness and more costly; 6) less effective and less costly; 7) less effective and similar costs; and 8) less effective and more costly. Results from possibilities 1-3 are considered to be cost-effective; whereas possibility 5 is not cost-effective and possibilities 6-8 are less effective. Situation 4 requires judgment by the decision-maker to interpret whether it is cost-effective [94]. In such cases, a study should report an incremental cost-effectiveness ratio (ICER) that has calculated the relative difference in costs to the difference in effectiveness between the intervention and comparator using this calculation: (Cost

of the intervention – Cost of the comparator) ÷ (Effectiveness of the intervention – Effectiveness of the comparator). Smaller values indicate better cost-effectiveness [18].

Out of 35 cost-effectiveness studies (CEAs/CUAs) reviewed, 12 were deemed to be of higher methodological quality based on having established effectiveness. Of these 12, seven reported cost-effective results for the intervention studied. For patients with venous ulcers, pentoxifylline plus usual care versus standard compression with external treatment [92], and four-layer high compression bandages versus standard compression with external treatment [64] or versus short-stretch high compression bandages [63] were found to be cost-effective (and these cost-effective interventions were also found to be effective in the higher quality meta-analyses discussed above). For patients with pressure ulcers, multi-disciplinary community wound care teams comprising of trained community pharmacists and nurses in the nursing home versus usual nursing care in the nursing home [74] were found to be cost-effective. For patients with diabetic ulcers, hyperbaric oxygen therapy plus standard care versus standard care alone [81], and Becaplermin gel containing recombinant human platelet derived growth factor plus standard care versus good wound care alone [84] were found to be cost-effective. Finally, for patients with diabetic foot infections, Ertapenem versus piperacillin/tazobactam [88] was cost-effective.

One of the 12 high quality CEAs/CUAs examined community based leg ulcer clinics with trained nurses using a unique graduated four layer compression bandaging system versus patients' usual home care. The authors found that the intervention was more effective yet more costly than usual care with an incremental cost-effectiveness ratio result of £2.46 per ulcer-free week gained (i.e. it costs an extra £2.46 for each additional week without an ulcer) [68]. Four of the 12 high quality CEAs/CUAs did not find the interventions were cost-effective [80, 95-97].

Our results suggest the need for a network meta-analysis, given the numerous interventions and comparators available. Network meta-analysis is a statistical technique that can be used to select the best treatment option available. In a situation where we may have direct comparisons of treatments (e.g. T1 versus T3 and T2 versus T3); indirect methods attempt to use the common comparator link T3 to yield an indirect comparison of T1 versus T2. There are various reasons that lead to a lack of availability of a direct comparison, such as the lack of comparison between interventions based on usual treatment or the scarcity of resources to conduct RCTs for every single intervention comparison. In these situations, performing an indirect treatment comparison is beneficial. Based on our preliminary findings, a suitable topic for network meta-analysis is to examine stockings versus bandages for patients with venous or arterial leg ulcers. This will be a more focused review and the results will likely be of interest to decision-makers, including those at the TC LHIN.

Few of the included systematic reviews were rated as being of high methodological quality according to the AMSTAR tool [17]. Consistent methodological shortcomings include not using a protocol to guide their conduct, not including a list of excluded studies at level 2 screening, and not addressing or at least mentioning publication bias. Furthermore, some studies only gave wound care patients 2 days of treatment or followed patients for 2 days. The utility of these short studies is questionable and studies of longer duration are recommended.

The major methodological quality limitation found in the CEAs/CUAs reviewed was that the majority did not adequately establish the effectiveness of the wound care intervention using data from systematic reviews, RCTs or other types of studies (e.g., observational studies) that had sufficiently large sample sizes. Many of the cost-effectiveness studies did not include information on patient-reported quality of life outcomes or adverse events. Furthermore, many of

the CEAs/CUAs did not assess long-term cost-effectiveness. The choice of timeframe for an economic evaluation might significantly affect the cost-effectiveness results. Given the chronic nature of many types of wounds, economic modeling of a longer time horizon would provide a clearer picture in many circumstances. For example, an intervention might be more effective yet more costly in the first two months but this might result in better cost-effectiveness due to overall fewer additional interventions required in the future.

Given the large scope of our scoping review and short timeline for its completion, it is difficult for us to make any recommendations on important elements for the TC LHIN to consider regarding the Canadian context. Eight of the systematic reviews were from authors with a Canadian affiliation [36, 42, 98-103], yet we do not know if the studies included in these reviews were conducted in Canada. Of note, only one of these systematic reviews was rated as being high quality [42]. However, all of the interventions found to be effective from data from systematic reviews are likely transferrable to the Canadian context. For example, the effective bandages, stockings, dressings, and skin grafts, are widely available and likely of relevance to the TC LHIN. Furthermore, the results from a low quality systematic review without a meta-analysis might be of interest to the TC LHIN. This systematic review was conducted by the Medical Advisory Secretariat of the Ontario Ministry of Health and Long-term Care and they found that multidisciplinary wound care teams effectively healed wounds for patients with chronic wounds compared to patients managed without a wound care team [99].

Specific to the Canadian context for the CEAs/CUAs, only one of the 12 high quality cost-effectiveness analyses was conducted in Canada [81]. Half of the 12 high quality CEAs/CUAs were conducted in the UK, while three were from the rest of Europe (i.e. Sweden, The Netherlands and Ireland) and two from Australia and New Zealand. In considering the possible

applicability of these 11 other cost-effectiveness studies to the Canadian context, several factors need to be assessed, including the perspective (e.g., healthcare system, society, provider, etc.) of the economic evaluation (which are provided in the Tables below), the type of healthcare system (e.g., publicly-funded healthcare), the local practice of medicine, the local costs, and the sensitivity analyses. The results of the sensitivity analyses indicate the changes to parameters that could significantly change the study's overall findings, thereby providing an estimate of the uncertainty of the results. Of the 11 non-Canadian high quality CEAs/CUAs, one found that healing rates may affect the overall findings(with the intervention no longer being cost saving if the improvement in monthly healing rates decreases to 24%) [84]. Three studies did not report sensitivity analyses [80, 95, 104] and the other seven reported that none were significant. A comparison of local costs (e.g., for the intervention materials used, personnel time, hospitalization) to the Canadian context needs to be assessed on a case-by-case basis for each study. In addition, some of the studies did not report a detailed breakdown of the costs involved, rendering comparisons to the Canadian context more difficult.

There are some limitations to our scoping review. Although we appraised the methodological quality of the included studies (which is a step that is usually skipped in scoping reviews [13]), we are unable to comment on the quality of the included studies in the systematic reviews and cost-effectiveness analyses. Due to the three month timeline for conduct of this rapid scoping review, we were unable to fully scan the reference lists of included reviews and economic analyses and we were unable to contact study authors for further information. We identified 25 studies that were written in languages other than English and these will need to be assessed for inclusion in the future. We also need to continue searching for grey literature and contacting authors of systematic review protocols and conference abstracts. These activities will be

conducted for the systematic review publications that result from this report, including an overview of the 110 systematic reviews and a systematic review of the 35 CEAs/CUAs.

Acknowledgements

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Figure 1: Study flow

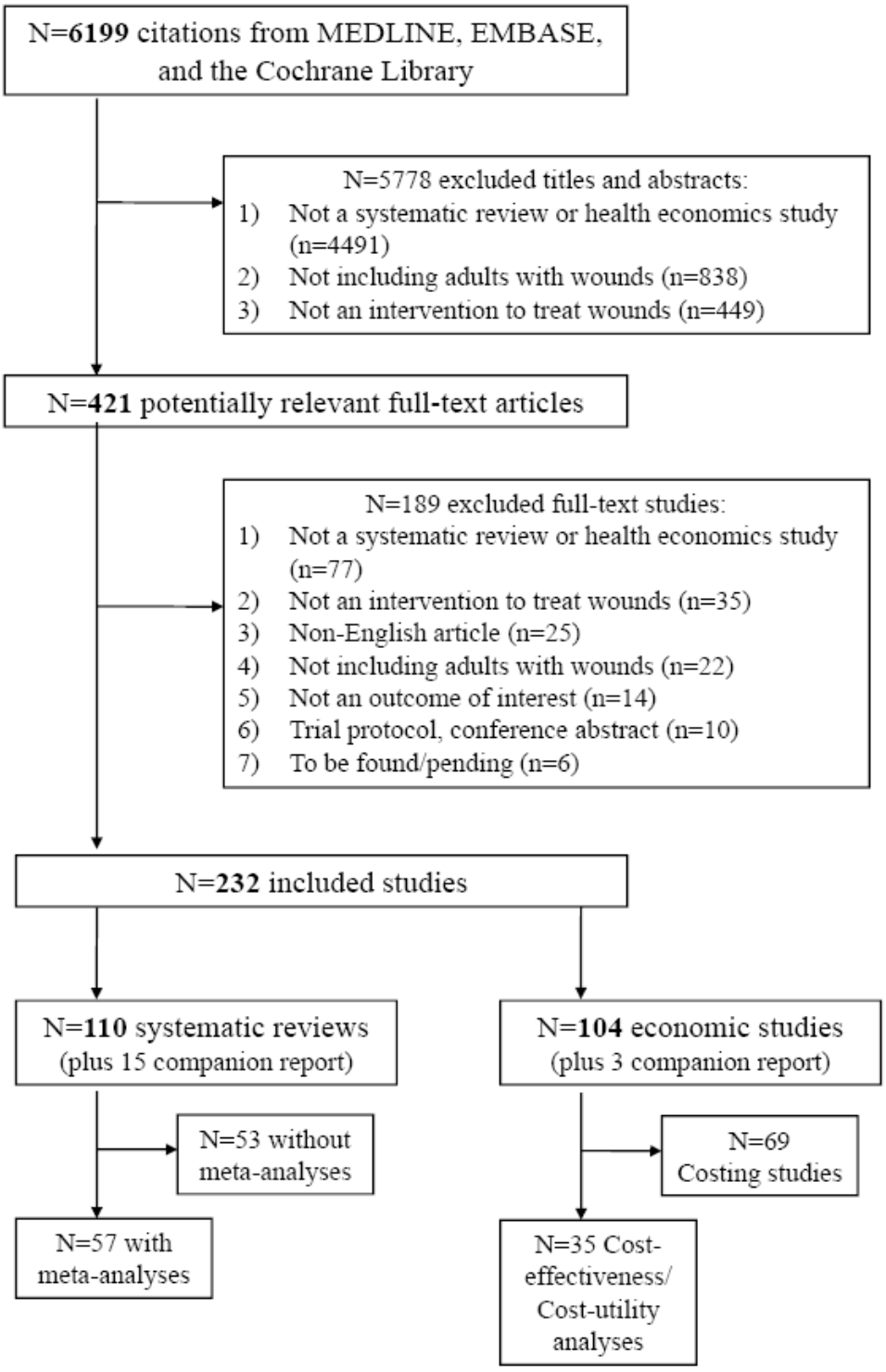

Figure 2: Cost-effectiveness plane

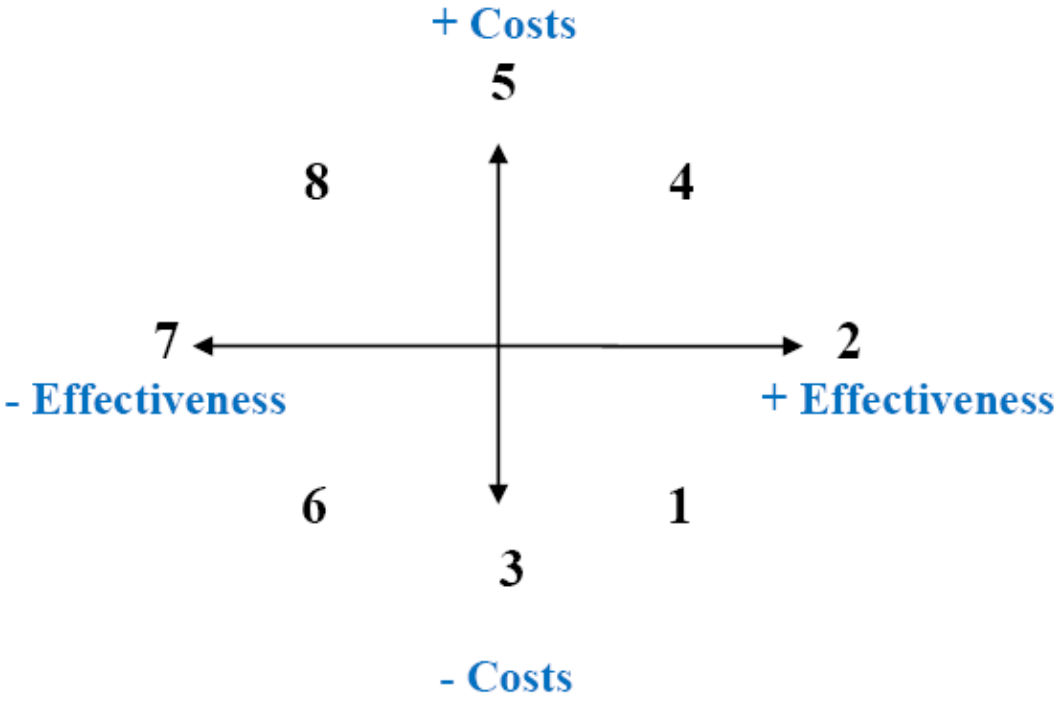

Table 1: Systematic review summary characteristics

Characteristic	# of systematic reviews (N=110 total)	% of systematic reviews
Year		
1997-2000	8	7.27
2001-2005	23	20.91
2006-2010	51	46.36
2011 - present	28	25.45
Country of conduct		
Europe (39 of these are from the UK)	72	65.45
North America	22	20.00
Asia	7	6.36
Australia	6	5.45
South America	2	1.82
Not reported	1	0.91
Number of studies included		
0-1	5	4.55
2 - 10	55	50.00
11 - 20	22	20.00
21-30	11	10.00
31-40	6	5.45
41-100	8	7.27
>100	3	2.73
Study designs included*		
RCT	99	68.28
OBS	27	18.62
NRCT	18	12.41
CBA/ITS	1	0.69
Patient population		
Not reported/specified	75	68.18
Diabetes	17	15.45
Chronic venous disease	9	8.18
Elderly	3	2.72
Chronic lower limb wounds	2	1.82
Inpatients/institutionalized	2	1.82
Ambulatory patients	1	0.91
Cancer	1	0.91
Type of wound		
Leg ulcers	27	24.55
Diabetic ulcer/infection	21	19.09
Mixed chronic wounds	20	18.18
Pressure ulcers/sores	17	15.45
Mixed acute and chronic wounds	12	10.91
Surgical wounds/infection	5	4.55
Wound infection	5	4.55
Mixed acute wounds	2	1.82
Not reported	1	0.91
Interventions examined*		
Dressings	45	29.03
Adjuvant therapies	21	13.55

Characteristic	# of systematic reviews (N=110 total)	% of systematic reviews
Biologic agents	14	9.03
Wound cleansing	12	7.74
Topical negative pressure	12	7.74
Support surfaces	12	7.74
Skin replacement therapy	9	5.81
Bandages	8	5.16
Nutritional supplementation	6	3.87
Stockings	5	3.23
Surgical	5	3.23
Oral treatment	3	1.94
Wound care programs	2	1.29
Chinese herbal medicine	1	0.65
Comparators examined*		
Dressings	51	26.15
Standard care	40	20.51
Placebo	37	18.97
Any therapy/Unspecified	15	7.69
Bandages	11	5.64
Wound cleansing	9	4.62
Support surfaces	7	3.59
Oral treatment	5	2.56
Nutritional supplementation	4	2.05
Surgical	4	2.05
Adjuvant therapies	4	2.05
Stockings	3	1.54
Skin replacement therapy	2	1.03
Wound care programs	2	1.03
Biologic agents	1	0.51

Note: * Numbers do not add up to 110, as the systematic reviews contributed data to more than one category. **Abbreviations**: CBA controlled before-after, ITS interrupted time-series, NRCT non-randomized clinical trial, OBS observational study, RCT randomized clinical trial, UK United Kingdom.

Table 2: Systematic review methodological quality

SYSTEMATIC REVIEW	An 'a priori' designed provided	Duplicate study selection	Comprehensive literature search performed	Status of publication used as an inclusion criterion	A list of included and excluded studies provided	Characteristics of included studies provided	Scientific quality of included studies assessed and documented	Scientific quality of the included studies used appropriately in formulating conclusions	Methods used to combine findings of studies is appropriate	Likelihood of publication bias is assessed	Conflict of interest is stated	AMSTAR RATING*
Adderley 2007	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	**9**
Sari 2006	Y	N	Y	Y	UC	Y	Y	Y	Y	N	Y	**8**
Amsler 2009	UC	UC	Y	N	N	Y	N	NA	N	N	Y	**3**
Aziz 2011	Y	Y	Y	Y	UC	Y	Y	Y	Y	N	Y	**9**
Barber 2008	UC	Y	Y	UC	N	Y	Y	Y	Y	N	Y	**7**
Bardy 2008	N	Y	Y	N	N	Y	Y	Y	N	Y	N	**6**
Bergin 2006	Y	UC	Y	Y	NA	NA	Y	NA	Y	NA	Y	**6**
Berliner 2003	UC	N	Y	UC	N	Y	N	NA	N	N	Y	**3**
Blozik 2008	UC	UC	Y	UC	N	N	Y	N	N	N	N	**2**
van den Boogaard 2008	UC	N	Y	Y	N	Y	Y	Y	N	N	N	**5**
Bouza 2005	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	**8**
Bouza2005	UC	UC	Y	N	N	Y	Y	Y	N	Y	Y	**6**
Bradley 1999	UC	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**
Bradley 1999	UC	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	**9**
Carter 2010	UC	N	Y	N	N	Y	Y	Y	Y	Y	Y	**7**
Chambers 2007	UC	Y	Y	Y	N	Y	Y	Y	Y	N	N	**7**
Chen 2010	UC	UC	Y	UC	N	Y	Y	Y	Y	N	Y	**6**
Coleridge-Smith 2005	UC	UC	Y	Y	N	Y	Y	Y	N	N	Y	**6**
Cruciani 2005	UC	UC	Y	Y	N	Y	Y	Y	Y	Y	N	**7**

SYSTEMATIC REVIEW	An 'a priori' designed provided	Duplicate study selection	Comprehensive literature search performed	Status of publication used as an inclusion criterion	A list of included and excluded studies provided	Characteristics of included studies provided	Scientific quality of included studies assessed and documented	Scientific quality of the included studies used appropriately in formulating conclusions	Methods used to combine findings of studies is appropriate	Likelihood of publication bias is assessed	Conflict of interest is stated	AMSTAR RATING*
Cruciani 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Cullum 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	**10**
Cullum 2001	UC	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	**9**
Cullum 2008	UC	UC	Y	N	N	N	Y	Y	N	NA	Y	**4**
Cullum 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	**10**
Damini 2010	UC	Y	Y	N	N	Y	Y	N	Y	N	Y	**6**
Dat 2012	Y	Y	Y	UC	Y	Y	Y	Y	Y	N	Y	**9**
Dumville 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Dumville 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Dumville 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Dumville 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
E.C.R.I. 2001	UC	UC	Y	Y	N	Y	Y	Y	N	UC	N	**5**
Edwards 2012	Y	UC	Y	Y	Y	Y	Y	Y	Y	N	Y	**9**
Evans 2001	N	Y	N	Y	N	N	Y	Y	N	N	N	**4**
Falagas 2006	UC	Y	Y	N	N	Y	Y	Y	Y	Y	N	**7**
Fernandez 2012	Y	Y	Y	UC	Y	Y	Y	Y	Y	NA	N	**8**
Fitzgerald 2010	UC	N	Y	UC	N	Y	Y	N	N	N	Y	**4**
Flemming 2008	Y	Y	Y	Y	Y	Y	Y	UC	Y	N	Y	**9**
Fletcher 1997	UC	Y	Y	Y	N	N	N	Y	Y	N	Y	**6**
MAS Ontario 2009	UC	UC	Y	N	N	Y	Y	Y	Y	N	Y	**6**
MAS Ontario 2005	UC	UC	Y	Y	N	Y	Y	Y	UC	N	Y	**6**
MAS Ontario 2009	UC	N	Y	Y	N	Y	Y	Y	Y	N	Y	**7**
Heyneman 2007	UC	N	Y	N	N	Y	Y	Y	Y	N	N	**5**

SYSTEMATIC REVIEW	An 'a priori' designed provided	Duplicate study selection	Comprehensive literature search performed	Status of publication used as an inclusion criterion	A list of included and excluded studies provided	Characteristics of included studies provided	Scientific quality of included studies assessed and documented	Scientific quality of the included studies used appropriately in formulating conclusions	Methods used to combine findings of studies is appropriate	Likelihood of publication bias is assessed	Conflict of interest is stated	AMSTAR RATING*
Hinchliffe 2012	UC	Y	Y	N	N	Y	Y	Y	Y	Y	Y	**8**
Hinchliffe 2008	UC	Y	Y	N	N	Y	Y	Y	Y	N	Y	**7**
Ho 2005	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	**9**
Hu 2010	N	Y	Y	N	N	Y	Y	Y	Y	N	Y	**7**
Hunt 2011	N	N	Y	N	N	Y	Y	Y	N	N	Y	**5**
Johannsen 1998	N	Y	Y	N	Y	Y	N	N	N	N	N	**4**
Jones 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	**10**
Jull 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Jull 2011	Y	Y	Y	UC	Y	Y	Y	Y	Y	Y	Y	**10**
Kranke 2012	Y	Y	Y	UC	Y	Y	Y	Y	Y	N	Y	**9**
Langer 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	**10**
Lewis 2001	UC	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	**9**
Lima 2010	N	Y	Y	N	N	Y	N	N	N	N	Y	**4**
Lo 2009	N	UC	Y	Y	Y	Y	Y	Y	Y	Y	N	**8**
Lo 2008	N	UC	Y	Y	N	Y	Y	Y	Y	N	N	**6**
Lucas 2000	N	Y	Y	Y	N	Y	Y	Y	Y	N	N	**7**
Margolis 1999	N	N	Y	Y	N	Y	UC	N	N	N	N	**3**
Martinez-Zapata 2012	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	**9**
Martinez-Zapata 2008	UC	Y	Y	N	Y	Y	Y	Y	Y	N	N	**7**
Mason 1999	UC	UC	UC	UC	N	Y	N	NA	N	N	N	**1**
McGaughey 2009	UC	Y	Y	N	N	Y	Y	Y	Y	N	N	**6**
McGinnis 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
McInnes 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**

SYSTEMATIC REVIEW	An 'a priori' designed provided	Duplicate study selection	Comprehensive literature search performed	Status of publication used as an inclusion criterion	A list of included and excluded studies provided	Characteristics of included studies provided	Scientific quality of included studies assessed and documented	Scientific quality of the included studies used appropriately in formulating conclusions	Methods used to combine findings of studies is appropriate	Likelihood of publication bias is assessed	Conflict of interest is stated	AMSTAR RATING*
Moore 2012	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	Y	**5**
Moore 2001	N	Y	Y	N	N	N	Y	Y	N	NA	N	**4**
Moore 2008	Y	Y	Y	Y	N	N	Y	Y	UC	N	N	**6**
Moore 2010	Y	Y	Y	UC	NA	NA	NA	NA	Y	NA	Y	**5**
Mwipatayi 2004	N	N	Y	N	N	N	Y	Y	N	NA	N	**3**
Nawijn 2005	N	Y	Y	N	N	Y	Y	Y	N	N	N	**5**
Nelson 2011	UC	N	Y	N	N	Y	Y	UC	N	NA	Y	**4**
Nelson 2009	Y	Y	Y	Y	Y	Y	Y	UC	Y	N	Y	**9**
Nelson 2006	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Nelson 2011	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y	**8**
Nble-Bell 2008	N	Y	Y	UC	Y	Y	Y	Y	Y	N	N	**7**
O'Donnell 2006	UC	UC	Y	N	N	N	Y	Y	Y	N	N	**4**
O'Meara 2001	UC	Y	Y	Y	N	Y	Y	Y	Y	N	N	**7**
O'Meara 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
O'Meara 2009	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	**8**
O'Meara 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**11**
Palfreyman 1998	UC	Y	Y	N	N	Y	Y	Y	Y	N	N	**6**
Palfreyman 2007	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Pan 2010	UC	UC	Y	N	N	Y	Y	Y	UC	N	Y	**5**
Peters 2012	UC	UC	Y	N	N	Y	Y	Y	Y	N	Y	**6**
Pham 2003	UC	UC	Y	Y	N	Y	Y	Y	N	N	Y	**6**
Ramundo 2009	UC	UC	Y	N	N	Y	N	NA	N	N	UC	**2**
Reddy 2010	UC	UC	Y	UC	N	Y	Y	Y	Y	N	Y	**6**

SYSTEMATIC REVIEW	An 'a priori' designed provided	Duplicate study selection	Comprehensive literature search performed	Status of publication used as an inclusion criterion	A list of included and excluded studies provided	Characteristics of included studies provided	Scientific quality of included studies assessed and documented	Scientific quality of the included studies used appropriately in formulating conclusions	Methods used to combine findings of studies is appropriate	Likelihood of publication bias is assessed	Conflict of interest is stated	AMSTAR RATING*
Reddy 2008	UC	UC	Y	N	N	Y	Y	Y	N	N	Y	**5**
Roeckl-Wiedmann 2005	Y	UC	Y	Y	N	N	Y	Y	Y	Y	N	**7**
Roukis 2009	UC	UC	Y	Y	N	Y	UC	Y	N	N	Y	**5**
Sadat 2008	UC	UC	Y	UC	N	Y	N	NA	N	N	N	**2**
Schuren 2005	UC	UC	Y	Y	N	Y	Y	Y	Y	N	Y	**7**
Singh 2004	UC	UC	N	Y	N	Y	Y	Y	N	N	N	**4**
Smith 2011	Y	Y	Y	Y	Y	Y	Y	Y	N	UC	Y	**9**
Storm-Versloot 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	**10**
Stratton 2005	UC	UC	Y	UC	Y	Y	Y	Y	Y	Y	Y	**8**
Suissa 2011	UC	UC	Y	UC	N	Y	N	NA	N	N	Y	**3**
TenBrook 2004	UC	UC	N	UC	N	Y	N	NA	N	Y	Y	**3**
Ubbink 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y	**10**
Ubbink 2008	UC	Y	Y	Y	N	Y	Y	Y	Y	N	N	**7**
Vermeulen 2012	Y	Y	Y	UC	Y	Y	Y	Y	Y	UC	Y	**9**
Vermeulen 2010	Y	Y	Y	Y	Y	Y	Y	UC	Y	UC	Y	**9**
Villela 2010	UC	UC	Y	N	N	N	Y	Y	Y	N	Y	**5**
Voigt 2012	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Voigt 2011	UC	Y	Y	Y	N	UC	Y	Y	Y	Y	Y	**8**
Wang 2003	UC	UC	UC	N	N	Y	Y	Y	UC	N	N	**3**
Wilkinson 2012	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	**9**
Xie 2010	UC	UC	Y	N	N	Y	Y	Y	Y	Y	N	**6**
Zarchi 2012	UC	UC	Y	N	N	Y	Y	Y	N	N	N	**4**

Note: Score of 8 or higher is considered high methodological quality. **Abbreviations:** N no, NA not applicable, UC unclear, Y yes.

Table 3: Results for high quality systematic reviews for which a meta-analysis was not conducted (N=16)

Author, year	# of studies included	Intervention	Comparator	Conclusion
Leg ulcers (3 reviews)				
Vermeule, 2010	3	Wound dressings containing silver or with added silver	Dressing with silver at different dosages, no silver, other antiseptics	Silver-containing foam dressings did not significantly increase complete ulcer healing as compared with standard foam dressings or best local practice after up to four weeks of follow-up, although a greater reduction of ulcer size was observed with the silver-containing foam. The use of antibiotics was assessed in two trials, but no significant differences were found.
Nelson, 2009	1	Ketanserin ointment (2%) or 2 drops lavender and 1 drop German chamomile in half a teaspoon grape seed oil (6% solution).	Polyethylene glycol, standard care	There is insufficient evidence to determine whether the choice of topical agent or dressing affects the healing of arterial leg ulcers.
Aziz, 2011	3	EMT	Sham EMT	There is no high quality evidence that electromagnetic therapy increases the rate of healing of venous leg ulcers
Pressure ulcers (4 reviews)				
McGinnis, 2011	1	Relief of pressure (Nimbus system)	Cairwave system	One small study at moderate to high risk of bias was identified, which provided no evidence to inform practice.
McInnes, 2011	18	Pressure-relieving support surfaces	UC	There is no conclusive evidence about the superiority of any support surface for the treatment of existing pressure ulcers.
Langer, 2008	4	500 mg ascorbic acid twice daily, very high protein, 3x200 mg zinc sulphate per day	10 mg ascorbic acid, high protein, placebo	It was not possible to draw any firm conclusions on the effect of enteral and parenteral nutrition on the prevention and treatment of pressure ulcers.
Bradley, 1999	35	Debridement methods	UC, other debriding agents	No studies were found that compared debridement with no debridement. Without these studies it is unclear whether wound debridement is a beneficial

Author, year	# of studies included	Intervention	Comparator	Conclusion
				process that expedites healing and there is insufficient evidence to promote the use of one debriding agent over another. There was only a single comparison between two debriding agents that produced a significant result (hydrogel significantly reduced necrotic wound area compared with dextranomer polysaccharide paste).
Diabetes foot ulcers (3 reviews)				
Nelson, 2006	23	All interventions including antibiotics (oral and IV), topical agents and G-CSF.	All comparators including antibiotic and topical agents.	The available evidence is too weak to be able to draw reliable implications for practice.
Hinchliffe, 2012	49	Revascularization (percutaneous transluminal angioplasty, vein bypass, endovascular plaque excision, popliteal inflow)	All comparators	At 1-year follow-up, 60% or more ulcers had healed following revascularization with either open bypass surgery or endovascular revascularization. Studies appeared to demonstrate improved rates of limb salvage associated with revascularization compared with the results of medically treated patients in the literature. There were insufficient data, however, to recommend one method of revascularization over another.
Ubbink, 2008	7	Topical negative pressure	Gauze soaked in saline, dressings (hydrocolloid gel, cadexomer iodine, hydrogels, alignate, foam)	There is little evidence to support the use of topical negative pressure in the treatment of wounds.
Mixed acute and/or chronic wounds (1 review)				
Dat, 2012	7	Aloe vera	Placebo, other creams not containing aloe vera	There is currently an absence of high quality clinical trial evidence to support the use of aloe vera topical agents or aloe vera dressings as treatments for acute and chronic wounds.

Author, year	# of studies included	Intervention	Comparator	Conclusion
Surgical wounds (3 reviews)				
Smith, 2011	5	Debridement (surgical, biosurgical, autolytic, mechanical, chemical, enzymatic)	Placebo, an alternative method of debridement, any other therapy, no treatment	There is a lack of large, high-quality published RCTs evaluating debridement per se, or comparing different methods of debridement for surgical wounds, to guide clinical decision-making.
Lewis, 2001	17	Autolytic methods of debridement (foam dressings, alginate dressings, hydrocolloid dressings, dextranomer polysaccharide beads dressings)	Gauze or gauze based dressings, impregnated or otherwise	There is a suggestion that the debriding agents have a beneficial effect on healing compared to traditional gauze dressings. However, these results should be interpreted with caution due to the poor quality of the studies. In view of the lack of data and the poor methodological quality of the trials, there is no evidence to support the superiority of one type of the debriding agents dressing over another.
Vermeule, 2012	13	Dressings and topical agents (foam, alginate, gauze -with or without a topical agent, bead dressing, hydrocolloids, plaster cast, aloe vera gel)	Other dressings, UC	Wound healing: Whilst a single small trial of aloe vera supplementation versus gauze suggests delayed healing with aloe vera, the results of this trial are un-interpretable since there was a large differential loss to follow up. A plaster cast applied to an amputation stump accelerated wound healing compared with elastic compression. There were no statistically significant differences in healing for other dressing comparisons (e.g. gauze, foam, alginate; 11 trials). Hospitalization: Four trials showed no difference in length of hospital stay. One trial found shorter hospital stay in people after amputation when plaster casts were applied compared with elastic compression.
Infected wounds (1 review)				
Adderley, 2007	2	Metronidazole gel or Miltefosine solution	Placebo	There is weak evidence that a 6% solution of miltefosine, applied as a fluid to small, superficial fungating wounds on the breast, may slow down the progression of the disease.

Author, year	# of studies included	Intervention	Comparator	Conclusion
Burns (1 review)				
Storm-Versloot, 2010	26	Wound dressings or topical applications containing silver	Topical agent without silver, dressings without silver, alternative silver-containing dressings or topical preparations	There is not enough evidence to support the use of silver-containing dressings or creams, as generally these treatments did not promote wound healing or prevent wound infections. Some evidence from a number of small, poor-quality studies suggested that one silver-containing compound (silver sulphadiazine) has no effect on infection, and actually slows down healing in patients with partial thickness burns.

Abbreviations: EMT electromagnetic therapy, G-CSF granulocyte-colony stimulating factors, IV intravenous, UC usual care.

Table 4: Healing outcomes for reviews including venous and arterial leg ulcers (N=66 meta-analyses)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Number/proportion of ulcers healed (44 meta-analyses)										
4-layer compression bandage	O'Meara, 2009	4	Multi-layer short stretch bandage	1.12	0.96, 1.31	NR	NR	NR	NR	Not different*
	O'Meara, 2009	2	Compression system with paste bandage as the base	1.34	0.78, 2.28	NR	NR	NR	NR	Not different*
4-layer bandage	Cullum, 2001	3	Other multilayer high compression bandages	1.02	0.87, 1.18	NR	NR	NR	NR	Not different*
Compression stockings	Cullum, 2001	2	Compression bandage	1.39	1.00, 1.92	NR	NR	NR	NR	High compression stockings more effective than compression bandage*
Components including elastic bandage	O'Meara, 2009	2	Components including inelastic bandage	1.83	1.26, 2.67	NR	NR	NR	NR	Elastic bandage more effective than inelastic bandage*
Elastic multi-layer high compression bandages	Fletcher, 1997	3	Inelastic compression	NR	NR	2.26	1.4, 3.7	NR	NR	Elastic multi-layer high compression bandage more effective than inelastic compression
Cadexomer iodine plus compression therapy	O'Meara, 2010	2	UC plus compression therapy	6.72	1.56, 28.95	NR	NR	NR	NR	Cadexomer iodine plus compression therapy more effective than UC plus

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
										compression therapy*
Intermittent pneumatic compression	Fletcher, 1997	2	Compression stockings or Unna's boot	NR	NR	10.0	3.33, 33.80	NR	NR	Intermittent pneumatic compression more effective than compression stockings or Unna's boot
	Palfreyman, 1998	2	No intermittent compression	NR	NR	8.45	0.63, 113.91	NR	NR	Not different
	Nelson, 2011	3	Compression	1.09	0.91, 1.30	NR	NR	NR	NR	Not different*
Multi-layer high compression	Cullum, 2001	5	Inelastic compression	1.08	0.79, 1.49	NR	NR	NR	NR	Not different*
	Cullum, 2001	4	Single-layer compression	1.41	1.12, 1.77	NR	NR	NR	NR	Multi-layer high compression more effective than single-layer compression*
	Fletcher, 1997	4	Single layer systems	NR	NR	2.2	1.3, 3.5	NR	NR	Multi-layer high compression more effective than single layer systems
Pentoxifylline with compression	Jull, 2011	7	Placebo	1.56	1.14, 2.13	NR	NR	NR	NR	Pentoxifylline with compression more effective than placebo*
Pentoxifylline without compression	Jull, 2011	4	Placebo	2.25	1.49, 3.39	NR	NR	NR	NR	Pentoxifylline without compression more effective than placebo*

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
2-component (outer elastic)	O'Meara, 2009	2	2-component (outer inelastic)	1.23	0.67, 2.25	NR	NR	NR	NR	Not different*
2-layer stocking	O'Meara, 2009	2	Short-stretch bandage	1.72	1.14, 2.58	NR	NR	NR	NR	2-layer stocking more effective than short-stretch bandage*
Unna 's boot	Palfreyman, 1998	3	Other therapies (unspecified)	NR	NR	5.8	P=0.16	NR	NR	Not different
Laser (any)	Flemming, 2008	2	Sham laser	1.21	0.73, 2.03	NR	NR	NR	NR	Not different*
Autologous platelet rich plasma	Martinez-Zapata, 2012	2	UC with/without placebo	1.02	0.81, 1.27	NR	NR	NR	NR	Not different*
	Martinez-Zapata, 2008	2	UC with/without placebo	1.02	0.81, 1.27	NR	NR	NR	NR	Not different
High frequency US	Cullum, 2011	6	No US	1.34	0.99, 1.80	NR	NR	NR	NR	Not different*
Low frequency US	Cullum, 2011	2	No US	3.91	0.47, 32.85	NR	NR	NR	NR	Not different*
US	Johannsen, 1998	5	No US	NR	NR	NR	NR	15.0	1.00, 30.00	US more effective than no US
Growth factor	O'Donnell, 2006	8	Comparator	0.2	0.1-0.3	NR	NR	NR	NR	Not different
Honey	Jull, 2009	2	Control	1.15	0.96-1.38	NR	NR	NR	NR	Not different*
Foam dressing	Palfreyman, 2007	2	Low adherent dressings	1.35	0.93, 1.94	NR	NR	NR	NR	Not different

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
	Palfreyman, 2007	2	Foam dressing	1.2	0.77, 1.87	NR	NR	NR	NR	Not different
Hydrocolloid dressings	Bouza, 2005	8	Traditional dressing	0.99	0.85, 1.15	NR	NR	NR	NR	Not different
	Bradley, 1999	8	Traditional dressing	NR	NR	1.45	0.83, 2.54	NR	NR	Not different*
	Bradley, 1999	2	Foam dressing	NR	NR	1.00	0.48, 2.08	NR	NR	Not different*
	Palfreyman, 2007	8	Low adherent dressings	1.02	0.83, 1.25	NR	NR	NR	NR	Not different
	Palfreyman, 2007	4	Foam dressing	0.98	0.79, 1.22	NR	NR	NR	NR	Not different
	Palfreyman, 2007	3	Alginite dressing	0.72	0.15, 3.42	NR	NR	NR	NR	Not different
	Palfreyman, 2007	3	Hydrocolloid dressing	1.56	0.67, 3.63	NR	NR	NR	NR	Not different
	Palfreyman, 2007	2	Low adherent dressing	1.53	0.96, 2.42	NR	NR	NR	NR	Not different
Silver dressings	Chambers, 2007	2	Placebo/no treatment	1.79	0.19 , 17.11	NR	NR	NR	NR	Not different
	Chambers, 2007	2	Placebo/no treatment	1.66	0.68, 4.05	NR	NR	NR	NR	Not different
Silver-impregnated dressing	Carter, 2010	7	Non-silver	0.02	0.01, 0.06	NR	NR	NR	NR	Not different
Topical negative	Sadat, 2008	2	UC	NR	NR	1.93	1.05, 3.56	NR	NR	Topical negative

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
pressure										pressure more effective than UC
Dermagraft	Barber, 2008	2	Standard compression therapy	NR	NR	4.48	1.01, 19.8	NR	NR	Dermagraft more effective than standard compression therapy
Artificial skin graft and standard wound care	Ho, 2005	3	UC	1.6	0.57, 4.46	NR	NR	NR	NR	Not different*
Ciprofloxacin	O'Meara, 2010	2	UC/placebo	1.72	0.57, 5.16	NR	NR	NR	NR	Not different*
Zinc	Wilkinson, 2012	4	Placebo	1.22	0.88, 1.68	NR	NR	NR	NR	Not different*
Healing/improvement of ulcers (8 meta-analyses)										
Stockings	Amsler, 2009	8	Bandages	NR	NR	0.44	0.32, 0.61	NR	NR	Stockings more effective than bandages
Elastic high compression	Cullum, 2001	3	Multi-layer inelastic compression	1.54	1.19, 1,99	NR	NR	NR	NR	Elastic high compression more effective than multi-layer inelastic compression*
Granulocyte-macrophage colonystimulating factor	Hu, 2010	2	Placebo	NR	NR	6.5	2.15, 19.7	NR	NR	Granulocyte-macrophage colonystimulatingfactor more effective than placebo
Cryopreserved allografts	Jones, 2007	2	Dressing	1.62	0.79, 3.33	NR	NR	NR	NR	Not different*

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Tissue engineered skin	Jones, 2007	2	Dressing	1.51	1.22, 1.88	NR	NR	NR	NR	Tissue engineered skin more effective than dressing*
Cultured keratinocytes / epidermal grafts	Jones, 2007	4	Dressing	1.73	0.91, 3.28	NR	NR	NR	NR	Not different*
Fresh allografts	Jones, 2007	2	Dressing	2.06	0.54, 7.9	NR	NR	NR	NR	Not different*
Pentoxifylline	Jull, 2011	11	All other treatments	1.7	1.30, 2.24	NR	NR	NR	NR	Pentoxifylline more effective than all other treatments*
Rate of ulcer healing (4 meta-analyses)										
Polyurethane	Bouza , 2005	3	UC	0.92	0.14, 1.98	NR	NR	NR	NR	Not different
Alginite	Bouza , 2005	2	UC	1.1	0.86, 1.43	NR	NR	NR	NR	Not different
Micronized purified flavonoid	Coleridge-Smith, 2005	4	Placebo or standard compression	Reduction of RR 32%	3%, 70%	NR	NR	NR	NR	Micronized purified flavonoid more effective than placebo or standard compression
4-layer bandage	O'Meara, 2009	2	Compression system with paste bandage as the base	0.52	0.06, 0.97	NR	NR	NR	NR	Not different*

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Time to ulcer healing (5 meta-analyses)										
Stockings	Amsler, 2009	7	Bandages	NR	NR	NR	NR	SMD -0.33	-0.50, -0.16	Bandages more effective than stockings
Micronized purified flavonoid	Coleridge-Smith, 2005	-	Placebo or standard compression	Hazard ratio 1.33	P=0.0034	NR	NR	NR	NR	Micronized purified flavonoid more effective than placebo or standard compression
4-layer bandage	O'Meara, 2009	5	Short stretch bandage	1.31	1.09, 1.58	NR	NR	NR	NR	4-layer bandage more effective than short-stretch bandage*
	O'Meara, 2009	4	Multi-layer short-stretch bandage	Hazard ratio 0.8	0.66, 0.97	NR	NR	NR	NR	4-layer bandage more effective than multi-layer short-stretch bandage*
Topical negative pressure	Sadat, 2008	2	UC	NR	NR	1.93	1.05, 3.56	1.04	1.83, -0.25	Topical negative pressure more effective than UC
Ulcer size/area reduction (5 meta-analyses)										
Silver treatments and silver-impregnated dressings	Carter, 2010	5	Placebo or conservative wound care, could not be another type of silver treatment	NR	NR	NR	NR	10.29	3.86, 16.71	Silver treatments more effective than placebo or conservative wound care or non-silver therapies
Silver-impregnated dressing	Carter, 2010	3	Non-silver	NR	NR	NR	NR	0.01	-0.02, 0.05	Not different

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Micronized purified flavonoid fraction	Coleridge-Smith, 2005	5	Control (unspecified)	Reduction of RR 44%	7%, 94%	NR	NR	NR	NR	Micronized purified flavonoid fraction more effective than control
US	Johannsen, 1998	6	UC, placebo	NR	NR	NR	NR	14.50 %	6.6, 22.3	US more effective than UC or placebo
Cadexomer iodine	O'Meara, 2010	2	UC	NR	NR	NR	NR	0.47	0.26, 0.69	Cadexomer iodine more effective than UC*

Note: *these are high quality systematic reviews (AMSTAR ≥8). **Abbreviations:** CI confidence interval, MA meta-analysis, MD mean difference, NR not reported, OR odds ratio, RR relative risk, UC usual care, US ultrasound.

Table 5: Healing outcomes for reviews including pressure ulcers and sores (N=36 meta-analyses)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Ulcers/sores completely healed (25 MAs)										
Collagenase debridement	MAS Ontario, 2009	2	Hydrocolloid occlusive dressing	1.33	0.80, 2.23	NR	NR	NR	NR	Not different
Dextranomer paste	MAS Ontario, 2009	2	Hydrogel dressing	0.88	0.51, 1.53	NR	NR	NR	NR	Not different
Hydrocolloid dressing	MAS Ontario, 2009	4	Traditional dressing	3.84	2.30, 6.41	NR	NR	NR	NR	Hydrocolloid more effective than traditional dressing
	MAS Ontario, 2009	2	Povidine-soaked gauze	0.99	0.71, 1.37	NR	NR	NR	NR	Not different
Hydrocellular dressing	MAS Ontario, 2009	2	Hydrocolloid dressing	1.38	0.78, 2.45	NR	NR	NR	NR	Not different
Hydrogel dressing	MAS Ontario, 2009	2	Hydrocolloid dressing	1.71	1.05, 2.79	NR	NR	NR	NR	Hydrogel more effective than hydrocolloid dressing
Hydropolymer dressing	MAS Ontario, 2009	2	Hydrocolloid dressing	1.1	0.77, 1.59	NR	NR	NR	NR	Not different
Noncontact normothermic dressing	MAS Ontario, 2009	4	UC	1.31	0.86, 1.98	NR	NR	NR	NR	Not different

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Growth factor	MAS Ontario, 2009	4	Placebo	2.29	0.52, 9.98	NR	NR	NR	NR	Not different
	MAS Ontario, 2009	4	Placebo	0.29	0.52, 9.98	NR	NR	NR	NR	Not different
Recombinant PDGF (100mg/ml)	MAS Ontario, 2009	2	Placebo	4.43	0.48, 40.56	NR	NR	NR	NR	Not different
Recombinant PDGF (300 micro g/ml)	MAS Ontario, 2009	2	Placebo	2.17	0.06, 81.31	NR	NR	NR	NR	Not different
Polyurethane foam	MAS Ontario, 2009	3	Hydrocolloid	1.18	0.85, 1.64	NR	NR	NR	NR	Not different
Low-air-loss beds	Cullum, 2001	2	Foam overlay	1.25	0.84, 1.86	NR	NR	NR	NR	Not different*
	MAS Ontario, 2009	2	Foam overlay	1.25	0.84, 1.86	NR	NR	NR	NR	Not different
Nimbus 3 AP mattress	MAS Ontario, 2009	2	Another AP mattress replacement/overlay	0.69	0.18, 2.57	NR	NR	NR	NR	Not different
	MAS Ontario, 2009	4	Another AP mattress in hospital setting	1.4	1.08, 1.80	NR	NR	NR	NR	Nimbus AP more effective than other AP mattresses in hospital

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
										setting
Electrical stimulation	MAS Ontario, 2009	3	Placebo	3.08	0.58, 16.41	NR	NR	NR	NR	Not different
Electromagnetic therapy	MAS Ontario, 2009	3	Sham therapy	3.43	0.35, 33.61	NR	NR	NR	NR	Not different
Low-level laser therapy	MAS Ontario, 2009	3	UC	1.26	0.92, 1.95	NR	NR	NR	NR	Not different
	MAS Ontario, 2009	3	Sham laser	1.17	0.85, 1.63	NR	NR	NR	NR	Not different
US	Cullum, 2001	2	No US	0.97	0.65, 1.45	NR	NR	NR	NR	Not different*
	Sari, 2006	2	Sham US	0.97	0.65, 1.45	NR	NR	NR	NR	Not different*
	MAS Ontario, 2009	2	Sham US	0.97	0.65, 1.45	NR	NR	NR	NR	Not different
Zinc supplement	MAS Ontario, 2009	2	Placebo	0.97	0.22, 4.29	NR	NR	NR	NR	Not different
Healing/improvement of ulcers/sores (7 MAs)										
Hydrocolloid dressings	Bradley, 1999	5	UC	NR	NR	2.57	1.58, 4.18	NR	NR	Hydrocolloid more effective than UC*

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Polyurethane dressings	Bradley, 1999	4	Other dressings	NR	NR	0.8	0.44, 1.44	NR	NR	Not different*
Air-fluidized supports	Cullum, 2008	3	UC	NR	NR	NR	NR	NR	NR	Air-fluidized supports more effective than UC (data NR)
Air-fluidized bed	Cullum, 2004	2	Standard care	1.4	1.04, 1.88	NR	NR	NR	NR	Air-fluidized bed more effective than standard care*
	MAS Ontario, 2009	2	Conventional mattress	1.4	1.04-1.88	NR	NR	NR	NR	Air-fluidized bed more effective than conventional mattress
Alternative foam mattress	Cullum, 2004	5	Standard foam mattress	0.4	0.21, 0.74	NR	NR	NR	NR	Alternative foam more effective than standard foam mattress*
Electrotherapy	Cullum, 2001	2	Sham therapy	7.92	2.39, 26.31	NR	NR	NR	NR	Electrotherapy more effective than sham*
Healing rate of ulcers/sores (3 MAs)										
Debridement agents	Cullum, 2008	32	Other debridement agent	NR	NR	NR	NR	NR	NR	Not different (data NR)
Hydrocolloid dressing	Cullum, 2008	6	Standard dressings	NR	NR	NR	NR	NR	NR	Not different (data NR)
AP mattresses	Cullum, 2008	5	UC	NR	NR	NR	NR	NR	NR	Not different (data NR)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Incidence of pressure ulcers (1 MA)										
Nutritional support	Stratton, 2005	4	UC	NR	NR	0.75	0.62, 0.89	NR	NR	Nutritional support more effective than UC*

Note: *these are high quality systematic reviews (AMSTAR ≥8).**Abbreviations:** AP alternating pressure, CI confidence interval, MA meta-analysis, MAS Medical Advisory Secretariat, MD mean difference, NR not reported, OR odds ratio, PDGF platelet-derived growth factor, RR relative risk, UC usual care, US ultrasound.

Table 6: Healing and hospitalization outcomes for reviews including diabetes ulcers and infections (N=25 meta-analyses)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Ulcers completely healed/resolved (15 MAs)										
Dermagraft	Barber, 2008	3	Standard saline dressings	NR	NR	1.78	0.92, 3.45	NR	NR	Not different
Skin replacement therapy	Blozik, 2008	5	UC	NR	NR	1.46	1.21, 1.76	NR	NR	Skin replacement therapy more effective than UC
Artificial skin graft with standard care	Ho, 2005	9	UC	1.4	1.21, 1.63	NR	NR	NR	NR	Artificial skin graft with standard care more effective than UC alone*
Fibrous-hydrocolloid dressing	Dumville, 2012a	2	Basic wound contact dressing	1.01	0.74, 1.38	NR	NR	NR	NR	Not different*
Foam dressing	Dumville, 2011a	2	Basic wound contact dressing	2.03	0.91, 4.55	NR	NR	NR	NR	Not different*
	Dumville, 2011a	2	Alginate dressing	1.5	0.92, 2.44	NR	NR	NR	NR	Not different*
Alginate dressing	Dumville, 2012b	2	Basic wound contact dressing	1.09	0.66, 1.80	NR	NR	NR	NR	Not different*
	Dumville, 2012b	2	Foam dressing	0.67	0.41, 1.08	NR	NR	NR	NR	Not different*
Hydrogel dressing	Dumville, 2011b	3	Basic wound dressing	1.8	1.27, 2.56	NR	NR	NR	NR	Hydrogel dressing more effective than basic wound dressing*

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
	Edwards, 2012	3	Gauze/UC	1.84	1.30, 2.61	NR	NR	NR	NR	Hydrogel more effective than gauze with UC*
HBOT	Kranke, 2012	3	Hyperbaric air/sham	9.53	0.44, 207.76	NR	NR	NR	NR	Not different*
	Roeckl-Wiedmann, 2005	2	Control	4.78	0.94, 24.24	NR	NR	NR	NR	Not different
G-CSF	Cruciani, 2005	NR	Placebo/UC	NR	NR	NR	NR	NR	NR	Not different (data NR)
PRP	Villela, 2010	4	Control (unspecified)	NR	NR	7.7	2.94, 20.31	NR	NR	PRP more effective than control
CHM plus standard treatment	Chen, 2010	4	UC	0.62	0.39, 0.97	NR	NR	NR	NR	CHM more effective than standard therapy
Ulcer healing/ improvement (3 MA)										
CHM	Chen, 2010	3	UC	0.81	0.71, 0.92	NR	NR	NR	NR	CHM more effective than standard therapy
G-CSF	Cruciani, 2005	NR	Placebo/UC	NR	NR	NR	NR	NR	NR	Not different (data NR)
	Cruciani, 2011	2	Placebo/UC	9.45	0.54, 164.49	NR	NR	NR	NR	Not different*
Ulcer healing rate (1 MA)										
UC	Margolis, 1999	6	UC	NR	NR	NR	NR	30.9 %	26.6, 35.1	Not different

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Non-healing ulcers/no improvement (5 MAs)										
CHM	Chen, 2010	6	UC	0.34	0.21, 0.53	NR	NR	NR	NR	CHM more effective than UC
HA scaffold and keratinocytes	Voigt, 2012	2	UC	0.9	0.76, 1.07	NR	NR	NR	NR	Not different*
HA derivative	Voigt, 2012	2	UC	0.24	0.12, 0.49	NR	NR	NR	NR	HA derivatives more effective than UC*
LFLINU	Voigt, 2011	2	Sharps debridement	0.74	0.58, 0.95	NR	NR	NR	NR	LFLINU more effective than sharps debridement*
LFHICU	Voigt, 2011	2	Sharps debridement	0.64	0.46, 0.89	NR	NR	NR	NR	LFHICU more effective than sharps debridement*
Length of hospitalization (1 MA)										
G-CSF	Cruciani, 2011	2	Control	NR	NR	NR	NR	-1.4 days	-2.27, -0.53	G-CSF more effective than control*

Note: *these are high quality systematic reviews (AMSTAR ≥8).**Abbreviations:** AP alternating pressure, CHM Chinese herbal medicine, CI confidence interval, G-CSF granulocyte-colony stimulating factor, HA hyaluronic acid, HBOT hyperbaric oxygen therapy, LFHICU low frequency high intensity contact ultrasound, LFLINU low frequency low intensity noncontact ultrasound, MA meta-analysis, MD mean difference, NR not reported, OR odds ratio, PRP platelet-rich plasma, RR relative risk, UC usual care, US ultrasound.

Table 7: Healing outcomes for reviews including mixed acute and/or chronic wounds (N=17 meta-analyses)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Number/proportion of wounds healed (10 MAs)										
Hydrocolloid dressing	Bouza, 2005	6	Other modern dressings	1.13	0.86, 1.48	NR	NR	NR	NR	Not different*
	Singh, 2004	12	Conventional dressing	RD 0.02	0.19, 0.02	1.73	1.08, 2.78	NR	NR	Hydrocolloid dressings more effective than conventional dressings
US	Cullum, 2001	4	No US	1.44	1.01, 2.05	NR	NR	NR	NR	Not different*
	Cullum, 2001	4	Sham US	1.18	0.89, 1.54	NR	NR	NR	NR	Not different*
Laser therapy	Cullum, 2001	2	Sham	1.21	0.73, 2.03	NR	NR	NR	NR	Not different*
Low-level laser therapy	Lucas, 2000	3	Placebo or any other intervention	0.76	0.41, 1.40	NR	NR	NR	NR	Not different
Apligraf and UC	Ho, 2005	5	UC	1.71	1.34, 2.17		NR	NR	NR	Apligrafmore effective than UC*
Dermagraft and UC	Ho, 2005	6	UC	1.36	1.11, 1.66	NR	NR	NR	NR	Dermagraftmore effective than UC*
Any artificial skin graft and standard wound care	Ho, 2005	13	UC	1.44	1.22, 1.71	NR	NR	NR	NR	Any artificial skin graft plus standard wound care more effective than UC*

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Autologous platelet-rich plasma	Martinez-Zapata, 2012	4	UC with/ without placebo	1.85	0.76, 4.51	NR	NR	NR	NR	Not different*
Wounds not healed (1 MA)										
Tap water	Fernandez, 2012	2	No cleansing	1.26	0.18, 8.66	NR	NR	NR	NR	Not different*
Time to healing (1 MA)										
Honey	Jull, 2009	3	Control	NR	NR	NR	NR	1.55	-1.91, 5.00	Not different*
Ulcer size/area reduction or epithelialization (5 MAs)										
Silver dressings	Lo, 2009	8	Non-silver dressings	NR	NR	NR	NR	0.28	0.16, 0.39	Silver dressings more effective than non-silver dressings*
Autologous platelet-rich plasma	Martinez-Zapata, 2012	2	UC with/ without placebo	51.78 %	32.70%, 70.86%	NR	NR	NR	NR	Autologous platelet-rich plasma more effective than UC with or without placebo*
	Martinez-Zapata, 2012	3	UC with/ without placebo	NR	NR	NR	NR	-1.94	-4.74, 0.86	Not different*
	Martinez-Zapata, 2008	6	UC	1.4	0.58, 2.31	NR	NR	NR	NR	Not different
Topical negative pressure	Suissa, 2011	9	Standard wound care	0.77	0.63, 0.96	NR	NR	NR	NR	Not different

Note: *these are high quality systematic reviews (AMSTAR ≥8). **Abbreviations:** CI confidence interval, MA meta-analysis, MD mean difference, NR not reported, OR odds ratio, RD risk difference, RR relative risk, UC usual care, US ultrasound.

Table 8: Healing and hospitalization outcomes for reviews including wound infections (N=4 meta-analyses)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Treating infection (2 MAs)										
Fluoroquinolones (without concomitant antibiotics against anaerobics)	Falagas, 2006	14	Beta-lactam	NR	NR	1.29	1.00, 1.66	NR	NR	Fluoroquinolonemore effective than beta-lactam
Ciprofloxacin	Falagas, 2006	8	Beta-lactam (ceftazidime andcefotaxime)	NR	NR	2.49	1.45, 4.26	NR	NR	Ciprofloxacin more effective than beta-lactam
Wound resolution (1 MA)										
Topical negative pressure/vacuum associated closure	Pan, 2010	6	UC	NR	NR	6.43	3.81, 10.85	NR	NR	Topical negative pressure/vacuum associated closure more effective than UC
Length of hospitalization (1 MA)										
Vacuum assisted closure	Damini, 2010	6	UC	NR	NR	NR	NR	-7.18 days	-10.82, -3.54	Vacuum assisted closure more effective than UC

Abbreviations: CI confidence interval, MA meta-analysis, MD mean difference, NR not reported, OR odds ratio, RR relative risk, UC usual care.

Table 9: Healing outcomes for reviews including burns (N=4 meta-analyses)

Intervention	Author, year	# of studies in MA	Comparator	Results of meta-analysis						Conclusion
				RR	(95%CI)	OR	(95%CI)	MD	(95%CI)	
Healing rate (2 MAs)										
GM-CSF	Hu, 2010	2	Placebo	NR	NR	NR	NR	0.84	0.37, 1.3	Not different
GM-CSF on deep second-degree burns	Hu, 2010	2	Placebo	NR	NR	NR	NR	0.96	0.22, 1.69	Not different
Time to healing (2 MAs)										
Honey	Jull, 2009	3	Silver sulfadiazine	NR	NR	NR	NR	-4.37 days	-8.94, 0.19	Honey more effective than silver sulfadiazine*
Honey on partial-thickness burns	Jull, 2009	2	Conventional dressings	NR	NR	NR	NR	-4.68 days	-5.09, -4.28	Honey more effective than conventional dressings*

Note: *these are high quality systematic reviews (AMSTAR ≥8).**Abbreviations:** CI confidence interval, GM-CSF granulocyte-macrophage colony-stimulating factor, MA meta-analysis, MD mean difference, NR not reported, OR odds ratio, RR relative risk.

Table 10: Economic study summary characteristics

Characteristic	# of cost studies (N=104 total)	% of cost studies
Year of publication		
1982-1996	15	14.4
1997-2000	24	23.1
2001-2005	24	23.1
2006-2010	33	31.7
2011-present	8	7.7
Country of conduct		
Europe (22 of these are from the UK)	45	43.3
North America	43	41.3
Asia	9	6.7
Australia& NZ	6	5.8
South America& Caribbean	1	1.0
Study design		
CUA/CEA	12	11.5
CEA	23	22.1
Costing	69	66.3
Sample size*		
10-30	19	18.3
31-50	20	19.2
51-100	19	18.3
101-150	7	6.7
151-200	8	7.7
201-400	13	12.5
>400 (includes 2 RCTs and 2 SRs)	13	12.5
Not reported	5	4.8
Patient population†		
Elderly	62	59.6
Chronic venous disease	29	27.9
Diabetes	22	21.2
Surgical/trauma	12	11.5
Setting		
Inpatient/institutionalized	38	36.6
Outpatient clinic	16	15.4
Home care	19	18.3
Mixed settings	23	22.1
Not reported	8	7.7
Type of wound		
Venous ulcers	29	27.9
Diabetic ulcers/infection	22	21.2
Pressure ulcers	23	22.1
Surgical wounds/infection	12	11.5
Mixed wounds	17	16.3
Other wound infection	1	1.0
Interventions examined†		
Dressings	62	59.6

Characteristic	# of cost studies (N=104 total)	% of cost studies
Cleansers	1	1.0
Bandages/Stockings	6	5.8
Topical negative pressure	7	6.7
Mattresses/off-loading devices	8	7.7
Skin replacement therapy	3	2.9
Other surgical	8	7.7
Oral or IV treatments	8	7.7
Programs/guidelines/systems	24	23.1
Biologic agents	2	1.9
Nutritional/herbal supplementation	3	2.9
Hyperbaric oxygen/other device	8	7.7
Larval therapy	2	1.9
Unspecified	1	1.0
Comparators examined†		
Standard/usual wound care	28	26.9
Placebo	4	3.8
Dressings	38	36.5
Cleansers	0	0
Bandages/Stockings	3	2.9
Topical negative pressure	5	4.8
Mattresses/off-loading devices	6	5.8
Skin replacement therapy	0	0
Other surgical	4	3.8
Oral or IV treatments	5	4.8
Programs/guidelines/systems	7	6.7
Biologic agents	0	0
Nutritional/herbal supplementation	0	0
Hyperbaric oxygen/other device	1	1.0
Unspecified	2	1.9

Notes: *For modeling studies, this refers to the total sample size of the studies that the model data were estimated from, †numbers do not add up to 104 studies or 100%, as the cost studies contributed data to more than one category. **Abbreviations**: IV intravenous, NZ New Zealand, RCT randomized clinical trial, SR systematic review, UK United Kingdom.

Table 11: Results for costing studies (N=69)

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
Gary, US$ 1991	US, 36 weeks	Home air-fluidized bed therapy including nurse specialist	16,415	NR	NR	13,263 [NR]
		UC (included alternating pressure pads, air-support mattresses, water mattresses, and high-density foam pads)	16,800	NR	NR	25,736 [NR]
Mosher, US$ 1995	US, 4 weeks	Collagenase	610.96	NR	NR	NR
		Autolysis	920.73	NR	NR	NR
		Fibrinolysin (fibrinolysin and desoxyribonuclease combined)	986.38	NR	NR	NR
		Wet-to-dry saline dressings (mechanical debridement)	1008.72	NR	NR	NR
Motta, US$ 1999	US, 8 weeks	Polymer hydrogel dressing (FlexigelAcryDerm Sheet)	57.76	19.05	NR	NR
		Hydrocolloid dressing (DuoDERM CGF)	91.48	47.35	NR	NR
Mulder, US$ 1995	US, 4 weeks or until 50% eschar removal	Hypertonic saline hydrogel (Hypergel) plus covered by polyurethane dressing (Alldress)	193.93 [SD88.63]	135.78 [SD 62.06]	NR	NR
		Saline moistened gauze dressing, held by tape (standard wet-to-dry dressing)	NR	NR	NR	NR
Narayanan, US$ 2005	US, until healed	Balsam Peru, hydrogenated castor oil, and trypsin ointment (Xenaderm)	NR	NR	stage 1 ulcers:50.8 [95% CI 47.1-54.4]; stage 2: 58.1 [95% CI 53.5-62.8]	NR
		Balsam Peru, hydrogenated castor oil, and trypsin + other treatments (not necessarily simultaneously used)	NR	NR	stage 1: 54.5 [95% CI 48.9-60.1]; stage 2: 63.4 [95% CI 60.0-66.8]	NR

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
		Other treatments	NR	NR	stage 1: 61.7 [95% CI 58.7-64.7]; stage 2: 62.3 [95% CI 60.7-63.9]	NR
Sanada, Yen 2007	Japan, 3 weeks	Hospital incentive system including wound, ostomy, continence nurses	65,310.5 [SD 36,675.1]	NA	57,277.9 [SD 33,842.9]	NA
		Hospital without incentive system	66,936.6 [SD 60,535]	NA	55,421.8 [SD 56,190.2]	NA
Schulze, £ 2000	Germany, 4 weeks or less	Hydropolymer dressing	125.73	NR	NR	NR
		Alginate dressing plus film dressing	174.09	NR	NR	NR
		Alginate dressing plus sterile swab	142.03	NR	NR	NR
Sebern, US$ 1989	US, 8 weeks	Transparent film dressing	grade II: 845; grade III: 1470	NR	NR	NR
		Gauze	grade II: 1359; grade III: 1412	NR	NR	NR
Shalom, 2008 US$	Israel, 4 weeks (median 12 days)	Homemade negative pressure device	NR	1.35 per day	NR	NR
		Vacuum-assisted closure system	$22 during hospitalization[devices costing $7000–9000]	NR	NR	NR
Shinohara, Yen 2008	Japan, 1 week	Occlusive hydrocolloid dressing	714.9 [SD 262.8]	NR	NR	NR
		Gauze dressing	779.9 [SD 345.3]	NR	NR	NR
Sotto, € 2003-2007	France, tx duration	Guidelines in hospital for management of DFIs	232	NR	NR	NR
		Before implementation of guidelines	823	NR	NR	NR
Stotts, US$ 1997	US, mean 4.2 days	Clean dressings	12.38/dc [SD 5.8]	NR	NR	NR
		Sterile dressings	21.97 [12.8]	NR	NR	NR
Tan, NZ$ 1993	NZ, until healed (range 0-2 weeks)	Zenoderm (semi-occlusive hydrogel)	16.16	NR	NR	NR
		DuoDERM E (occlusive hydrocolloid)	36	NR	NR	NR
Taylor, £ 1987	UK, 12 weeks	4-layer high compression bandage	116.87 [range 52.63–261.74]	NR	62.22 [range 29.25–126.23]	NR
		Standard home care without high compression bandages	240.28 [range 74.65–588.05]	NR	111 [range 41.65–272.83]	NR

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
Terry, US$ 2009	US, NR	Telemedicine with wound care specialist consults	4021.84	NR	NR	NR
		Wound care specialist consults	1937.01	NR	NR	NR
		UC at home	2595.68	NR	NR	NR
Tice, US$ 2005	US, mean 8 days	Ertapenem	355.55 [SD172.8]	NR	NR	NR
		Piperacillin/Tazobactam	502.76 [SD 236.33]	NR	NR	NR
Ukat, € 2003	Germany, 12 weeks	Multilayer elastic compression (Profore) bandage	587	46.37	7	NR
		Short-stretch compression (Comprilin) bandage	1345	19.37	7	NR
Vickery, £ 1993	UK, until healed	District-wide leg ulcer service	15.74/ulcer	NR	NR	NR
		before the leg ulcer service	17.95	NR	NR	NR
Villasin, US$ 1996	US, until healed	Dermagran spray + Dermagran ointment, mean 15 days	104.75 [SE12.92]	4.65 [SE 0.57]	100.1 [SE 12.35]	NR
		Saline spray + topical triple-antibiotic ointment, mean 48 days	323.23 [SD 171.7]	11.23 [SD 5.97]	312 [SD 165.75]	NR
Vogt, € 2007	Denmark, 4 days	Aquacel (occlusive moist) dressing	NR [20.3-48.7]	NR	NR	NR
		Mepore (viscose self-adhesive) dressing	NR [10-11.8]	NR	NR	NR
Wayman, £ 2000	UK, 4 weeks or until debrided	Larval therapy, 3 days	78.64	NR	10.77	NR
		Hydrogel dressing, max. 1 month	136.23	NR	53.85	NR
Wynne, AU$ 2004	Australia, 2-5 days	Dry absorbent dressing (Primapore)	NR	0.52 [IQR 0.52-0.52]	NR	NR
		Hydrocolloid dressing (Duoderm Thin)	NR	3.93 [IQR 3.93-7.86]	NR	NR
		Hydroactive dressing (Opsite)	NR	1.59 [IQR 1.59-3.18]	NR	NR
Xakellis, US$ 1990	US, until healed (median 10 days)	Hydrocolloid dressing	15.58 [25%, 75% 12.04, 30.22]	13.32 [25%, 75%10.27, 25.70]	2.26 [25%, 75%1.78, 4.52]	NR
		Saline gauze dressing	22.65 [25%, 75% 13.54, 53.56]	3.97 [25%, 75% 2.84, 9.46]	18.67 [25%, 75% 10.84, 44.09]	NR
Abidia, £ 2000	UK, 1 year	Hyperbaric oxygen therapy	4972/px	3000	NR	1972/dc
		Hyperbaric air	7946/px	NR	NR	7946/dc
Akagi, US$	Japan, NR	Sterilize surgical wound and change gauze	61.80/ulcer healed	61.80	NR	NR

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
2003		dressing,1 week				
		sterilize surgical wound and change gauze dressing, 2 days	14.70	14.70	NR	NR
Albert, US$ 2008	US, 2 weeks	Negative Pressure Wound Therapy (foam-based dressing)	365.42 [range 152.37, 819.18]	195.25/dc [range 152.37, 359.42)]	NR	NR
		Negative Pressure Wound Therapy (gauze-based dressing)	310.78 [range 282.98, 406.21]	255.75/dc [range 141.49, 310.78]	NR	NR
Apelqvist, SEK 1990	Sweden, until healed/ amputation	Primary ulcer healing without amputation	51000 [range 3000 – 808000]	NR	NR	NR
		Major amputation	390105	NR	NR	NR
		Minor amputation	258320	NR	NR	NR
		Primary amputation	288931	NR	NR	NR
		Re-amputation	445678	NR	NR	NR
		Healing with amputation	344000 [range 27000 – 992000]	NR	NR	NR
Bale, £ 1994	UK, 8 weeks or until healed	Hydrocellular dressing (all ulcers)	2980	NR	NR	NR
		Hydrocolloid dressing (all ulcers)	2692	NR	NR	NR
		Hydrocellular dressing (leg ulcer)	1290	NR	NR	NR
		Hydrocolloid dressing (leg ulcer)	932	NR	NR	NR
		Hydrocellular dressing (pressure ulcer)	844	NR	NR	NR
		Hydrocolloid dressing (pressure ulcer)	1142	NR	NR	NR
		Hydrocellular dressing (other ulcer)	846 [	NR	NR	NR
		Hydrocolloid dressing(other ulcer)	618	NR	NR	NR
Bosanquet, £ 1991	UK, 12 weeks	Hospital-based venous ulcer care clinics	433600/yr	1334.40/yr	NR	NR
		Six community leg ulcer clinics	169000/yr	867.20/yr	NR	NR
Braakenburg, € 2004	Netherlands, until healed	Vacuum-assisted closure, median 16 days	353 [range 113, 1503]	for material 259 [range 86, 1297]	81 [range 21, 282]	NR
		Modern wound dressings (AlgiSite, Cutinova-Foam, Cutinova-Cavity), median 20 days	273 [range 40, 1123]	for materials 94 [range 16, 431]	176 [range 16, 750]	NR
Branom, US$ 2001	US, 8 weeks	Pressure Guard (Constant Force Technology) mattress	1080 (buy mattress)	NR	NR	NR
		Low Air Loss mattress, 8 weeks	1960 (rent mattress)	NR	NR	NR

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
Burgos, Pts 1998	Spain, 12 weeks	Collagenase Ointment (Iruxol)	41488 [95% CI 26191, 56784]	20845 [95% CI 10420, 31269)]	16093/px [95% CI 9977, 24300)]	NR
		Hydrocolloid dressing (Varihesive)	32963 [95%CI 23389, 42538]	20971 [14098, 27845)]	9045/px [95% CI 6874, 11848)]	NR
Cannavo, AU$ 1996	Australia, 38 days (SD 7.8)	Calcium Alginate Dressing	15.25/day	12.94/day	NR	NR
		Sodium Hypochlorite dressing	19.36/day [95%CI 0.35, 8.58)]	11.54/day	NR	NR
		Combined dressing pad	14.14/day [95%CI 5.49, 3.29)]	8.78/day	NR	NR
Capasso, US$ 2003	US, 7 weeks	Wet-to-dry normal saline gauze dressing	3774	133	3641	NR
		Amorphous hydrogel dressing	2634	180	2454	NR
Carls, US$ 2008	US, 1 year prior to ulcer	Podiatric medical care (Commercial insurance)	48318	NR	NR	NR
		No podiatric medical care (Commercial insurance)	61792	NR	NR	NR
		Podiatric care (Medicare)	38668	NR	NR	NR
		No podiatric care (Medicare)	43537	NR	NR	NR
		Amputation (Commercial insurance)	110530	NR	NR	NR
		No amputation (Commercial insurance)	50733	NR	NR	NR
		Amputation (Medicare)	79658	NR	NR	NR
		No amputation (Medicare)	39578	NR	NR	NR
Chang,RM 1997	Malaysia, 8 weeks or until healed	Hydrocellular dressing (DuoDERM CGF)	271.45	NR	45.89	NR
		Saline gauze dressing	173.05	NR	105.30	NR
Cherry, £ 2004	UK, mean 15 weeks	Vibro-Pulse (24-volt cycloidal vibration) and standard compression bandages	1590	180	1140	NR
		Standard dressing and compressive bandaging (no vibration therapy)	9416	1284	8132	NR
Chuangsuwanich, US$ 2011	Thailand, 8 weeks	Silver mesh dressing (Tegaderm)	US$ 263	NR	NR	NR
		Silver sulfadiazine cream	US$ 1812	NR	NR	NR
Clay, US$ 2004	US, 96 hours	IV ceftriaxone and metronidazole	NR	18.71/day	NR	NR
		Ticarcillin/clavulanate potassium	NR	30.56/day	NR	NR
DePalma, US$ 1998	US, 12 weeks	Unna'sboot	901.73 [SD576.45]	160.86 [SD 96.86]	331.37 [SD 255.75]	NR

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
		Theraboot	559.41 [SD290.75]	122.79 [SD 27.59]	201.91 [SD131.17]	NR
Fujimoto, Yen 2007	Japan, NR	Hydrocolloid dressing (Karayahesive)	NR	340	NR	NR
		Conventional gauze and tape dressing	NR	83	NR	NR
Gibbons, US$ 1984 and 1990	US, NR	Team changes emphasizing aggressive surgical limb revascularization	1990: 19594	15981	NR	NR
		Conventional approach (non-aggressive vascular surgical approach)	1984: 21323	19808	NR	NR
Granick, US$ 2003	US, during hospital stay	Wound debridement using Versajet	Net cost savings of 1900/px	NR	NR	NR
		Conventional sharp debridement	3393/procedure	NR	NR	NR
Greer, US$ 1988	US, NR	Air-fluidized therapy support system	16352.80	5760.00	112.80	10480.00
		Conventional hospital bed	23211.50	1080.00	7721.50	14410.00
Hansson, US$ 1994	Sweden, UK, Denmark, Netherlands, 12 weeks	Cadexomer iodine paste	517.30 [range 321.00, 845.90]	7.79/dc (Sweden)	12.00 (nurse - Sweden)	NR
		Hydrocolloid dressing	480.30 [range 96.90, 935.10]	1.63/dc (Sweden)	12.00 (nurse - Sweden)	NR
		Parrafin gauze dressing	581.70 [range 283.80, 1043.50]	0.19/dc (Sweden)	12.00 (nurse - Sweden)	NR
Hiskett, £ 2008	UK, 2 - 74 days	Topical negative pressure in hospital	628.2 [SD671.90]	NR	NR	34/day [SD 2.8]
		Topical negative pressure at home	628.2 [SD 371.10]	NR	NR	45.9/day [SD 17.0]
Horswell, US$ 1999	US, 1 yr	Staged management foot care	4776	NR	NR	NR
		Standard foot care	9402	NR	NR	NR
Hurd, CAN$ 2006	Canada, 1 yr	Comprehensive community wound care	4952	1714	3239	NR
		UC	17575	1204	16371	NR
Junger, DM2008	Germany, until healed	Low-frequency pulsed current (Dermapulse)	13967/ulcer	NN	NR	NR
		Placebo electrostimulation	17425/ulcer	NR	NR	NR
Kerstein, US$ 2000	US, 12 weeks	Saline gauze (pressure ulcer)	NR	92.43	1335.37	NR
		Hydrocolloid C dressing (pressure ulcer)	NR	270.50	509.24	NR
		Hydrocolloid D dressing (pressure ulcer)	NR	260.06	490.50	NR
		Impregnated gauze (venous ulcer)	NR	111.97	1269.07	NR

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
		Hydrocolloid D (venous ulcer)	NR	223.23	937.71	NR
		Human skin construct (venous ulcer)	NR	6130.02	848.57	NR
Kerstein, US$ 2000	US, until healed	Hydrocolloid dressing	4700/ulcer	NR	NR	NR
		Unna's boot	8200/ulcer	NR	NR	NR
		Saline gauze dressing	2500/ulcer	NR	NR	NR
Kerstein, US$ 2000	US, 12 weeks	Hydrocolloid dressing (Protocol D, or DuoDerm)	NR	265	230	NR
		Human skin construct (Apligraf)	NR	7021	138	NR
		Saline gauze dressing	NR	93	560	NR
Kikta, US$ 1998	US, until healed	DuoDermhydroactive dressing (HD)	NR	14.24/week [SD 1.63]	NR	NR
		Unna's boot	NR	11.76/week [SD 0.59]	NR	NR
Lafferty, £ 2011	UK, 20 weeks	Oxyzyme (enzyme containing hydrogel)	NR	85.40/week/ulcer	36.00/hour	NR
		lodozyme (an enzyme containing hydrogel)	NR	85.40	NR	NR
		UC	NR	76.80/week/ulcer	36.00/hour	NR
Lavery, US$ 2007	US, 20 weeks	Negative pressure wound therapy	16733.00	NR	NR	NR
		Wet-to-moist dressing therapy	15258 (1nurse visit/day); 28691 (2 nurse visits/ day)	NR	NR	NR
Levy, ₣ 1996	France, until healed (max. 6 months)	Debridement and dressings	6697	NR	NR	1167
		Debridementwithout dressings	4864	NR	NR	0
		Dressings without debridement	4385	NR	NR	739
Luckraz, US$ 2003	UK, NR	Vacuum-assisted closure (VAC)	16400	NR	NR	NR
		Sternal rewiring and irrigation	20000	NR	NR	NR
McIsaac, CAN$ 2000	Canada, 10 months	Home care wound management protocol	540.38/month	NR	NR	NR
		UC	1487.02/month	NR	NR	NR
McKinnon, US$ 1994	US, until healed	Ampicillin/ Sulbactam	14084	NR	NR	NR
		Imipenem/ Cilaststin	17008	NR	NR	NR
Nasar, £ 1982	UK, NR	Debrisan	1053.05	84.05	NR	969.00
		Eusol and paraffin	1667.00	66.00	NR	1601.00
Nather, SGD 2007	Singapore, 2002 to 2007	Multidisciplinary team with clinical pathway	NR	NR	NR	7698.98
		UC	NR	NR	NR	8847.17

First author, unit† year of costing values*	Country, study duration	Intervention/ Comparator	Total Cost [variation‡]	Intervention Cost [variation‡]	Personnel Cost [variation‡]	Hospital Cost [variation‡]
O'Brien, € 2003	Ireland, 12 weeks	4-layer bandage	NR	NR	99.6 (nurse)	NR
		UC	NR	NR	144.2 (nurse)	NR
O'Brien, US$ 1999	US, NR	Home care wound management	NR [range 145, 300/week]	NR [range 75, 150/week]	54/nurse visit	16/office visit
		Formal health facility care as an inpatient	NR [range 2800, 6300/week]	NR	NR	NR
Ohlsson, SEK 1994	Sweden, 6 weeks	Hydrocolloidal dressing (DuoDERM)	1565	653	912	NR
		Saline soaked gauze dressing	4126	608	3518	NR
Perez, HTG 2010	Haiti, until healed	Wet dressing (0.9% saline soaked gauze)	271 [range 264, 284]	50 [range 23, 58]	105 [range 97, 119]	121 [range 118, 132]
		Homemadewound vacuum-dressing system	360 [range 343, 370]	81 [range 62, 101]	188 [range 178, 198]	83 [range 72, 97]
Philbeck Jr., US$ 1999	US, NR	Low-air-loss therapy	23465	NR	NR	NR
		Negative pressure wound therapy	14546	NR	NR	NR
Rerkasem, US$ 2009	Thailand, until healed	Diabetic foot protocol	1127.02 [SE1762.51]	NR	NR	NR
		UC	1824.58 [SE 2239.3]	NR	NR	NR
Robson, US$ 2009	US, 5 weeks	Recombinant basic fibroblast growth factor	2200/ulcer	NR	NR	NR
		Placebo	3000/ulcer	NR	NR	NR
Seretariat, CAN$	Canada, NR	Hyperbaric oxygen therapy	6200/tx	NR	NR	NR
		Amputation	60000/tx	NR	NR	NR

Notes:*Publication date is used where year of values was not reported in the publication, †units are average cost per patient for the study period (unless otherwise noted), ‡variation is blank if not reported by the study authors. **Abbreviations:** AU Australia, CI confidence interval, dc dressing change, DFI diabetic foot infection, DM Deutsche Mark, HTG Haitian Gourde, IQR interquartile range, IV intravenous, MAX maximum,NR not reported, NZ New Zealand, Pts Spanish Peseta, px patient, RM Ringgit Malaysia, SD standard deviation, SE standard error, SEK Swedish Kronor, SGD Singapore Dollar, tx treatment,UK United Kingdom, UC usual care, US United States, yr year.

Table 12: Cost-effectiveness/cost-utility analyses methodological quality

STUDY	Q1 (well-defined)	Q2 (alter-natives)	Q3 (effective-ness)	Q4 (all costs)	Q5 (measure-ment)	Q6 (valuat-ion)	Q7 (discount-ing)	Q8 (incre-mental)	Q9 (sensitivity)	Q10 (discussion)	TOTAL # Yes
Apelqvist 2008	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	**9**
Apelqvist 1996	Y	Y	N	Y	Y	Y	NA	Y	Y	N	**7**
Augustin 1999	Y	Y	N	Y	Y	Y	Y	Y	N	Y	**8**
Chuck 2008	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	**9**
Clegg 2007	Y	N	N	Y	Y	Y	NA	Y	Y	N	**6**
Colwell 1993	Y	Y	N	Y	Y	Y	NA	N	N	Y	**6**
Dumville 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Edmonds 1999	Y	Y	N	Y	Y	Y	Y	Y	N	Y	**8**
Ferrell 1995	Y	Y	N	N	Y	Y	Y	Y	Y	Y	**8**
Foglia 2012	Y	N	N	N	Y	Y	Y	Y	Y	Y	**7**
Glinski 1999	Y	Y	N	Y	Y	Y	Y	Y	N	N	**7**
Gordon 2006	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	**9**
Graumlich 2003	Y	Y	N	N	Y	Y	Y	Y	Y	N	**7**
Guest 2012	Y	N	N	Y	Y	Y	Y	Y	Y	Y	**8**
Guo 2003	Y	N	N	N	Y	Y	Y	Y	Y	Y	**7**
Habacher 2007	Y	N	N	Y	Y	Y	Y	Y	Y	Y	**8**
Harris 2008	Y	Y	N	N	Y	Y	N	Y	N	N	**5**
Iglesias 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Iglesias 2004	Y	Y	Y	N	Y	Y	Y	Y	Y	N	**8**
Jansen 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Jeffcoate 2009	Y	Y	N	Y	Y	Y	NA	Y	N	Y	**7**
Jull 2008	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	**8**
Michaels 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**10**
Morrell 1998	Y	Y	Y	N	Y	Y	N	Y	Y	Y	**8**
Muller 2001	Y	Y	N	Y	Y	Y	NA	Y	Y	N	**7**
O'Brien 2003	Y	Y	Y	Y	Y	Y	NA	Y	N	N	**7**
Oien 2001	Y	Y	N	Y	Y	Y	NA	Y	N	Y	**7**
Patanwala 2007	Y	Y	N	Y	Y	Y	Y	Y	Y	N	**8**
Payne 2009	Y	Y	N	N	Y	Y	Y	Y	Y	N	**7**
Persson 2000	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	**9**
Piaggesi 2007	Y	Y	N	N	Y	Y	NA	Y	N	Y	**6**
Sibbald 2001	Y	Y	N	Y	Y	Y	NA	Y	Y	Y	**8**
Ubbink 2008	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	**8**
Vu 2007	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	**9**
Watson 2011	Y	Y	N	Y	Y	Y	Y	Y	Y	N	**8**

Table 13: Cost-effectiveness/cost-utility analyses results for venous ulcers (N=14)

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators							Conclusion
		Traditional home based treatment	Pinch grafting in hospital	Standard compression with external treatments	Short-stretch high compression bandages	Four-layer high compression bandages	Vaseline gauze dressing	Standard debride-ment (Hydrogel)	
Ulcer clinics using four-layer high compression bandaging	Morrell et al. (CEA, UK, £, 1995, health-care system, 233, 1 year[b])	For a gain of an additional week without an ulcer, it costs an extra £2.46 per px (ICER: £2.46 per ulcer-free week gained)							Intervention was more effective yet more costly than usual care*
Pinch grafting surgery conducted in primary care	Oien et al. (CEA, Sweden, £, 1997, NR, 58, 12 weeks)		Intervention was significantly less costly (£3876 saved per px healed) with similar healing rate (31%)						Intervention had similar effectiveness & was less costly compared to pinch grafting in hospital
Micronised Purified Flavonoid Fraction plus standard therapy	Glinski et al. (CEA, Poland, €, 1998, healthcare system, 140, 24 weeks)			ICER: - €849.58 per ulcer healed					Intervention was more effective &less costly than conventional care alone
Low-dose ultrasound plus standard care	Watson et al. (CUA/CEA, UK, £, 2007, healthcare system, 337, 12			No statistically significant difference in healing rates					Intervention had similar effectiveness and was more costly compared to standard care alone

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators							Conclusion
		Traditional home based treatment	Pinch grafting in hospital	Standard compression with external treatments	Short-stretch high compression bandages	Four-layer high compression bandages	Vaseline gauze dressing	Standard debride-ment (Hydrogel)	
	weeks[b])			or QoL					
Skin protectant DBC[c] plus compression with dressings; vs. skin protectant NSFB[d] plus compression with dressings	Guest et al. (CUA/CEA, UK, £, 2009/ 2010, health-care system, 510, 6 months[b])			NSFB had statistically greater reduction in wound size. DBC had no statistically significant differences from control group					NSFB was more effective &had similar costs than the other 2 groups. DBC had similar costs & similar effectiveness to comparator
Pentoxifylline plus usual care[e]	Iglesias & Claxton (CUA/CEA, UK, £, 2004, healthcare system, 434, 1 year)			Intervention had £98 cost savings and 6.55 ulcer-free weeks gained per px					Intervention was more effective &less costly than the comparator*
Four-layer high compression bandages	Iglesias et al. (CUA/CEA, UK, £, 2001, healthcare system, 387, 1 year)				Intervention group had a significantly higher probability of healing				Intervention was more effective and less costly than the comparator*
	O'Brien et al. (CEA, Ireland, €, NR[f], health-care system, 200, 12 weeks)			Intervention had 20% better healing rate and €25 cost savings per px					Intervention was more effective and less costly than the comparator*

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators							Conclusion
		Traditional home based treatment	Pinch grafting in hospital	Standard compression with external treatments	Short-stretch high compression bandages	Four-layer high compression bandages	Vaseline gauze dressing	Standard debride-ment (Hydrogel)	
Calcium alginate dressings with manuka honey (ApiNate UMF 12+) plus compression bandaging	Jull et al. (CEA, New Zealand, NZ$, NR[g], health-care system, 368, 12 weeks)			No statistically significant differences in healing outcomes. Intervention was less[h] costly (by NZ$55.68 per px)					Intervention had similar effectiveness compared to usual care & cost analysis was inconclusive[h]*
Silver antimicrobial dressings plus compression bandages	Michaels et al. (CUA/CEA, UK, £, 2007, healthcare system, 213, 12 weeks[b])			ICER: £489,250 per QALY gained					Intervention had similar effectiveness &was more costly compared to low-adherence dressings plus compression bandages*
Skin substitute (Apligraf) plus four-layer high compression bandage	Sibbald et al. (CEA, Canada, CAN$, 1996-1997, society, 293[i], 3 months)					For a gain of an additional day without an ulcer, it costs an extra $14 per px (ICER: $14 per ulcer-free day gained)			Intervention was more effective yet more costly than comparator alone
Hydrocolloid dressing (Comfheel or	Augustin (CUA/CEA, Germany, DM,						Interventio n had DM1139		Intervention had similar effectiveness &was less costly

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators							Conclusion
		Traditional home based treatment	Pinch grafting in hospital	Standard compression with external treatments	Short-stretch high compression bandages	Four-layer high compression bandages	Vaseline gauze dressing	Standard debride-ment (Hydrogel)	
Varihesive)	NR[j], NR, 25, 6 months)						cost savings per px		compared to Vaseline gauze
Larval therapy[k]	Dumville et al. (CUA/ CEA, UK, £, 2006, health-care system, 267, 6-12 months)							Intervention had similar health outcomes (but debrided faster)	Intervention had similar effectiveness &similar costs compared to Hydrogel debridement*
Lindsay Leg Club model[l]	Gordon et al. (CEA, Australia, €, 2005, society, 56, 6 months)	For a gain of an additional ulcer healed, it costs an extra €318 (ICER: €318 per ulcer healed)							Intervention was more effective yet more costly than home nursing

Notes:[a]For modeling studies, this refers to the total sample size of the studies that the model data were estimated from, [b]Or less (i.e. until wound healed), [c]Cavilon Durable Barrier Cream (DBC), [d]Cavilon No Sting Barrier Film (NSBF), [e]The comparator also included a placebo, [f]Trial conducted in 1999-2000; publication date 2003, [g]Trial conducted in 2004-2005; publication date 2008, [h]Mean total cost was less for Intervention group due to 3 fewer hospitalizations but Authors concluded Intervention was probably generally more expensive, [i]The RCT included in the model was not directly comparable, [j]Publication date 1999, [k]Cost-effectiveness was reported for pooled loose & bagged groups, [l]Ulcer care provided in an informal 'drop-in' centre promoting social interaction, *Denotes from a higher quality CEA/CUA. **Abbreviations:** CAN Canadian, CEA cost-effectiveness analysis, CUA cost-utility analysis, DM Deutsche Marks, ICER incremental cost-effectiveness ratio, NR not reported, NZ New Zealand, PX patient, QALY quality-adjusted life year, QoL quality of life, UK United Kingdom.

Table 14: Cost-effectiveness/cost-utility analyses results for pressure ulcers (N=7)

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators					Conclusion
		Moist gauze dressing (saline)	Conventional foam mattress	Conventional simple and saline dressings	Hydrocolloid (DuoDerm)	Usual nursing care	
Hydrocolloid wafer dressing (DuoDERM CGF)	Colwell et al. (CEA, USA, US$, 1989-1990, NR, 94, mean 17 days[b])	Intervention saved nursing time due to less frequent dressing changes					Intervention was more effective & less costly than saline gauze
Low-Air-Loss Bed (Kinair Bed)	Ferrell et al. (CEA, USA, US$, 1992, provider, 84, median 33 & 40 days per group)		For mild ulcers and good healing characteristics, to gain an additional day without an ulcer it costs an extra$26 (in 1st year)				Intervention was more effective & more costly than Comparator
Advanced dressings	Foglia et al. (CEA, Italy, €, 2010, healthcare system, 362, 30 days)			Intervention group had a greater reduction in ulcer size (an additional 6% decrease)			Intervention was more effective & less costly than conventional simple dressings
Type I collagen (Medifil, Kollagen)	Graumlich et al. (CEA, USA, US$, 2001, provider, 65, 8 weeks[c])				No statistically significant differences in healing outcomes		Intervention had similar effectiveness yet was more costly compared to Hydrocolloid
Self-adhesive polyurethane foam dressing (Allevyn Thin)	Payne et al. (CEA, USA, US$, 2006-2007, health-care system, 36, 4 weeks[c])	Intervention saved $118/ week per px compared to Comparator (95% CI: $13, $223)					Intervention had similar effectiveness & was less costly compared to saline gauze

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators					Conclusion
		Moist gauze dressing (saline)	Conventional foam mattress	Conventional simple and saline dressings	Hydrocolloid (DuoDerm)	Usual nursing care	
Collagenase containing ointment (Novuxol) plus paraffin gauze (Jelonet) and absorbent bandages after saline	Muller et al. (CEA, The Netherlands, NLG, 1998, provider, 24, mean 11 & 14 days per group)				11 of 12 patients were completely healed in Intervention group versus 7 of 11 in Comparator group		Intervention was more effective & less costly than Hydrocolloid
Multi-disciplinary community wound care team[d,e]	Vu et al. (CEA, Australia, AU$, 2000, healthcare system, 176[f], max. 6 months)					The cost of training of AU$14.2 per wound was offset by a saving of AU$263.7 per wound	Intervention was more effective & less costly than usual nursing care*

Notes: [a]For modeling studies, this refers to the total sample size of the studies that the model data were estimated from, [b]Range: 8-56 days, [c]Or less (i.e. until wound healed), [d]Most patients had pressure ulcers (78% & 75% in Intervention & Comparator groups, respectively) and the rest had uncomplicated leg ulcers, [e]Consisting of trained community pharmacists and nurses who undertook a wound management training course and applied a standardized treatment protocol developed for the study. Nurses and pharmacists in the control arm received no wound care training and the pharmacists were not involved in wound management, [f]176 participants with 342 total ulcers studied, *Denotes from a higher quality CEA/CUA. **Abbreviations:** AU Australian, CEA cost-effectiveness analysis, CI confidence interval, max maximum, NLG Dutch Guilders, NR not reported, px patient, US United States, USA United States of America.

Table 15: Cost-effectiveness/cost-utility analyses results for surgical wounds (N=3)

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators			Conclusion
		Standard moist wound therapy (alginates, hydrocolloids, foams, or hydrogels)	Gauze dressings (dry, moist, or paraffin gauzes)	IV vancomycin during hospitalization and after discharge: 11 d. in hospital and 3 d. after discharge	
Negative pressure wound therapy (Vacuum-Assisted Closure System)	Apelqvist et al. (CEA, US, US$, 2005, health-care system, 162, 16 weeks max.[b])	Intervention had a statistically significant higher proportion of wounds healed versus Comparator (55.8% vs. 38.8%)			Intervention was more effective & less costly than moist wound therapy
Occlusive moist-environment, nongauze-based materials (foams, alginates, hydrogels, hydrocolloids, hydrofibers, and films)	Ubbink et al. (CEA, The Netherlands, US$, 2005, NR, 285[c], 6 months[b])[d]		Intervention had higher total cost for local wound care per patient per day during hospitalization versus Comparator (US$11.74 vs. US$6.25)		Intervention had similar effectiveness yet was more costly compared to gauze dressings*
Intervention A - Oral linezolid during hosp-italization and after discharge: 8 d. in hospital and 6 d. after discharge. Intervention B - IV vancomycin during hospital-	Patanwala et al. (CEA, US, US$, provider, 2006, 41, 14 days total)			Intervention A was the most cost-effective. Intervention B (IV vancomycin during hospitalization followed by oral linezolid after discharge) would be was the most cost-effective only if the length of hospitalization was less than 6 days or if the probability of cure with oral	Oral linezolid during hospitalization and after discharge (Intervention A) was the most cost-effective of the 3 groups. The Comparator (IV vanco-mycin during hospital-ization and after discharge) was the least cost-effective of the 3 groups.

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators			Conclusion
		Standard moist wound therapy (alginates, hydrocolloids, foams, or hydrogels)	Gauze dressings (dry, moist, or paraffin gauzes)	IV vancomycin during hospitalization and after discharge: 11 d. in hospital and 3 d. after discharge	
ization followed by oral linezolid after discharge: 8 d. in hospital and 6 d. after discharge.				linezolid (Intervention A) was less than or equal to 72%.	

Notes: [a]For modeling studies, this refers to the total sample size of the studies that the model data were estimated from, [b]Or less (i.e. until wound healed), [c]285 participants with 417 total wounds studied, [d]Most patients had surgical wounds (62% were postoperative wounds, 24% were from trauma, and 14% chronic wounds), *Denotes from a higher quality CEA/CUA. **Abbreviations:** CEA cost-effectiveness analysis, d days, IV intravenous, max maximum, NR not reported, US United States.

Table 16: Cost-effectiveness/cost-utility analyses results for diabetic ulcers (N=9)

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators						Conclusion
		Standard care	Standard dressings (gentamicin solution, streptodornase/streptokinase, or dry saline gauze)	Non-adherent, knitted, viscose filament gauze (N-A)	Total contact casting (TCC; standard off-loading device)	Piperacillin/ Tazobactam	Placebo, (plus combination of 4 IV antibiotics: ceftazidime, amoxicillin, flucloxacillin and metronidazole)	
Hyperbaric oxygen therapy (HBOT) plus standard care	Chuck et al. (CUA/CEA, Canada, CAN$, 2004, healthcare system, 305, 12 years)	Intervention saved CAN$9,091 compared to standard care alone (over 12 years)						Intervention was more effective & less costly than the comparator*
	Guo et al. (CUA/CEA, US, US$, 2001, society, 126, 12 years[c])	ICERs at years 1, 5, and 12 were: US$27,310, US$5,166 & US$2,255 per QALY gained, respectively[d]						Intervention was more effective yet more costly than standard care alone. Intervention was more cost-effective† in the longer-term (more than 1 year).
Cadexomer iodine ointment (Iodosorb)	ApelqvistRagnarsonTennvall (CEA, Sweden, SEK, 1993, society, 41, 12 weeks[b])		Intervention saved SEK418 per week compared to standard dressings					Intervention had similar effectiveness & was less costly compared to Comparator
Intensified treatment in a specialized	Habacher et al. (CEA, Austria, €, 2001, society, 86[e],	Intervention group had fewer						Intervention was more effective & less

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators						Conclusion
		Standard care	Standard dressings (gentamicin solution, streptodornase/streptokinase, or dry saline gauze)	Non-adherent, knitted, viscose filament gauze (N-A)	Total contact casting (TCC; standard off-loading device)	Piperacillin/ Tazobactam	Placebo, (plus combination of 4 IV antibiotics: ceftazidime, amoxicillin, flucloxacillin and metronidazole)	
outpatient hospital department	15 years[c])	amputations and longer life expectancy						costly than standard care
Intervention A: A hydrocolloid dressing (Aquacel) Intervention B: A modern iodine antiseptic (Inadine)	Jeffcoate et al. (CUA/CEA, UK, £, 2007, healthcare system, 317, 24 weeks)			Intervention A (hydrocolloid) was the most costly. Nearly 70% of the dressing changes were undertaken by non-professionals in this study				All 3 groups had similar effectiveness. Intervention A (hydrocolloid) was the most costly. Comparator (non-adherent gauze) was the least costly.
Becaplermin gel (Regranex), containing recombinant human platelet derived growth factor, plus standard care	Persson et al. (CEA, Sweden, US$, 1999, NR, 194, 12 months[f])	Intervention had 42% of patients with healed ulcer versus 30% with Comparator (20-week healing rate)						Intervention was more effective & less costly than good wound care alone*
Optima Diab walker (non-removeable off-loading device; off-the-shelf "instant"	Piaggesi et al. (CEA, Italy, €, NR[g], NR, 40, 12 weeks)				Intervention reduced cost of treatment by 78% compared to			Intervention had similar effectiveness & was less costly compared to

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators						Conclusion
		Standard care	Standard dressings (gentamicin solution, streptodornase/streptokinase, or dry saline gauze)	Non-adherent, knitted, viscose filament gauze (N-A)	Total contact casting (TCC; standard off-loading device)	Piperacillin/ Tazobactam	Placebo, (plus combination of 4 IV antibiotics: ceftazidime, amoxicillin, flucloxacillin and metronidazole)	
TCC)					Comparator			standard total contact casting
Diabetic Foot Infections:								
Ertapenem	Jansen et al. (CUA/CEA, UK, £, 2006, healthcare system, 402, 1 month[h])					The model's (estimated) results found that any difference in AMR over time with the 2 groups will likely result in increasing CE favouring Ertapenem.		Intervention was more effective & less costly than Comparator*
Filgrastim, (plus combination of 4 IV antibiotics: ceftazidime, amoxicillin, flucloxacillin and metronidazole)	Edmonds et al. (CEA, UK, £, 1996, provider, 40, range 7-15 days)						Intervention saved £2666 (36%) compared to Comparator	Intervention was more effective & less costly than placebo (plus antibiotics)

Notes:[a]For modeling studies, this refers to the total sample size of the studies that the model data were estimated from, [b]Or until stoppedexudating, at which time vaseline gauze was used, [c]Or less (i.e. until wound healed or amputation), [d]There were an average of 29 HBOT treatments, [e]86 participants with 119 total wounds studied, [f]Extrapolated from treatment duration of up to 5 months (which was the limit of indicated use), [g]Trial conducted in 2005; publication date 2007, [h]Or less (i.e. until infection cured or treatment failure). Average was 11 days treatment, *Denotes from a higher quality CEA/CUA, †Using a conservative cost-effectiveness "threshold" of ≤$20,000 per QALY gained.

Abbreviations: AMRantimicrobial resistance, CAN Canadian, CE cost-effectiveness, CEA cost-effectiveness analysis, CUA cost-utility analysis, HBOT hyperbaric oxygen therapy, ICER incremental cost-effectiveness ratio, IV intravenous, NR not reported, QALY quality-adjusted life year, SEK Swedish Krona, TCC total contact casting, UK United Kingdom, US United States.

Table 17: Cost-effectiveness/cost-utility analyses results for mixed acute and/or chronic ulcers (N=2)

Interventions	Study (study type, country, currency, year of values, perspective, sample size[a], duration/ horizon)	Comparators		Conclusion
		Standard care	Hybrid nursing care model[b]	
Chronic Non-Healing Wounds (11 venous, 9 pressure, & 1 trauma):				
Bio-electric stimulation therapy (Posifect)	Clegg & Guest (CUA/ CEA, UK, £, 2005/2006, healthcare system, 18, 16 weeks)	Intervention group had 33% of wounds healed versus Comparator (previous standard care) which had none healed for at least the past 6 months		Intervention was more effective & less costly than patients' previous standard care
Chronic & Acute Wounds (360 various chronic wounds & 54 acute surgical wounds):				
Specialty ET/AWOS nursing agency only[c]	Harris & Shannon (CEA, Canada, CAN$, 2005, NR, 414, until DC from homecare)		For chronic wounds: Intervention group healed 45 days faster than Comparator group	For chronic wounds: Intervention was more effective & less costly than Hybrid nursing care model. For acute wounds: within the Hybrid model, over 50% involvement by ET/AWOS was more cost-effective compared to less than 50% involvement by ET/AWOS.

Notes:[a]For modeling studies, this refers to the total sample size of the studies that the model data were estimated from, [b]Specialty ET nursing agency (i.e. with ET nurses and RNs with AWOS) coordinated visits with RN and RPN visiting nurses from other community nursing agencies, [c]Patients were seen exclusively by the specialty agency. **Abbreviations:** AWOS advanced wound and ostomy skills, CAN Canadian, CEA cost-effectiveness analysis, CUA cost-utility analysis, DC discharged, ET enterostomal, NR not reported, RN registered nurse, RPN registered practical nurse, UK United Kingdom.

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Appendix 1: Description of interventions

Apligraf – type of artificial skin graft consisting of a dermal layer of human fibroblasts in type 1 bovine collagen with an epidermal layer formed by human keratinocytes

Autologous platelet rich plasma – blood plasma obtained from a blood sample from the patient containing fibrin and high concentrations of growth factors

Cryopreserved allografts – frozen bioengineered skin grown from donor cells

Dermagraft – type of artificial skin graft consisting of a dermal layer of human neonatal fibroblasts

Granulocyte-macrophage colony-stimulating factor (GM-CSF)–type of topical cream that binds to stem cells and most myelocytes, stimulating wound healing

Intermittent pneumatic compression – medical device that applies compression treatment to the wound by expanding with air

Micronized purified flavonoid - edema-protective agent consisting of 90%diosmin and 10% flavonoids expressed as hesperidin

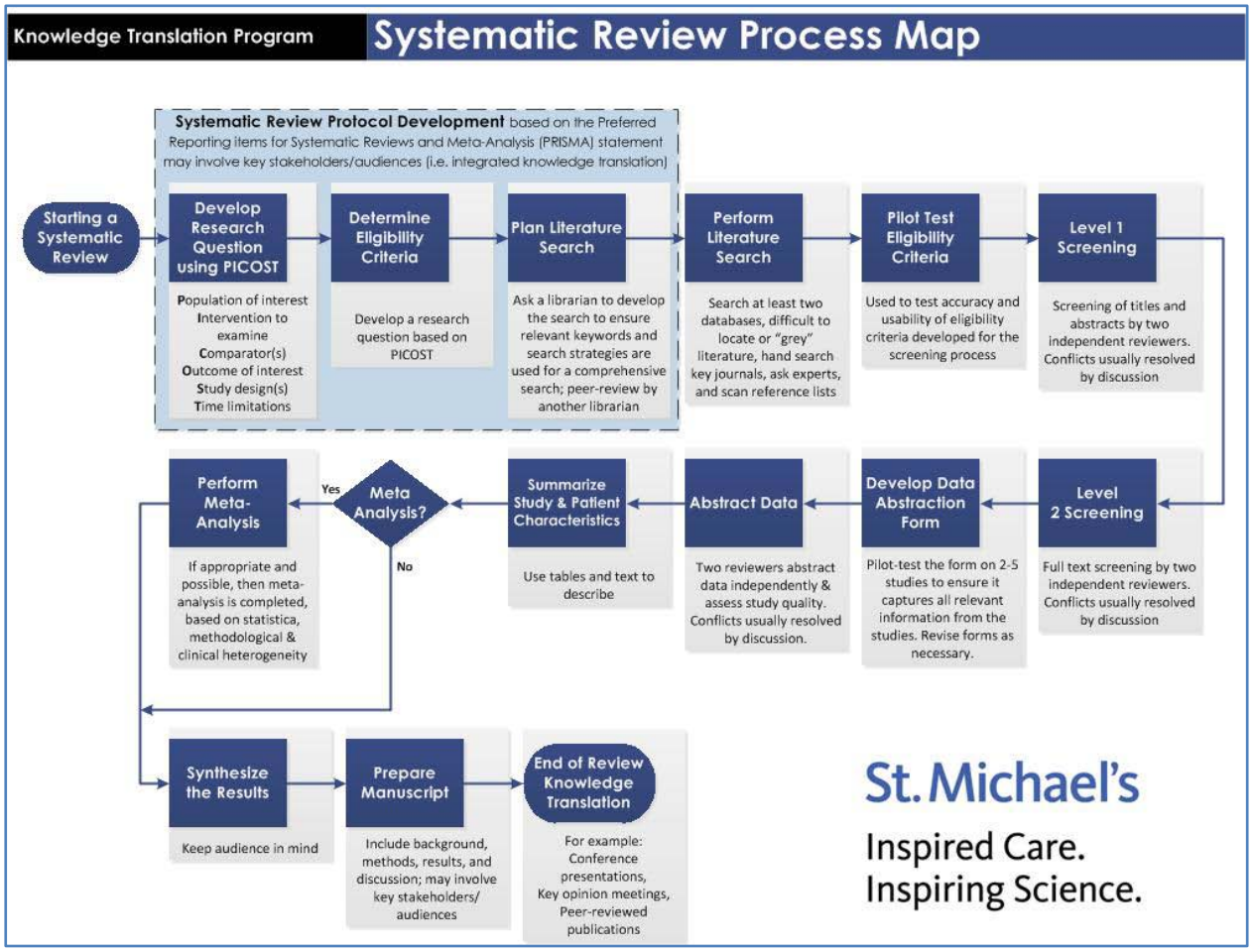
Recombinant human platelet-derived growth factor – B chain dimeric protein available as a sodium carboxymethycellulose-based gel that promotes the growth of tissue at the wound site using recombinant DNA technology

Topical negative pressure (TNP) – medical devices that can be used to apply localized negative pressure to the wound

Unna's boot – type of paste bandageimpregnated with glycerine, calamine lotion, and zinc oxide

Vacuum assisted closure (VAC) – type of medical device that applies controlled, localized negative pressure to the wound

Appendix 2: Scoping review approach



Note: The scoping review entails all steps until the meta-analysis.

Appendix 3: Search strategy for the MEDLINE database

1 Pressure Ulcer/ [Wound terms]

2 (pressureadj ulcer$).tw.

3 (pressureadj sore$).tw.

4 (decubitusadj ulcer$).tw.

5 (decubitusadj sore$).tw.

6 (bedadj ulcer$).tw.

7 (bedadj sore$).tw.

8 Surgical Wound Infection/

9 Surgical Wound Dehiscence/

10 (surg$ adj2 wound$).tw.

11 (surg$ adj infect$).tw.

12 (surg$ adj2 dehiscence).tw.

13 (arterial adj2 ulcer$).tw.

14 (ischemicadj ulcer$).tw.

15 (neuropathicadj ulcer$).tw.

16 (vascul$ adj ulcer$).tw.

17 Varicose Ulcer/

18 (varicoseadj ulcer$).tw.

19 (venous adj2 ulcer$).tw.

20 (stasisadj ulcer$).tw.

21 Skin Ulcer/

22 exp Foot Ulcer/

23 (footadj ulcer$).tw.

24 Leg Ulcer/

25 (legadj ulcer$).tw.

26 (diabeticadj foot).tw.

27 (diabeticadj feet).tw.

28 (cruraladj ulcer$).tw.

29 (ulcusadjcruris).tw.

30 (chronicadj wound$).tw.

31 (chronicadj sore$).tw.

32 (chronicadj ulcer$).tw.

33 or/1-32

34 exp Adult/ [adult search filter - validated]

35 adult.mp.

36 Middle Aged/

37 age$.tw.

38 or/34-37

39 meta analysis.mp,pt. [systematic review filter - validated]

40 review.pt.

41 search$.tw.

42 or/39-41 (1912330)

43 cost$.mp. [economics filter - validated]

44 cost benefit analys$.mp.

45 health care costs.mp.

46 or/43-45

47 42 or 46

48 33 and 38 and 47

49 exp Animals/ not (exp Animals/ and Humans/)

50 48 not 49

Appendix 4: Screening criteria for titles and abstracts (level 1 screening)

Question 1

This report is a

a.systematic review/economic protocol
b.conference abstract
c.letter to the editor without data
d.non-English article

Please indicate if the report fulfills the study eligibility criteria BUT is a study protocol (i.e. from Cochrane, PROSPERO, registries), a conference proceeding/abstract, a letter to the editor or a non-English article.

Note: *If none of the above, please leave unanswered.*

Question 2

Is this a systematic review (according to the Cochrane Collaboration definition) or a health economics study?

Systematic review - A review of a clearly formulated question that uses systematic and explicit methods to identify (e.g. search multiple databases), select (e.g. screen for inclusion), collect and critically appraise relevant research. Statistical methods (e.g. meta-analysis) may or may not be used to analyse and summarize the results of the included studies [The Cochrane Handbook – www.cochrane-handbook.org].

Note:*Quality appraisal or statistical analysis is not necessary for inclusion; however, reportMUSTbea review or synthesis of evidence AND include a description of the methods.*

Health Economics– include all economic analyses comparing the relationship between costs and outcomes of healthcare interventions. Examples include cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis. We will also include costing studies.

Note: *Only include study if there is a focus on cost. Exclude case-series, case reports or studies that do not have an adequate comparison group.*

Costing study – examines costing data associated with providing an intervention

Cost-benefit analysis – converts effects into the same monetary terms as costs and compares them

Cost-effectiveness analysis – views effects in terms of overall health specific to the problem, and describes the costs for some additional health gain (e.g. cost per additional stroke prevented)

Cost-utility analysis – expresses effects as overall health improvement and describes how much it costs for some additional utility gain (e.g. cost per additional quality-adjusted life-year)

Definitions from the Cochrane Collaboration Glossary at http://www.cochrane.org/glossary/5#letterc

Note:*For citations with NO ABSTRACTS, there must be some indication in the title that the report is a systematic review or costing study AND is related to wound care to be included.*

Question 3

Does the report include adult patients in need of wound care?

Note:*This is a mandatory question.*

Adult patients – aged 16 years and older.***Note:*** *Exclude studies ONLY looking at children or animals.*

Patients in need of wound care – including those with pressure ulcers (e.g. decubitus ulcers, bed sores), post-surgical wounds (e.g. incisions, surgical dehiscence, surgical infections), wounds due tochronic disease (e.g. arterial and venous ulcers, diabetic foot, pyodermagangrenosum) and non-superficial burns (e.g. deep dermal burn, burn infections).

Note: *We will include patients with a variety of wounds, sores, ulcers and/or burns; however we will exclude superficial burns, anal fissures, and hemorrhoids).*

Question 4

Does this report examine an intervention or a care program to treat wounds?

We are EXCLUDING diagnosing wounds, preventing wounds, assessing wounds, prognosis of wounds, epidemiology of wounds, incidence of wounds, prevalence of wounds, and frequency of wounds. Instead, we are focusing on the **management and treatment** of wounds.

Note: *If report is a review or costing study of both prevention AND treatment, we will include.*

Potential interventions include:

Pharmacological agents - e.g. topical agents.

Non-pharmacological agents - e.g. dressing, vacuum, honey, hyperbaric therapy.

Wound care programs – e.g. care management, self-management or other quality improvement interventions (see box below).

> **Case management** - is a QI strategy involving coordinating diagnosis, treatment, or ongoing patient management (e.g., arrangement for referrals, follow-up of test results) by a person or multi-disciplinary team in collaboration with or supplementary to the primary care clinician. In order for a trial to qualify as case management, it has to be ongoing (i.e. occur more than once). Usually these studies involved less involvement compared with team changes (i.e. case manager does not have to speak with primary care physician). If the study called the intervention "case management" we will classify it as such.
>
> **Team changes** - is a QI strategy involving changes to the structure or organization of the primary health care team, defined as present if any of the following applied:
>
> - Adding a team member or "shared care," i.e. routine visits with personnel other than the primary physician (including physician or nurse specialists in diabetic care, pharmacists, nutritionists, podiatrists).
> - Use of multidisciplinary teams, i.e. active participation of professionals from more

than 1 discipline (i.e. medicine, nursing, pharmacy, nutrition) in the primary, ongoing management of patients.
- Expansion or revision of professional roles (e.g., nurse or pharmacist plays more active role in patient monitoring or adjusting medication regimens).

In order to ensure that not every study classified as case management will also qualify as a team change, if the study was already classified as case management, it could also be a team change if at least two of the above conditions were met. Team changes generally involve more communication. If the study calls the intervention "joint visits" or "shared care", we will classify it as a team change. To qualify, the intervention had to be done by a health-care professional and had to happen more than once.

Promotion of Self-management – is a QI strategy involving provision of equipment (e.g., home glucometers) or access to resources (e.g., system for electronically transmitting home glucose measurements and receiving insulin dose changes based on those data) to promote self-management. We will also include established goals or a print off of a self-management plan (i.e. didn't necessarily require equipment or resources). This was generally considered a more active strategy than patient education. If the study calls the intervention promotion of self-management, personalized goal-setting or action-planning then we will include it here.

Decision support – is a QI strategy which occurs as an operational process of adjustment in the case of a system that generates regular feedback for clinical teams on guideline compliance from registry data, or simply an organizational support to help facilitate other coordination mechanisms.

Clinical information system – is a QI strategy encompassing systems performing a wide variety of functions. A general feature that serves to distinguish clinical information systems from administrative information systems is that the former require data entry or data retrieval by clinicians at the point of care.

Patient education – is a QI strategy designed to promote increased understanding of a target condition or to teach specific prevention or treatment strategies, or specific in-person patient education (e.g., individual or group sessions with diabetes nurse educator; distribution of printed or electronic educational materials). If the patient education is optional, it will be excluded.

Patient reminder systems – is a QI strategy involving any effort (e.g., postcards or telephone calls) to remind patients about upcoming appointments or important aspects of self-care. Examples include reminders to monitor glucose. If the intervention included case management, reminders to patients needed to be explicit and an extra task to the normal case management.

Clinician education – is a QI strategy designed to promote increased understanding of principles guiding clinical care or awareness of specific recommendations for a target disorder or population of patients. Subcategories of clinician education included conferences or workshops, distribution of educational materials (written, video, or

other), and educational outreach visits (i.e. academic detailing). Exclude: teaching how to educate patients, counseling skills, motivational interviewing, self-directed learning, and skills related to the intervention (i.e. teaching how to use the website for the randomized clinical trial). If the education was part of the individual's role (i.e. teaching a case manager about diabetes) we will NOT categorize it as clinician education.

Clinician reminders – is a QI strategy involving paper-based or electronic systems intended to prompt a health professional to recall patient-specific information or to do a specific task. An example is a yellow piece of paper clipped to the medical record with the patient's information on it. This approach had to be systematic and part of the implementation of the intervention—ad-hoc clinician reminders will be excluded.

Audit and feedback – is a QI strategy involving a summary of clinical performance of health care delivered by an individual clinician or clinic over a specified period, which was then transmitted back to the clinician (i.e. the percentage of a clinician's patients who achieved a target HbA1c concentration or who underwent dilated-eye examinations with a specified frequency). It could also include the number of patients with missing tests and dropouts. This strategy is strictly based on clinical data and excludes clinical skills.

Financial incentives - is a QI strategy encompassing interventions with positive or negative financial incentives directed at providers (i.e. linked to adherence to some process of care or achievement of some target outcome). This strategy also includes positive or negative financial incentives directed at patients or system-wide changes in reimbursement (i.e. capitation, prospective payment, or a shift from fee-for-service to salary pay structure).

Continuous QI - is a QI strategy involving interventions explicitly identified as involving the techniques of continuous QI, total quality management, or plan-do-study-act, or any iterative process for assessing quality problems, developing solutions to those problems, testing their effects and then reassessing the need for further action.

Facilitated relay of information to clinicians – Clinical information collected from patients and transmitted to clinicians by means other than the existing medical record. We will exclude conventional means of correspondence between clinicians. For example, if the results of routine visits with a pharmacist were sent in a letter to the primary-care physician, the use of routine visits with a pharmacist would count as a "team change", but the intervention would not also be counted as "facilitated relay". However, if the pharmacist issued structured diaries for patients to record self-monitored glucose values, which were then taken to office visits to review with the primary physician, we would count the intervention as "facilitated relay". Other examples include electronic web-based methods through which patients provided self-care data and which clinicians reviewed, as well as point-of-care testing supplying clinicians with immediate HbA1c values. We will include passports, referral systems, and dietary information (versus purely clinical information). In general, the patient should be facilitating the relay. To be included, the information must get to someone

with prescribing or ordering ability. For example, if the nurse's role was expanded to make drug changes, the patient had a passport, and the nurse could directly make a change, we would classify the intervention as case management and facilitated relay of clinical information. If the nurse alerted the primary-care provider that the patient had run out of drugs, we did not deem this facilitated relay of information, because that is a normal part of a nurse's role.

Adapted from: Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J, Halperin I, Vachon B, Ramsay T, Manns B, Tonelli M, Shojania K. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet. 2012 Jun 16;379(9833):2252-61.

Appendix 5: Screening criteria for full-text articles (level 2 screening)

Question 1

This report is a

e.study protocol
f. conference abstract
g.letter to the editor without data
h.non-English article

Please indicate if the report fulfills the study eligibility criteria BUT is a study protocol (i.e. from Cochrane, PROSPERO, registries), a conference proceeding/abstract, a letter to the editor or a non-English article.

Note:*If none of the above, please leave unanswered.*

Question 2

Is this a systematic review (according to the Cochrane Collaboration definition) or a health economics study?

Systematic review - A review of a clearly formulated question that uses systematic and explicit methods to identify (e.g. search multiple databases), select (e.g. screen for inclusion), collect and critically appraise relevant research. Statistical methods (e.g. meta-analysis) may or may not be used to analyse and summarize the results of the included studies [The Cochrane Handbook – www.cochrane-handbook.org].

Note:*Quality appraisal or statistical analysis is not necessary for inclusion; however, reportMUSTbea review or synthesis of evidence AND include a description of the methods.*

Health Economics– include all economic analyses comparing the relationship between costs and outcomes of healthcare interventions. Examples include cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis. We will also include costing studies.

Note: *Only include study if there is a focus on cost. Exclude case-series, case reports or studies that do not have an adequate comparison group.*

Costing study – examines costing data associated with providing an intervention

Cost-benefit analysis – converts effects into the same monetary terms as costs and compares them

Cost-effectiveness analysis – views effects in terms of overall health specific to the problem, and describes the costs for some additional health gain (e.g. cost per additional stroke prevented)

Cost-utility analysis – expresses effects as overall health improvement and describes how much it costs for some additional utility gain (e.g. cost per additional quality-adjusted life-year)

Definitions from the Cochrane Collaboration Glossary at http://www.cochrane.org/glossary/5#letterc

Note:*For citations with NO ABSTRACTS, there must be some indication in the title that the report is a systematic review or costing study AND is related to wound care to be included.*
Question 3

If you selected YES or UNSURE to Question 2, please check all that apply from the following:

- ☐ *This is a systematic review*
- ☐ *This is a health economics study*

Indicate whether the report is a systematic review, health economics study or both by checking the appropriate boxes.

Note:*Ifyou selected NO to Question 2, please leave unanswered.*

Question 4

Does the report include adult patients in need of wound care?

Note:*This is a mandatory question.*

Adult patients – aged 16 years and older.***Note:*** *Exclude studies ONLY looking at children or animals.*

Patients in need of wound care – including those withexisting*pressure ulcers* (e.g. decubitus ulcers, bed sores),*post-surgical wounds* (e.g. incisions, surgical dehiscence, surgical infections), *wounds due to chronic disease* (e.g. arterial and venous ulcers, diabetic foot, pyodermagangrenosum) and *non-superficial burns* (e.g. deep dermal burn, burn infections).

Note: *We will include patients with a variety of wounds, sores, ulcers and/or burns; however we will exclude superficial burns, anal fissures, and hemorrhoids).*

Question 5

Does this report examine an intervention or a care program to treat wounds?

We are *EXCLUDING* diagnosing wounds, preventing wounds/infections, assessing wounds, prognosis of wounds, epidemiology of wounds, incidence of wounds, prevalence of wounds, and frequency of wounds. Instead, we are focusing on the **management and treatment** of wounds.

Note: *If report is a review or costing study of both prevention AND treatment, we will include.*

Potential interventions - *pharmacological agents* **(**e.g. topical agents), *non-pharmacological agents***(**e.g. dressing, vacuum, honey, hyperbaric therapy), *wound care programs* **(**e.g. care management, self-management or other quality improvement interventions found in box below).

Question 6

Does this report examine any of the following outcomes: healing, recovery, admission/readmission to hospital, human resources, or cost?

Outcomes of interest - *healing/recovery* (e.g. time to heal, duration of recovery, extent of healing), *admission/readmission to hospital* (as a result of the wound), *human resources* (necessary staff required to deliver/implement treatment) and *cost* (e.g. cost-effectiveness, cost-benefit, cost-utility, costing data).

Quality Improvement Strategies

Case management - is a QI strategy involving coordinating diagnosis, treatment, or ongoing patient management (e.g., arrangement for referrals, follow-up of test results) by a person or multi-disciplinary team in collaboration with or supplementary to the primary care clinician. In order for a trial to qualify as case management, it has to be ongoing (i.e. occur more than once). Usually these studies involved less involvement compared with team changes (i.e. case manager does not have to speak with primary care physician). If the study called the intervention "case management" we will classify it as such.

Team changes - is a QI strategy involving changes to the structure or organization of the primary health care team, defined as present if any of the following applied:

- Adding a team member or "shared care," i.e. routine visits with personnel other than the primary physician (including physician or nurse specialists in diabetic care, pharmacists, nutritionists, podiatrists).
- Use of multidisciplinary teams, i.e. active participation of professionals from more than 1 discipline (i.e. medicine, nursing, pharmacy, nutrition) in the primary, ongoing management of patients.
- Expansion or revision of professional roles (e.g., nurse or pharmacist plays more active role in patient monitoring or adjusting medication regimens).

In order to ensure that not every study classified as case management will also qualify as a team change, if the study was already classified as case management, it could also be a team change if at least two of the above conditions were met. Team changes generally involve more communication. If the study calls the intervention "joint visits" or "shared care", we will classify it as a team change. To qualify, the intervention had to be done by a health-care professional and had to happen more than once.

Promotion of Self-management – is a QI strategy involving provision of equipment (e.g., home glucometers) or access to resources (e.g., system for electronically transmitting home glucose measurements and receiving insulin dose changes based on those data) to promote self-management. We will also include established goals or a print off of a self-management plan (i.e. didn't necessarily require equipment or resources). This was generally considered a more active strategy than patient education. If the study calls the intervention promotion of self-management, personalized goal-setting or action-planning then we will include it here.

Decision support – is a QI strategy which occurs as an operational process of adjustment in the case of a system that generates regular feedback for clinical teams on guideline compliance from registry data, or simply an organizational support to help facilitate other coordination mechanisms.

Clinical information system – is a QI strategy encompassing systems performing a wide variety of functions. A general feature that serves to distinguish clinical information systems from administrative information systems is that the former require data entry or data retrieval by clinicians at the point of care.

Patient education – is a QI strategy designed to promote increased understanding of a target condition or to teach specific prevention or treatment strategies, or specific in-person patient education (e.g., individual or group sessions with diabetes nurse educator; distribution of printed or electronic educational materials). If the patient education is optional, it will be excluded.

Patient reminder systems – is a QI strategy involving any effort (e.g., postcards or telephone calls) to remind patients about upcoming appointments or important aspects of self-care. Examples include reminders to monitor glucose. If the intervention included case management, reminders to patients needed to be explicit and an extra task to the normal case management.

Clinician education – is a QI strategy designed to promote increased understanding of principles guiding clinical care or awareness of specific recommendations for a target disorder or population of patients. Subcategories of clinician education included conferences or workshops, distribution of educational materials (written, video, or other), and educational outreach visits (i.e. academic detailing). Exclude: teaching how to educate patients, counseling skills, motivational interviewing, self-directed learning, and skills related to the intervention (i.e. teaching how to use the website for the randomized clinical trial). If the education was part of the individual's role (i.e. teaching a case manager about diabetes) we will NOT categorize it as clinician education.

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Audit and feedback – is a QI strategy involving a summary of clinical performance of health care delivered by an individual clinician or clinic over a specified period, which was then transmitted back to the clinician (i.e. the percentage of a clinician's patients who achieved a target HbA1c concentration or who underwent dilated-eye examinations with a specified frequency). It could also include the number of patients with missing tests and dropouts. This strategy is strictly based on clinical data and excludes clinical skills.

Financial incentives - is a QI strategy encompassing interventions with positive or negative financial incentives directed at providers (i.e. linked to adherence to some process of care or achievement of some target outcome). This strategy also includes positive or negative financial incentives directed at patients or system-wide changes in reimbursement (i.e. capitation, prospective payment, or a shift from fee-for-service to salary pay structure).

Continuous QI - is a QI strategy involving interventions explicitly identified as involving the techniques of continuous QI, total quality management, or plan-do-study-

act, or any iterative process for assessing quality problems, developing solutions to those problems, testing their effects and then reassessing the need for further action.

Facilitated relay of information to clinicians – Clinical information collected from patients and transmitted to clinicians by means other than the existing medical record. We will exclude conventional means of correspondence between clinicians. For example, if the results of routine visits with a pharmacist were sent in a letter to the primary-care physician, the use of routine visits with a pharmacist would count as a "team change", but the intervention would not also be counted as "facilitated relay". However, if the pharmacist issued structured diaries for patients to record self-monitored glucose values, which were then taken to office visits to review with the primary physician, we would count the intervention as "facilitated relay". Other examples include electronic web-based methods through which patients provided self-care data and which clinicians reviewed, as well as point-of-care testing supplying clinicians with immediate HbA1c values. We will include passports, referral systems, and dietary information (versus purely clinical information). In general, the patient should be facilitating the relay. To be included, the information must get to someone with prescribing or ordering ability. For example, if the nurse's role was expanded to make drug changes, the patient had a passport, and the nurse could directly make a change, we would classify the intervention as case management and facilitated relay of clinical information. If the nurse alerted the primary-care provider that the patient had run out of drugs, we did not deem this facilitated relay of information, because that is a normal part of a nurse's role.

Adapted from: Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J, Halperin I, Vachon B, Ramsay T, Manns B, Tonelli M, Shojania K. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet. 2012 Jun 16;379(9833):2252-61.

Appendix 6: Data abstraction form for systematic reviews

For all items, if not reported indicate by inserting 'NR'. Please do not leave blank.

Review Characteristics	*****Please abstract for ALL studies**

Excel Column	Description
RefID	Reference ID of review (5-digit file number)
First Author	Last name of first author listed on review
Year	Year of publication
Country of conduct	Name of country in which the review was conducted
No. of studies	Number of studies included in review
Study design_RCT	Does this review include randomized, quasi-randomized or cluster-randomized clinical trials? Select YES, NO or UNCLEAR from list.
Study design_NRCT	Does this review include non-randomized clinical trials or controlled clinical trials?
Study design_CBA/ITS	Does this review include controlled before-after or interrupted time series studies?
Study design_OBS	Does this review include prospective or retrospective observational (cohort, case-control, cross-sectional) studies?
Wound type_1	Name the primary type of wound included in review (e.g. pressure ulcers, post-surgical wounds, sores, etc). See Eligibility below.
No. wound type_1	Number of studies in review including patients with wound type 1
Wound type_2	If more than one type of wound included, name second type here
No. wound type_2	Number of studies in review including patients with wound type 2
Wound type_3	Name third type of wound included, if applicable
No. wound type_3	Number of studies in review including patients with wound type 3
Age category	Age range of included participants (i.e. 20-50, >65, etc)
Patient population	Describe patient population by giving main reason for wounds (e.g. diabetes, chronic venous insufficiency, surgery, etc).
Comorbidities	5 most prevalent comorbidities and conditions present in review participants (e.g. diabetes, heart condition, smokers, etc)
Wound txs	Name all wound care interventions included in review (e.g. silver dressing, vacuum, honey, case management). See Eligibility below.
Controls	Name all comparison groups included in review (e.g. no intervention, usual care, other wound care intervention, etc)
Care setting	Where was the intervention(s) delivered (e.g. hospital, burn centre, wound clinic, etc)?
Length of tx_range	Provide range (shortest – longest) of the intervention periods in weeks (e.g. 0-1 week, 1-3 weeks, 1-12 weeks, etc)
Length of F/U_range	Provide range (shortest – longest) of follow-up periods in weeks (e.g. 2-6 weeks, 0-12 weeks, etc).
Abstract Results Textbox	Copy and paste results section of review abstract. If no summary data provided, please indicate by entering NSD.

Meta-analysis Outcomes***Use data from meta-analysis (MA) for these outcomes

If multiple outcomes of interest analyzed, repeat steps below for all relevant meta-analyses (e.g. MA2, MA3, MA4, etc). Room to abstract up to 10 MAs.

Excel Column	Description
Wound type_MA1	Name wound type(s) included in this meta-analysis.
Wound tx_MA1	Name intervention analyzed in this MA.
Wound control_MA1	Name comparison analyzed in this MA.
Outcome_MA1	Name outcome analyzed in this MA. See Eligibility below.
No. of studies_MA1	Number of studies included in this MA
Authors and years_MA1	List the last names and years of publication of each of the studies included in this meta-analysis (e.g. Rich 1994, McCorkle 200, etc).
No. in tx_MA1	Total number of participants in intervention arm of MA
No. in control_MA1	Total number of participants in comparison arm of MA
No. overall_MA1	Overall number of participants in MA
MA1_RR	Relative risk of MA1 outcome
MA1_RR95CI	95% confidence interval of MA1_RR
MA1_OR	Odds ratio of MA1 outcome
MA1_OR95CI	95% confidence interval of MA1_OR
MA1_MD	Mean difference of MA1 outcome
MA1_MD95CI	95% confidence interval of MA1_MD
MA1 Outcomes Textbox	Type in any other results from MA1 not captured above.

Quality Appraisal using AMSTAR tool

Choose either 'YES', 'NO', 'UNCLEAR' or 'NOT APPLICABLE' for each of the following:

A priori design	Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. This means that the authors must mention that they worked from a protocol or that they registered their review protocol or that they published their review protocol. All Cochrane reviews will automatically have a YES here.
Duplicate selection/DA	Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. Since this item lumps 2 questions into 1, data can be screened in duplicate and data abstraction verified or vice versa.
Literature search	Was a comprehensive literature search performed? The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.In order to score a YES, at least two electronic sources should be searched.

Publication status	Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. In order to score a YES, they should search/review/include unpublished data.
List of studies	Was a list of studies (included and excluded) provided? To score a YES, all included and excluded full-texts screened at L2 should be provided.
Study characteristics	Were the characteristics of the included studies provided? To score a YES, in an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes.
Quality assessed	Was the scientific quality of the included studies assessed and documented? To score a YES, they must appraise risk of bias or methodological quality.
Quality used	Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. To score a YES, discussion should include mention of quality results/limitations. If quality/risk of bias was not assessed, then this is NA.
Methods appropriate	Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?). For reviews that do not conduct a meta-analysis, authors should provide a rationale for this (e.g., the results were too homogenous so the results were described narratively). To score a YES, a test of homogeneity should be conducted and/or rationale for pooling results discussed. Reviews that do not describe their synthesis process should be scored as a NO.
Publication bias assessed	Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test). If a MA was not conducted, then to score a YES the possibility of publication bias should be at least mentioned in discussion section (e.g. didn't include unpublished data).
Conflicts stated	Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. Score as a YES even if a conflict of interest exists but it is stated. This item is asking whether it was reported (not whether conflicts of interest exist).

If AMSTAR Rating >7, then continue to abstract other Outcomes tab. If not, stop here.

Other Outcome Data	*****ONLY report these outcomes if no AMSTAR score >7**

No. of wounds healed_tx	Number of wounds healed in intervention group
No. of wounds healed_control	Number of wounds healed in comparison group
Mean wounds healed_tx	Average number of wounds healed in intervention
SD wounds healed_tx	Standard deviation of mean wounds healed in intervention
Mean wounds healed_control	Average number of wounds healed in comparison
SD wounds healed_control	Standard deviation of mean wounds healed in comparison
Wound Healed Textbox	Enter any aggregate outcome information regarding wounds healed not captured above. If no summary data provided, please indicate by entering NSD.
Rate of healing_tx	Rate of healing or recovery in intervention group
Rate of healing_control	Rate of healing or recovery in comparison
Healing time_tx (in days)	Time for wounds to heal or recover (in days) in treatment
Healing time_control	Time for wounds to heal or recover (in days) in control
Healing Time/Rate Textbox	Enter any aggregate outcome information regarding healing/recovery time or rate not captured above. If no summary data provided, please indicate by entering NSD.
No. of admissions_tx	Number of admissions/readmissions to hospital directly related to wounds in treatment group
No. of admissions _control	Number of admissions/readmissions related to wounds in control group
Mean admission_tx	Average number of admissions in treatment
SD admission_tx	Standard deviation of mean admission_tx
Mean admission_control	Average number of admissions in comparison
SD admission_control	Standard deviation of mean admission_control
No. of patients admitted_tx	Number of patients admitted due to wounds in treatment
No. of patients admitted _control	Number of patients admitted in control group
Admissions Textbox	Enter any aggregate outcome information regarding admissions/readmissions not captured above. If no summary data provided, please indicate by entering NSD.
LOS_tx	Length of hospital stay (in days) in intervention group
LOS_control	Length of hospital stay (in days) in control group
LOS Textbox	Enter any aggregate outcome information related to length of stay not captured above. If no summary data provided, please indicate by entering NSD.
Resources_tx	Outcomes on resources needed to implement intervention (e.g. cost of personnel, etc)
Resources_control	Outcomes on resources needed to implement control.
Resource Textbox	Enter any aggregate resource outcome information. If no summary data provided, please indicate by entering NSD.

Appendix 7: Data abstraction form for economic studies

NB - For all items if not applicable/reported, enter NA or NR. Please do not leave blank spaces.

If an article does not meet the inclusion criteria, please mark as To Exclude and do not abstract it.

Please do not abstract protocols, conference abstracts or non-English publications.

Excel Column	Description
RefID	Enter publication's RefID number
First author	Enter last name of the first author
Year of publication	Enter year of publication
Study design	Choose the type of study design as reported in the publication from the following 7 drop-down menu options: CEA (cost-effectiveness analysis), CUA (cost- utility analysis), RCT (randomized controlled trial), Other exp'l study (use this for other experimental study designs), Quasi-exp'l study (i.e. CBA and TSA studies), Observat'l study (observational studies), Unclear (use this if the study design is not clearly reported).
Country of conduct	Name of country in which the study was conducted
Setting	Where was the intervention delivered? (e.g., hospital, wound clinic, burn centre, primary care, tertiary care, research institution, etc.). If not applicable, enter NA
Currency	Enter currency used in the publication
Perspective	For economic evaluations, enter the point of view from which the costs and benefits are assessed (i.e. patient, provider, payer, health care system, societal). See definitions below. If not applicable, enter NA
Model type	For CEAs/CUAs, enter the type of model/framework used. If not applicable, enter NA
Funding	Choose funding source from the following 4 drop-down menu options: public, private, mixed (both public and private), NR.
Year of values	Enter year costs were calculated for
Time horizon/Length of study period	Enter the number of years used in the economic model, or the length of the study treatment period
Sample size – participants/cohort	For single studies, enter the total number of study participants (enrolled). For models, enter the total number of study participants (combined if multiple studies used) that are used for the model estimations/extrapolations. If not applicable, enter NA.
Sample size – wounds	For single studies, enter the total number of wounds studied. If not applicable, enter NA

Type of wounds	Brief description of the type of wounds
Population	Brief description of the population. If not applicable, enter NA
Comorbidities	Enter the 5 most prevalent comorbidities reported of the sample population. If not applicable, enter NA
Intervention #1 information	In the relevant marked columns, list separately the following details for the intervention (#1): Name, Dose, Duration, Frequency, Administration, and/or Program/protocol details. For any of these columns, if it is not applicable, enter NA
Intervention(s) # 2-10 information	In the relevant marked columns, list separately the following details for the next intervention(s), if applicable (#s 2-10): Name, Dose, Duration, Frequency, Administration, and/or Program/protocol details. For any of these columns, if it is not applicable, enter NA
Comparator information	In the relevant marked columns, list separately the following details for the comparator (e.g., active control, standard care): Name, Dose, Duration, Frequency, Administration, and/or Program/protocol details. For any of these columns, if it is not applicable, enter NA
Total cost results -for Tx #1	Enter the total cost findings (as reported in the publication) for the intervention (#1), and the conclusion. If not applicable, enter NA
Total cost variation - for Tx #1	Enter the variation of the total cost for the intervention (#1), i.e. standard deviation (SD), standard error (SE), 95% confidence interval (CI), range or interquartile range (IQR) reported. If not reported, enter NR
Intervention cost - for Tx 1	Enter the (direct) intervention cost for the intervention (#1). If not reported, enter NR
Intervention cost variation - for Tx #1	Enter the variation of the (direct) intervention cost for the intervention (#1), i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Personnel cost - for Tx	Enter the personnel costs results for the intervention (#1). If not applicable,

1	enter NA
Personnel cost variation - for Tx #1	Enter the variation of the personnel cost for the intervention (#1), i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Hospital cost - for Tx 1	Enter the hospital costs results for the intervention (#1). If not applicable, enter NA
Hospital cost variation - for Tx #1	Enter the variation of the hospital cost for the intervention (#1), i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Total cost results -for Tx(s) # 2-10	Enter the total cost findings for intervention(s) # 2-10 (if applicable), and the conclusion. If not applicable, enter NA
Total cost variation - for Tx(s) # 2-10	Enter the variation of the total cost for intervention(s) # 2-10 (if applicable), i.e. standard deviation (SD), standard error (SE), 95% confidence interval (CI), range or interquartile range (IQR) reported. If not reported, enter NR
Intervention cost - for Tx(s) # 2-10	Enter the (direct) intervention cost for intervention(s) # 2-10 (if applicable). If not reported, enter NR
Intervention cost variation - for Tx(s) # 2-10	Enter the variation of the (direct) intervention cost for intervention(s) # 2-10 (if applicable), i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Personnel cost - for Tx(s) # 2-10	Enter the personnel costs results for intervention(s) # 2-10 (if applicable). If not applicable, enter NA
Personnel cost variation - for Tx(s) # 2-10	Enter the variation of the personnel cost for intervention(s) # 2-10 (if applicable), i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Hospital cost - for Tx(s) # 2-10	Enter the hospital costs results for intervention(s) # 2-10 (if applicable). If not applicable, enter NA
Hospital cost variation - for Tx(s) # 2-10	Enter the variation of the hospital cost for intervention(s) # 2-10 (if applicable), i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Total cost results -for Comparator	Enter the total cost findings (as reported in the publication) for the comparator, and the conclusion. If not applicable, enter NA
Total cost variation - for Comparator	Enter the variation of the total cost for the comparator, i.e. standard deviation (SD), standard error (SE), 95% confidence interval (CI), range or interquartile range (IQR) reported. If not reported, enter NR
Intervention cost - for Comparator	Enter the (direct) intervention cost for the comparator. If not reported, enter NR
Intervention cost variation - for Comparator	Enter the variation of the (direct) intervention cost for the comparator, i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR
Personnel cost - for Comparator	Enter the personnel costs results for the comparator. If not applicable, enter NA
Personnel cost variation - for	Enter the variation of the personnel cost for the comparator, i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR

Comparator	
Hospital cost - for Comparator	Enter the hospital costs results for the comparator. If not applicable, enter NA
Hospital cost variation - for Comparator	Enter the variation of the hospital cost for the comparator, i.e. SD, SE, 95% CI, range or IQR. If not reported, enter NR

Study and Patient Characteristics:Outcomes of CEAs/CUAs:

Excel Column	Description
Relative/ Incremental costs results	For CEAs/CUAs, enter the relative/incremental costs results comparing the groups along with relevant explanatory textwords (e.g., ICER; whether the difference between groups was statistically significant; % savings from using tx 1 versus comparator, etc.). If not applicable, enter NA.
CEA/CUA cost results (#1): cost per LY	For CEAs/CUAs, enter the cost per life-year for intervention #1. If not applicable, enter NA
CEA/CUA costs (#1): cost per QALY	For CEAs/CUAs, enter the cost per quality-adjusted life-year for intervention #1. If not applicable, enter NA
CEA/CUA costs (#1): cost per wound healed	For CEAs/CUAs, enter the cost per ulcer/wound healed/improved for intervention #1, along with relevant text details (e.g., "per wound infection resolved", etc.). If not applicable, enter NA
CEA/CUA cost results (#1): other indicator costs	For CEAs/CUAs, enter costs reported for other indicator types (i.e. other than LY/QALY) for intervention #1. If not applicable, enter NA
Sensitivity analyses (#1) - for CEA/CUA	For CEAs/CUAs, enter (only) the key model parameters that were found to be sensitive in the sensitivity analysis for intervention #1. List up to 5 sensitive parameters. If none were significant, enter Nil. If not reported, enter NR.
CEA/CUA cost results (#s 2-10): cost per LY	For CEAs/CUAs, enter the cost per life-year for intervention(s) # 2-10 (if applicable). If not applicable, enter NA
CEA/CUA costs (#s 2-10): cost per QALY	For CEAs/CUAs, enter the cost per quality-adjusted life-year for intervention(s) # 2-10 (if applicable). If not applicable, enter NA
CEA/CUA costs (#s 2-10): cost per wound healed	For CEAs/CUAs, enter the cost per ulcer/wound healed/improved for intervention(s) # 2-10 (if applicable), along with relevant text details (e.g., "per wound infection resolved", etc.). If not applicable, enter NA
CEA/CUA cost results	For CEAs/CUAs, enter costs reported for other indicator types (i.e. other than

(#s 2-10): other indicator costs	LY/QALY) for intervention(s) # 2-10 (if applicable). If not applicable, enter NA
Sensitivity analyses (#s 2-10) – for CEA/CUA	For CEAs/CUAs, enter (only) the key model parameters that were found to be sensitive in the sensitivity analysis for intervention(s) # 2-10 (if applicable). List up to 5 sensitive parameters. If none were significant, enter Nil. If not reported, enter NR.
CEA/CUA cost results (Comparator): cost per LY	For CEAs/CUAs, enter the cost per life-year for the comparator. If not applicable, enter NA
CEA/CUA costs (Comparator): cost per QALY	For CEAs/CUAs, enter the cost per quality-adjusted life-year for the comparator. If not applicable, enter NA
CEA/CUA costs (Comparator): cost per wound healed	For CEAs/CUAs, enter the cost per ulcer/wound healed/improved for the comparator, along with relevant text details (e.g., "per wound infection resolved", etc.). If not applicable, enter NA
CEA/CUA cost results (Comparator): other indicator costs	For CEAs/CUAs, enter costs reported for other indicator types (i.e. other than LY/QALY) for the comparator. If not applicable, enter NA
Sensitivity analyses (Comparator) - for CEA/CUA	For CEAs/CUAs, enter (only) the key model parameters that were found to be sensitive in the sensitivity analysis for the comparator. List up to 5 sensitive parameters. If none were significant, enter Nil. If not reported, enter NR.

Quality Assessment* of CEAs/CUAs:

Excel Column	Description
Q1. Was a well-defined question posed in answerable form?	1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?
Q2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?	2.1. Were any relevant alternatives omitted? 2.2. Was (should) a do-nothing alternative (be) considered?

Q3. Was the effectiveness of the programme or services established?	3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Were effectiveness data collected and summarized through a systematic overview of clinical studies? If so, were the search strategy and rules for inclusion or exclusion outlined? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?
Q4. Were all the important and relevant costs and consequences for each alternative identified?	4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?
Q5. Were costs and consequences measured accurately in appropriate physical units (for example, hours of nursing time, number of physician visits, lost work-days, gained life-years)?	5.1. Were the sources of resource utilization described and justified? 5.2. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? 5.3. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?
Q6. Were costs and consequences valued credibly?	6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views, and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?
Q7. Were costs and consequences adjusted for differential timing?	7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was any justification given for the discount rate used?
Q8. Was an incremental analysis of costs and consequences of alternatives	8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

performed?	
Q9. Was allowance made for uncertainty in the estimates of costs and consequences?	9.1. If patient-level data on costs or consequences were available, were appropriate statistical analyses performed? 9.2. If a sensitivity analysis was employed, was justification provided for the ranges or distributions of values (for key study parameters), and the form of sensitivity analysis used? 9.3. Were the conclusions of the study sensitive to the uncertainty in the results, as quantified by the statistical and/or sensitivity analysis?
Q10. Did the presentation and discussion of study results include all issues of concern to users?	10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (for example, cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.3. Did the study discuss the generalizability of the results to other settings and patient/client groups? 10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (for example, distribution of costs and consequences, or relevant ethical issues)? 10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

*Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3nd ed. Oxford.Oxford University Press. 2005.

Included types of full economic evaluations†

Cost-effectiveness analysis:

"The cost-effectiveness analysis is an economic study in which the costs are expressed in monetary units and the results in non-monetary units. Non-monetary units may for example be: (1) years of life gained, (2) hospital days prevented, (3) clinical parameters (e.g. response or remission rates, reduction in cholesterol,etc)".

Cost-utility analysis:

“The cost-utility analysis follows the same principle as the cost-effectiveness analysis. Costs are assessed in monetary units and the benefit is measured as a non-monetary but utility-adjusted outcome, the quality adjusted life year (QALY). The concept combines life expectancy and quality of life. If quality of life is animportant aspect of therapy, this form of analysis should be chosen”.

†Walter E. et al. (April 2006). Guidelines on Health Economic Evaluation: Consensus paper. Institute for Pharmaeconomic Research; Vienna.

Perspective of the economic evaluation**

Patients

“The term patient refers to the person targeted by the health intervention under consideration (certain programs might refer to patients as clients).

The perspective of the patient is appropriate, for example, in a comparison of treating a disease on an outpatient versus an inpatient basis.

The difference in costs between the outpatient and inpatient options (e.g., work absenteeism, disturbance in family life, and length of recovery) might influence a patient's preference for one option or the other”.

Providers

“The term provider refers to all categories of persons and institutions providing health-related services.

Examples of providers include physicians, hospitals, nursing homes, public health clinics, and local and state health departments. The provider perspective can be that of:

- a conglomerate of providers (i.e., a managed-care organization [MCO]), or
- a provider within that conglomerate (i.e., one hospital or physician).

The provider perspective is appropriate, for example, when assessing the costs and benefits of establishing and operating a childhood immunization reminder system. From the clinic's perspective, direct medical costs would be included, but productivity losses associated with a patient's going to the clinic to receive the immunization would not be included”.

Payers

“The term payer refers to the person, entity, or institution ultimately responsible for the financial cost of a program, intervention, or medical procedure.

In the United States, payers include

- households that pay for care out-of-pocket or through insurance premiums,
- businesses that pay for part of the cost of health insurance,
- private insurers (e.g., MCOs),
- public insurance programs (e.g., Medicare and Medicaid), and
- federal or state governments.

An analysis of the impact of a law mandating health plans to cover the cost of fertility drug treatment is an example of an economic evaluation that could be implemented from the payer perspective — in this case, the private health insurer”.

Health Care System

“The health-care system perspective is broader than the perspective of the health-care provider. The health-care system perspective considers the costs and outcomes associated with providing care without differentiating between categories of providers or payers.

The health-care system perspective is useful and informative if the economic burden of a disease is frequently shared by all categories of payers and providers.

For example, the costs and outcomes of STDs are the responsibilities of

- public health clinics,
- public health laboratories,
- primary-care practitioners,
- obstetricians,
- gynecologists,
- family planning clinics, and
- hospitals.

The use of a health-care system perspective can provide a more complete estimate of the true medical costs and outcomes of treating STDs than can an estimate from a single category of payers or providers”.

Society

“The societal perspective is the broadest possible perspective, because it includes all costs (no matter who incurs them) and all consequences (both good and bad), regardless of who experiences them.

For example, when estimating the cost of acquired immunodeficiency (AIDS) from a societal perspective, the analyst should consider not only diagnosis and treatment costs but also

- productivity losses associated with the premature death of AIDS patients,
- the financial and emotional costs incurred by families and friends caring for AIDS patients, and
- the cost to families and society of caring for orphaned children of AIDS patients.

The government perspective is used in studies that are being conducted for the public sector, but the government perspective should not be confused with the societal perspective, which is broader because it encompasses all costs and consequences.

For example, costs incurred by the patient seeking care would not be included in a study conducted from a governmental or public budget perspective, but would be considered relevant from a societal perspective".

**From CDC website:Framing an EconomicEvaluation. Available at: http://www.cdc.gov/owcd/eet/framing3/fixed/1.html

Appendix 8: List of included studies

1 Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA, McCollum PT. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular & Endovascular Surgery* 2003, 25 (6): 513-518.

2 Adderley U, Smith R. Topical agents and dressings for fungating wounds. *Cochrane Database of Systematic Reviews* 2007, 2: 3948.

3 Akagi I, Furukawa K, Miyashita M, Kiyama T, Matsuda A, Nomura T, Makino H, Hagiwara N, Takahashi K, Uchida E. Surgical wound management made easier and more cost-effective. *Oncology Letters* 2012, 4 (1): 97-100.

4 Baba-Akbari Sari A, Flemming K, Cullum NA, Wollina U. Therapeutic ultrasound for pressure ulcers. *Cochrane Database Syst Rev.* 2006 Jul 19 (3):CD001275.

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6 Amsler F, Willenberg T, Blattler W. In search of optimal compression therapy for venous leg ulcers: a meta-analysis of studies comparing diverse corrected bandages with specifically designed stockings. *Journal of Vascular Surgery* 2009, 50 (3): 668- 674.

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14 Bardy J, Slevin NJ, Mais KL, Molassiotis AA. Systematic review of honey uses and its potential value within oncology care (Structured abstract). *Journal of Clinical Nursing* 2008, 17 (3): 2604-2623.

15 Bergin SM, Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. *Cochrane Database Systematic Reviews* 2006, Jan 25 (1): CD005082.

16 Berliner E, Ozbilgin B, Zarin DA. A systematic review of pneumatic compression for treatment of chronic venous insufficiency and venous ulcers. *Journal of Vascular Surgery* 2003, 37 (3): 539-544.
17 Blozik E, Scherer M. Skin replacement therapies for diabetic foot ulcers: systematic review and meta-analysis (Structured abstract). Diabetes Care 2008, 31(4): 693-4.
18 Boogaard M, Laat E, Spauwen P, Schoonhoven L. The effectiveness of topical negative pressure in the treatment of pressure ulcers: a literature review (Structured abstract). European Journal of Plastic Surgery 2008, 31 (1): 1-7.
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