TITLE: Negative Pressure Wound Therapy for Managing Diabetic Foot Ulcers: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines

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CONTEXT AND POLICY ISSUES

The rising prevalence of diabetes mellitus (DM) and associated complications represent a global public health care problem and financial burden.[1,2] The estimated prevalence of DM in Canada was 6.8% (2.4 million) in 2009, a 230% increase from estimates in 1998. Increasing prevalence and associated costs to Canada's publically funded healthcare system is projected to continue. As of 2010 the estimated economic burden of DM and its complications in Canada was $12.2 billion.[3] The most common chronic complication of DM is diabetic foot ulcers (DFUs), with a prevalence of four to ten percent among DM patients.[1,4] Several factors predispose DM patients to DFUs including long duration of diabetes, trauma, infection, poor glycemic control, improper footwear, old age, smoking, low socioeconomic status, and psychological factors, however neuropathy and peripheral vascular disease may be the most significant causative factors.[1] The presentation of DFUs varies considerably with underlying pathogenesis and with the presence or absence of infection and ischemia. Along with serious complications including wound infection, osteomyelitis, and cellulitis, DFU patients also suffer from complications associated with DM including nephropathy, retinopathy, ischemic heart disease, and cerebrovascular disease. Furthermore, the potentially preventable endpoint of untreated DFU is amputation, which is itself associated with immense social and psychological consequences, in addition to significant morbidity, mortality and financial impact on healthcare.[1,2]

Negative pressure wound therapy (NPWT) involves applying a controlled sub-atmospheric pressure environment across the surface of a wound in an airtight dressing. A pump is used to maintain negative pressure, usually between -75 and -125 mmHg, in a consistent or intermittent manner.[5,6] The mechanism by which NPWT is thought to promote wound healing is through increasing local perfusion, eliminating tissue edema, drawing wound edges together, removing exudates and proinflammatory cytokines, inhibiting bacterial growth, and promoting cell hyperplasia.[1,2,7] NPWT systems have been widely adopted for a broad range of wound indications including DFUs.[2] In 2011, the FDA published a warning regarding contraindications and risk factors to consider before NPWT use.[2,8] Application of NPWT on exposed organs, exposed vasculature, necrotic tissue with eschar present, untreated osteomylelitis, malignancy

in the wound, or anastomotic sites is contraindicated. Risk factors for NPWT use include patients at high risk for bleeding and hemorrhage, patients with infected wounds, sharp edges in the wound, patient size and weight, and circumferential dressing application.[8,9] This FDA update on serious complications was prompted by reports on 12 deaths and 174 injuries associated with NPWT use since 2007.[8]

NPWT is in widespread use, however, it is expensive and presents possible serious adverse events.[2] The purpose of this report is to retrieve and review existing evidence of clinical effectiveness and cost-effectiveness, and to retrieve and review the existing guidelines for NPWT treatment of DFUs.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of negative pressure wound therapy for the treatment of diabetic foot ulcers?

2. What is the cost-effectiveness of negative pressure wound therapy for the treatment of diabetic foot ulcers?

3. What are the evidence-based guidelines for the use of negative pressure wound therapy for the treatment of diabetic foot ulcers?

KEY FINDINGS

The evidence presented in this report supports greater clinical efficacy of negative pressure wound therapy over other conventional treatments of diabetic foot ulcers. Conclusions are associated with a degree of uncertainty due to small sample sizes and potential for bias in the trials on which the evidence is based. There was no evidence identified suggesting an increased frequency of adverse events associated with negative pressure wound therapy. The majority of analyses also suggest that negative pressure wound therapy is more cost-effective than appropriate comparators, however the evidence also suggests this may not be the case in every healthcare setting and that improvements in efficacy estimates are needed to improve the accuracy of cost-effectiveness analysis. Identified guidelines suggest considering negative pressure wound therapy for diabetic foot ulcers, although the most recent Canadian guidelines identified cite a lack of evidence to support any recommendations regarding the use of negative pressure wound therapy.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014 July, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2009 and July 30, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18+) with diabetic foot ulceration. Hospital or community care setting.
Intervention	Negative pressure wound therapy, Vacuum Assisted Closure (V.A.C.) dressing (KCI Medical Ltd, England). Any other manufacturer.
Comparator	Conventional wound dressings
Outcomes	Healing rate (% healed), time to healing, wound size, wound infection, formation of granulation tissue, lower limb amputation, safety (adverse effects) Costs, cost-effectiveness Evidence-based clinical practice guidelines.
Study Designs	Health Technology Assessments (HTA)/ Systematic review (SR)/Meta-analysis (MA); Randomized controlled trials (RCTs); Economic evaluations; and Evidence-based Guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicates or were published prior to 2009. Studies were excluded if they evaluated NPWT for non-diabetic wound types. Randomized controlled trials (RCTs) were excluded if they were a part of a subsequently published systematic review (SR). SRs and health technology assessments (HTAs) were excluded if more recent SRs or HTAs reviewed the same studies.

Critical Appraisal of Individual Studies

The quality of the included SR, MA and the HTA were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[10] The quality of the RCT included in this report was assessed using the Downs and Black checklist[11] and economic analyses were appraised using Drummond's Checklist.[12] Critical appraisal of included guidelines used the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[13] For all critical appraisals the strengths and limitations were described narratively instead of assigning a numerical score.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search strategy identified 173 articles. Following screening titles and available abstracts 139 citations did not meet the inclusion criteria (Table 1); as a result, 34 full text articles were retrieved for review. Nine additional relevant articles were identified in the grey literature. Upon review, three SRs,[2,14,15] one MA[1], one HTA (containing a relevant economic

assessment),[5] one RCT,[16] three economic studies,[17-19] and seven guidelines[3,7,9,20-23] containing relevant recommendations were included. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[24] describes the selection procedure of the included studies of this review (Appendix 1).

The 27 excluded studies consisted of five studies that examined an irrelevant population, two that examined an irrelevant intervention, two that examined an irrelevant comparator, two which were correspondence, seven that were review articles, and nine that were included in at least one of the selected systematic reviews or included studies that were included in more recent MAs or SRs. The duplication of reviewed studies in the identified SRs, MA and HTAs is summarized in Appendix 2, and references of potential interest therein are included in the bibliography.

Summary of Study Characteristics

Clinical Effectiveness

Included SR, MA, HTA, and RCT characteristics are tabulated in Appendix 3 Table 3.1.

Study design

Three SRs,[2,14,15] one MA,[1] and one RCT[16] were identified as meeting the inclusion criteria (Table 1) and were not included in another SR, MA, or HTA. The three SRs were published in 2014,[14] 2013,[2] and 2010[15] and included evidence from trials published from 2000 to 2011. The three SRs included in this report reviewed evidence from ten different trials[25-34], four different SRs,[35-38] and one set of guidelines that included an SR on which to base the recommendations.[9] One SR included only HTAs and previous SRs,[14] while the other two SRs only included RCTs.[2,15] The identified MA was published in 2014 and extracted data from eight trials, one of which was not included in the three identified SRs (Appendix 2 Table A2.1).[1] The identified RCT was published in 2014 and was not examined in the SRs, MAs, or HTAs included in this report.[16]

Population, Interventions and Comparators

Two SRs examined DFU specifically,[2,14] while one SR additionally examined NPWT treatment of pressure ulcers and mixed wounds.[15] The DFU population examined included DM patients who had foot wounds resulting from amputation in the three SRs.[2,14,15] One SR examined evidence for NPWT treatment of DFU exclusively[2] while another examined other DFU treatments including offloading, debridement, dressings, topical therapies, electrophysical therapy, platelet-rich plasma, cultured keratinocytes, growth factors and bioengineered skin substitutes, hyperbaric oxygen therapy, and alternative therapy.[14] Data specific to NPWT treatment of DFU was presented separately in the SRs with a broader scope.[14,15] Comparators in these SRs were standard wound care (SWC) and advanced moist wound care (AWMT). The SRs reported studies with a range of SWC, including standard wound dressing, wet-to-dry dressings, and standard moist gauze.[2,14,15] The other comparator in these studies, AMWT, included alginates, hydrocolloid, foam, or hydrogel dressings.[2,14]

The MA specifically examined NPWT treatment of DFU and referred to the comparators of included trials as non-NPWT. The non-NPWT therapies from the individual trials varied and

included AMWT, SWC, and saline-soaked gauze. The total sample size of the included trials was 669 DFU patients.[1]

The RCT also examined NPWT treatment of DFU. The study consisted of 23 DFU patients, ten of which received NPWT (V.A.C. Therapy, KCI Medical Ltd, England), while 13 received moist dressings.[16]

Outcomes

Outcomes common to the three SRs were DFU healing efficacy, time to heal, and change in ulcer size.[2,14,15] One SR reported the rate and efficacy of granulation tissue formation.[15] Two SRs reported adverse events and the occurrence of secondary amputations.[14,15]

The MA examined DFU healing efficacy, time to heal, change in ulcer size, amputation occurrence, the rate of granulation tissue formation, and quality of life measures. In addition, the MA evaluated treatment-related adverse events, examining available data on edema, pain, bleeding, and infection rates.[1]

The outcomes examined in the included RCT were DFU healing efficacy, change in ulcer surface area and depth, Wagner score both before and after treatment, patient satisfaction of treatment, and the incidence of major (above-knee or below-knee) and minor amputations (less than below-knee; toe or forefoot).[16] The Wagner wound classification system assessed ulcer depth, the presence of osteomyelitis, and gangrene. Based on this assessment wounds were graded on a scale of zero (best) to five (worst).[2,39]

Cost-effectiveness

Characteristics of the included economic analyses are tabulated in Appendix 3, Table A3.2.

Study design

The included HTA includes relevant cost-effectiveness data from two cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA).[5]

The most recent CEA was an analysis from a public health sector perspective in the USA.[17] This study was a post-hoc analysis of data obtained from an RCT of 342 patients, the results of which were published in 2008.[17,29] The RCT demonstrated superiority of NPWT treatment of DFU when compared to control.[29,39] Costs were calculated based upon the 12 week course of therapy during the trial.[17] Two older analyses, one CEA and one CUA, were based upon economic models.[18,19] One CEA was taken from both a Medicare and a private payer perspective in the USA.[18] The included CUA was from the payer perspective in France.[19] The time horizon of the modelled CEA was 16 weeks, while the CUA was modelled with 1000 DFU patients over 12 months.[19]

The HTA examined different wound types but includes two CEAs and a CUA specifically regarding NPWT of DFUs as compared to SWC and AMWT.[5] One CEA used an RCT as a clinical data source, and one CEA used data from a US national commercial claims dataset, while the CUA was based upon multiple sources of published data.[5]

Patient Population and Comparison

Based upon a previous RCT,[29] one CEA examined NPWT compared to AMWT with 162 DFU patients (Wagner grades two and three) in each study arm.[17] The CEA and CUA based upon economic models both examined DFU patients. The CUA specified that 28% DFUs were infected and 75% of those infected DFUs were gangrenous.[18,19] Both economic model studies were industry funded studies and examined specific NPWT apparatus. The industry funded CEA examined a generic NPWT, compared to SWC and a portable NPWT, the SNaP Wound Care System (Spiracur, Inc., Sunnyvale, CA). The industry funded CUA compared a specific NPWT apparatus, V.A.C. Therapy system, (KCI Medical Ltd., England) to AMWT (Algosteril, alginate with Adaptic).[19]

The identified HTA included one CEA that examined NPWT of DFU as compared to AMWT, one CEA that examined NPWT of DFU compared to wet-to-moist therapy and a CUA that examined NPWT of DFU compared to saline gauze and advanced dressings.[5]

Outcomes

The CEA from 2014 had economic analysis results for the total cost per DFU patient, and divided those costs into patients who achieved wound closure and those who did not.[17] This analysis also examined the total non-therapy related costs and also analyzed non-therapy costs for patients who achieved wound closure and those who did not. A breakdown of non-therapy related costs was provided.[17] The industry funded CEA examined total cost per patient and also included a breakdown of those costs.[18] The industry funded CUA provided a total cost per 1000 DFU patients, a breakdown of cost components and QALYs.[19]

Relevant outcomes from the identified HTA include total cost per patient, quality adjusted life years (QALYs), 20-week cost of care per patient, and incremental cost per patient to achieve wound closure.[5] Clinical effectiveness studies examined in this HTA are not a part of this report. These clinical effectiveness studies are examined in a more recently published SR and MA.[1,5,15] See Appendix 2, Table A2.1 for further information.

Assumptions

One CEA and one CUA specified the assumption of therapy effectiveness based upon previous results.[18,19] Additional assumptions were made by these economic analyses as they were economic models.[18,19] One CEA assumed an equal efficacy between different specific NPWT apparatus based upon preliminary studies and also modelled exponential healing rates without citing precedent for modeling such an assumption.[18] The CUA made assumptions regarding long-term outcomes and rational assumptions of some equivalent cost components between treatments.[19]

The included HTA summarized the assumptions of the included CEAs and CUA. One CEA assumed surgical costs based on a minimum commercial fee and did not include diagnostic investigation, anaesthesia services, laboratory results, and cleansing agents but did include costs for caregiver time and clinic visits. This CEA also assumed a weighted average of antibiotic costs, and only included patients participating for a minimum of eight weeks. The other CEA assumed one or two nursing visits for the control group, one physician visit every two weeks, and three dressing changes for the control group.[5] The CUA model assumed resources

consumed were equal between groups in each health state except the length of hospital stay and the frequency of dressing changes.[5]

Guidelines and Recommendations

Included guideline characteristics are tabulated in Appendix 3, Table A3.3.

Origin of Guidelines

The most recently published guidelines identified were from the Canadian Diabetes Association (CDA).[3] Two guidelines were from the USA and published in 2012, one from the Agency for Healthcare Research and Quality (AHRQ),[20] and one from the Infectious Diseases Society of America (IDSA).[21] Three included guidelines were published in 2011.[7,9,22] The National Health and Medical Research Council (NHMRC) guidelines are from Melbourne, Australia.[7] The National Institute for Health and Clinical Excellence (NICE) guidelines are from London, UK.[22] The International Expert Panel on NPWT formulated consensus guidelines in Hamburg, Germany.[9] Guidelines were published in 2010 from the Scottish Intercollegiate Guidelines Network (SIGN), in Scotland.[23]

Interventions

All of the guidelines identified and included in this report contain recommendations, or report insufficient evidence to formulate recommendations, specific to NPWT of DFUs.[3,7,9,20-23]

Grading of recommendations and levels of evidence

Guidelines from the CDA have levels of evidence rated 1A to 4 and recommendations graded A to D.[3] The AHRQ contains recommendations graded A to C with levels of evidence I to VI.[20] The IDSA assigns a level of evidence as high, moderate, low, or very low quality and recommendations are graded as strong or weak.[21] Guidelines from the NHMRC have levels of evidence from I to IV and recommendations graded A to D.[7] The NICE guidelines do not assign a level of evidence and only present a Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile (high, moderate, low, or very low) for individual studies included in the guidelines.[22] Two included guidelines use the SIGN classification for levels of evidence (1 to 4) and recommendation grades (A to D).[9,23] Grading systems used to assign levels of evidence and grades of recommendations for the included guidelines are summarized in Appendix 4.

Summary of Critical Appraisal

One of the three included SRs reported quantified conclusions of an MA, discussed publication bias, provided statistical tests of heterogeneity, outlined patient characteristics, and mentioned the conflict of interest (COI) statements of included studies.[2] This SR found patient characteristics were inclusive and therefore broadly representative of DFU patients. This SR discussed the large number of discontinued and unpublished NPWT RCTs and that unpublished NPWT studies represented 70% of planned or analyzed patients, raising concern of publication bias.[2] Data from studies in this SR were not pooled when assessment of statistical heterogeneity was very high (I^2>75%).[2] All three SRs contained a COI statement, and two SRs reported industry sponsorship of one author.[2,14] All three SRs additionally assessed included study quality, outlined literature search and selection methodology, described the data

extraction methodology, and tabulated study conclusions.[2,14,15] Quality assessments of the included studies in the SRS used different methodologies, however two SRs found unclear or moderate risk of bias due to lack of blinding in the trials.[2,14] One of the SRs used an instrument to evaluate the quality of included studies that did not penalize for failing to blind and therefore gave higher quality ratings to trials.[15] Literature search methodology included multiple databases, multiple relevant search terms, and defined inclusion and exclusion criteria.[2,14,15] Two SRs had two authors independently assess studies for inclusion.[2,14] Two SRs contained a PRISMA flowchart,[2,14] and two contained an examination of reported adverse events.[2,15]

The included MA was of a high quality.[1] It included a statement of no financial COI, a PRISMA flowchart, a defined research objective, assessment of study quality (Jadad scale), an examination of publication bias, sensitivity analyses, an examination of reported adverse events, and comprehensively described most of the methods used. The COI statements of studies were included in the MA. Literature search methods included multiple databases using defined search terms, inclusion, and exclusion criteria. Two authors independently evaluated studies for inclusion. Tabulated methodological qualities and quantitative assessments of study quality reported in the MA were used to classify seven of the included studies of high quality while one study was classified as poor quality.[1] The MA did not find any statistical evidence of publication bias, nor did sensitivity analysis identify differences in relative risk or heterogeneity for the outcome of wound healing.[1]

The included HTA provided details regarding the literature search and selection methodology, contained a PRISMA flowchart, a table of excluded studies, COI statements of included studies, detailed study characteristics, study quality, and included data from three relevant economic studies. The literature search methods were comprehensive and two researchers independently screened titles and abstracts against a predefined inclusion criteria.[5] The HTA itself did not include a COI statement.[5] A summary of critical appraisal of SRs, the MA, and HTA using AMSTAR[10] is available in Appendix 5, Table A5.1. The three studies in this HTA containing relevant economic data summarized in this report were identified as having industry funding.[5] Limitations of one CEA, which was based on an RCT, included patient selection bias, a lack of definitive endpoints and an underestimate of resource use. The RCT also gave treatments according to physician or manufacturer discretion.[5] The other CEA included in the HTA had limitations with respect to unequal patient characteristics between groups, and variation in the study endpoints. Limitations identified in the HTA of the included CUA were a lack of quality review of the studies used to derive the effectiveness estimates, and the patients in the studies used to populate the model may have not been comparable.[5]

The strengths of the identified RCT include well described patient and ulcer characteristics, simple randomization according to the date of admission, and statistical methods, as well as patient eligibility, intervention, and outcome descriptions. Additionally this RCT had a statement of no COIs. The limitations of the RCT include the small (n = 23) sample size of the trial conducted in a single center and a power calculation was not done. Also, due to the nature of the intervention, allocation concealment and blinding were not done in this study. There was also a statistically significant difference between groups in the number of patients entering the trial who had received prior ulcer treatment, 18.2% of the NPWT group had received no prior treatment while none of the control group had received no prior DFU treatment. Additionally this study did not present data on adverse event outcomes and did not find any evidence of efficacy in the control arm of the trial. The trial was set in Iran and therefore limits to the applicability of the findings in a Canadian setting may be present.[16] A summary of the critical appraisal of the RCT using the Downs and Black checklist[11] is available in Appendix 5, Table A5.2.

Included guidelines varied in quality. Three guidelines had graded recommendations presented next to the evidence level used to support it,[3,9,21] while three others had a recommendation grade that was directly dependent on the level of evidence.[7,20,23] Sufficient guideline development methodology was provided in four guidelines.[3,7,9,23] Literature search methodology description varied amongst the included guidelines with two lacking specificity to NPWT terms[3,20], two provided literature search methodology in a separate source,[7,22] and two guidelines did not have detailed literature search methods.[9,23] In regards to potential COIs, one guideline provided a statement of no COI,[20] one had a statement regarding methods used to avoid potential COI,[3] two had a statement suggesting potential COIs,[9,21] two guidelines did not have COI statements available[7,22] and one had a COI summary upon request.[23] One set of guidelines was specific to NPWT,[9] while the other guidelines had a broader focus on diabetes or DFU.[3,7,20-23] Four of the these guidelines with a broader focus did provide an explicit scope and/or purpose.[7,20,22,23] The degree of stakeholder representation was outlined in two guidelines and suggested inclusive input from primary caregivers, public health, patients and industry.[22,23] None of the guidelines provided an explicit statement or summary of the limitations of the recommendations. A summary of the critical appraisal of the included guidelines is available in Appendix 5, Table A5.4.

Three economic analyses were identified and included in this report.[17-19] An explicit objective was stated in two of the three analyses,[17,19] while all three stated the study perspective and described a relevant comparator.[17-19] The time horizon was well defined in the three studies,[17-19] one had limited long term data and endpoints,[17] another modelled a short term endpoint,[18] while another provided a 12 month economic model.[19] Sensitivity analysis was performed in two of the analyses.[18,19] Two of the studies were funded by industry,[18,19] while the remaining study had a statement of no COI.[17] The CEA based upon a published RCT contained a comprehensive cost breakdown derived from published sources, tabulated patient demographics, and had some incremental cost data.[17] The RCT on which this analysis is based has a moderate risk of bias due to no blinding,[1] but otherwise is a high quality RCT.[15] The CEA model made some assumptions based upon preliminary data, and the methods of selecting the data on which the model is based was not reported.[18] The apparatus capital costs in this CEA model are estimated from the manufacturer and there is an assumption regarding the rental structure of NPWT equipment that may not be valid in different healthcare settings.[18] The CUA model was based upon a previously published economic model for NPWT, described some characteristics of the modelled patients, provided previously published utility values, incorporated incremental costs, and consulted experts regarding the most relevant comparator for the setting of the model (France).[19]

Summary of Findings

Major findings and authors conclusions of the included SRs, MA and RCT are summarized in Appendix 6, Table A6.1.

Three SRs found no statistically significant evidence of NPWT inferiority in any outcome to SWC, gauze, or AMWT.[2,14,15] Consensus clinical effectiveness findings of the included SRs are that NPWT resulted in a greater proportion of DFU healing, and a shorter time to complete ulcer healing.[2,14,15] Additional outcomes reported by the included SRs that supported the superiority of NPWT of DFU are a reduced risk of secondary amputation,[2] and secondary minor amputations,[14] ulcer size, depth and volume reduction after treatment,[15] and an increased rate of granulation.[15] One SR examined evidence regarding adverse events and found evidence from one RCT that reported no statistically significant difference between NPWT and AMWT in

the occurrence of treatment-related adverse events and all adverse events, the most common of which was local wound infection.[2] The SRs narrative conclusions ranged from cautiously optimistic regarding NPWT of DFUs,[2] to confident in the superior clinical effectiveness of NPWT of DFUs.[15]

The MA included more primary studies than any one of the identified SRs and did not find any contradictory evidence.[1] Outcomes for which the MA found statistically significant superiority of NPWT over non-NPWT of DFU were the proportion of DFU healed, reduction in time to DFU healing, reduction in DFU area, reduction in secondary amputation, and a reduction in major amputation. No significant differences were found for the occurrence of secondary minor amputations or for treatment-related adverse events. The author's narrative conclusions acknowledge some remaining limitations to the conclusions however they state that NPWT appears to be a more effective treatment for DFU.[1]

One RCT was identified that was not part of an included SR.[16] With regard to clinical effectiveness, this trial's findings were generally consistent with the included SRs and MA of this report, however the lack of evidence for any efficacy of the control group in this study contradicts other studies. The proportion of DFUs healed completely was greater with NPWT, although the statistical significance of this finding in the small sample size was not evaluated. Statistically significant findings of NPWT superiority over moist dressings for the treatment of DFU were a greater reduction in ulcer surface area and depth, greater patient satisfaction, and decreased occurrence of secondary amputation.[16]

The findings of the economic studies included in this report are summarized in Appendix 6, Table A6.2.[17-19] Total cost per patient during a 12 week therapy course,[17] a modelled 16 week therapy course,[18] and a modelled 12 month treatment of 1000 DFU patients were lower for NPWT than the control.[19] Only one CEA modelled a higher total cost for conventional NPWT as compared to modern dressings when using lower NPWT efficacy values from literature sources that were not clearly identified.[18] From a public healthcare perspective a CEA found that NPWT treatment costs and NPWT non-treatment costs were both less than the associated AMWT costs.[17] This CEA also calculated a greater median cost per surface area wound closure for AMWT as compared to NPWT.[17] The CUA found that when modelling 1000 DFU patients over a 12 month time horizon NPWT results in more QALYs at a lower cost.[19] One HTA, NHS QIS 2010,[5] was also identified that included cost-effectiveness data from two CEAs and one CUA. One CEA found an incremental cost savings of $9,915 per patient using NPWT of DFUs, while the other CEA included in the NHS QIS HTA found that the comparative cost-effectiveness of a 20 week cost of care per patient depended on how often SWC required nursing visits.[5] The CUA found that NPWT resulted in more QALYs at a reduced cost as compared to both traditional dressings and AMWT.[5]

Relevant recommendations of the included guidelines are summarized in Appendix 6, Table 6.3. The levels of evidence and grades of recommendations referenced in the following text are described in Appendix 4.

One set of guidelines originating in Canada was developed by the CDA and was the most recent set of published guidelines identified but had no relevant recommendation. These guidelines did however state that there was insufficient evidence to support a recommendation regarding NPWT.[3] Guidelines published by AHRQ found level C evidence to recommend considering use of NPWT as it may increase DFU closure compared to SWC and is associated with a lower risk of secondary infections.[20] Guidelines published by the IDSA have a low graded

recommendation based upon weak evidence to consider using NPWT for selected DFUs that are slow to heal.[21] The NICE guidelines base a recommendation on low quality evidence to not use NPWT for DFU except in the context of a clinical trial or as a rescue therapy (when the only other option is amputation).[22] Other identified guidelines have moderately stronger recommendations.[7,9,23] Australian guidelines from the NHMRC published in 2011 have a grade B recommendation to consider NPWT for DFU in specialist centres as part of a comprehensive wound management program.[7] The recommendation from SIGN was graded B and states that NPWT should be considered in patients with DFU.[23] The strongest recommendations are from the industry sponsored International Expert Panel on NPWT.[9] Recommendations that are graded A state that NPWT must be considered as an advanced wound care therapy for postoperative Texas Grade 2 and 3 DFU without ischemia and must also must be considered to achieve healing by secondary intention. Two grade B recommendations are that NPWT should be stopped when the wound healing has progressed to the point when it can be closed by surgical means and that NPWT should be considered in an attempt to prevent amputation or re-amputation.[9]

Limitations

The cumulative evidence presented in this report is largely based upon small trials where, due to the nature of the intervention, appropriate blinding of investigators, allocation concealment, and blinded evaluation of outcomes are difficult or not attempted thus presenting potential for bias.[2,15] Additionally, although there was no evidence for publication bias as analyzed by Zhang et al., 2014,[1] there exist a number of unpublished trials on NPWT giving cause for concern.[2,5] The identified evidence may have limited applicability to the Canadian healthcare environment, in particular the identified economic studies evaluated costs may differ substantially.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence identified in this report is suggestive that NPWT treatment of DFU is more clinically effective than AMWT, SWC and traditional gauze. The consensus of the findings of the included SRs, MA and RCT is that NPWT for DFU results in superior clinical outcomes including proportion of DFUs healed, and time to DFU healing.[1,2,14-16] Evidence from three studies was also identified that suggested NPWT treatment of DFU resulted in less frequent secondary amputations.[1,2,14] Despite the overall consistent findings, the identified NPWT data are from relatively small trials with a low to moderate risk of bias.[2,15] Narrative conclusions from an SR and the MA included in this report also suggest that there is some uncertainty associated with the conclusions.[1,2]

There was no evidence identified suggesting that NPWT for DFU may result in an increased frequency of adverse events.[1,2] The size of the trials on which this evidence is based however may limit the potential for identification of potentially serious rare adverse events.

Two identified CEAs, one in an identified HTA,[5] found that NPWT is more cost-effective than AMWT.[5,17] Two identified CEAs found that NPWT was more cost-effective under certain conditions.[5,18] One found that NPWT is more cost-effective under the condition where SWC required two nursing visits per day instead of one.[5] The other CEA found that if the cost-effectiveness model is based on literature values with less NPWT efficacy, modern dressings become more cost-effective.[18] Both identified CUAs found that NPWT of DFUs resulted in more QALYs at less cost.[5,19] While there is no definitive consensus, the identified cost-effectiveness data suggest that NPWT is cost-competitive with appropriate comparators.

With the exception of guidelines originating from an industry sponsored panel,[9] recommendations to use NPWT for DFUs do not have high grades.[20-22] Identified guidelines with moderately highly graded recommendations recommend considering the use of NPWT for DFUs.[7,9,23] Guidelines from the CDA, published in 2013, suggest that there is insufficient evidence to make any recommendation regarding the use of NPWT for DFUs.[3]

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LIST OF ABBREVIATIONS

ACP	American College of Physicians
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AMWT	advanced moist wound care
CDA	Canadian Diabetes Association
CEA	cost-effectiveness analysis
COI	conflict of interest
CUA	cost-utility analysis
CRD	Centre for Reviews and Dissemination
DM	diabetes mellitus
DFU	diabetic foot ulcer
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HTA	health technology assessment
IDSA	Infectious Diseases Society of America
IEP on NPWT	International Expert Panel on negative pressure wound therapy
MA	meta-analysis
MUHC	McGill University Health Centre
NHMRC	National Health and Medical Research Council
NHS QIS	National Health Service Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NPWT	negative pressure wound therapy
OHTA	Ontario Health Technology Assessment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality adjusted life year
QOL	quality of life
RCT	randomized controlled trial
RCS	retrospective cohort study
RR	relative risk
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardized mean difference
SR	systematic review
SWC	standard wound care
UK	United Kingdom
USA	United States of America

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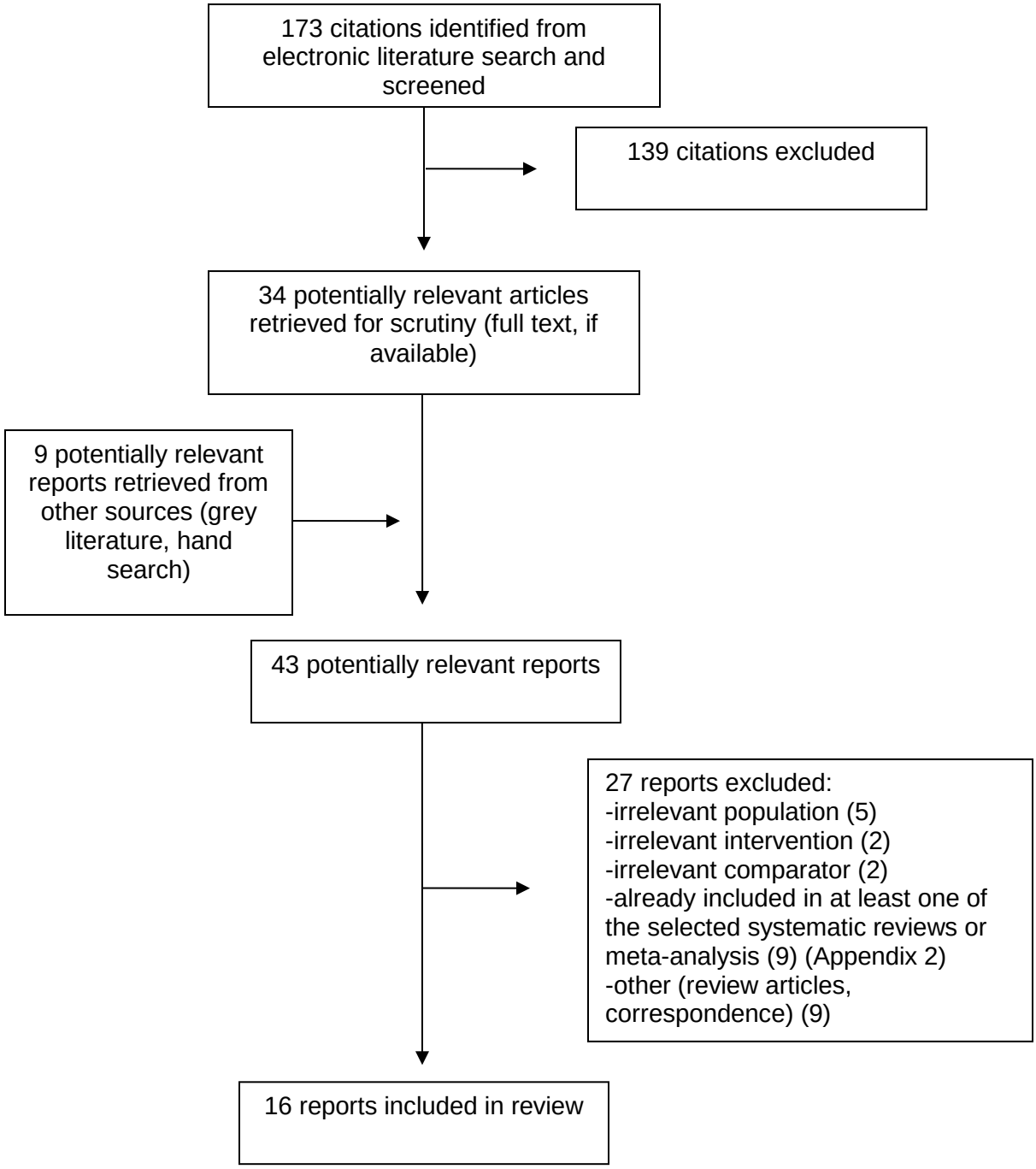
APPENDIX 1: Selection of Included Studies



APPENDIX 2: SUMMARY OF INCLUDED STUDIES

Table A2.1: Trials/SRs/Guidelines Included in Identified Studies

		Trials												SRs					G
		Karatepe et al., 2011[25]	Nain et al., 2011[40]	Novinscak et al., 2010[26]	Sepulveda et al., 2009[27]	Mody et al., 2008[28]	Blume et al., 2008[29]	Frykberg et al., 2007[41]	Akbari et al., 2007[30]	Armstrong et al., 2005[31]	Etöz et al., 2004[32]	Eginton et al., 2003[33]	McCallon et al., 2000[34]	Game et al., 2012[35]	OHTA 2010[36]	Noble-Bell et al., 2008[37]	Hinchliffe et al., 2008[38]	IEP on NPWT 2011[9]
SRs/MAs identified*	Guffanti et al., 2014[42]				X		X			X	X							
	Braun et al., 2014[14]													X	X	X	X	X
	Zhang et al., 2014[1]	X	X		X		X			X	X	X	X					
	Dumville et al., 2013[2]	X		X		X	X			X								
	Greer et al., 2013[6]	X					X						X					
	Game et al., 2012[35]				X		X	X										
	Xie et al., 2010[15]				X		X		X	X	X	X	X					
	OHTA 2010[36]						X			X								
	MUHC 2010[43]				X		X		X	X	X	X	X					
	NHS QIS 2010[5]						X			X		X	X					
	AHRQ 2009[44]						X			X			X					

*not all identified SR/MAs have been reviewed in this report, as some have been superseded by more recent or comprehensive reviews

AHRQ=Agency for Healthcare Research and Quality; **G**=guidelines; **IEP on NPWT**=International Expert Panel on negative pressure wound therapy; **MUHC**=McGill University Health Centre; **NHS QIS**=National Health Service Quality Improvement Scotland; **OHTA**=Ontario Health Technology Assessment; **RCT**=randomized controlled trial; **SR**=systematic review

APPENDIX 3: SUMMARY OF STUDY CHARACTERISTICS

Table A3.1: Summary of Study Characteristics of Included HTAs/SRs/MAs/RCT

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Braun et al., 2014[14]				
SR: DFU (5 SRs)	DFU	NPWT + other DFU therapies	SWC or AMWT	• DFU healing efficacy • Time to heal • Infection rates • Adverse events • Major amputation • Minor amputation
Zhang et al., 2014[1]				
MA: (8 RCTs)	DFU (n=669)	NPWT	Non-NPWT	*Effectiveness:* • DFU healing efficacy • Time to heal • Change in ulcer size • Amputation • Granulation tissue formation (rate) • QOL *Safety profile:* • Edema • Pain • Bleeding • Infection rates
Dumville et al., 2013[2]				
SR: (5 RCTs)	DFU (n=605)	NPWT	SWC, AMWT	*Effectiveness:* • DFU healing efficacy • Time to heal • Change in ulcer size (when adjusted for baseline size) • Rate of change in ulcer size • Major amputation • Minor amputation *Secondary outcomes:* • QOL • Adverse events • Resource use • Wound recurrence
Xie et al., 2010[15]				
SR: DFU (7 RCTs)	DFU (n=580) + pressure ulcers and mixed wounds	NPWT	SWC	• Granulation tissue formation (efficacy, rate) • DFU healing efficacy • Time to heal • Change in ulcer size (area, volume, depth)

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
NHS QIS 2010[5]				
HTA: DFU (2 SRs, 1 RCT, 1 RCS, 3 economic studies)	DFU (n=342 from RCT) + other diverse wounds types	NPWT	SWC, AMWT	• DFU healing efficacy • Time to heal • Granulation tissue formation (efficacy, rate) • Change in ulcer size (area, volume, depth) • Amputation • Resource use • Direct cost/patient • Expected 20 week costs • Total costs • QALYs
Ravari et al., 2014[16]				
RCT	DFU (n=23)	Vacuum-assisted closure (KCI Medical Ltd., England) (n=10)	Moist dressing (n=13)	• DFU healing efficacy • Change in ulcer size, depth • Wagner score • Patient satisfaction • Major amputation • Minor amputation

AMWT=advanced moist wound therapy; **DFU**=diabetic foot ulcer; **HTA**=heath technology assessment; **MA**=meta-analysis; **NPWT**=negative pressure wound therapy; **QALY**=quality adjusted life year; **QOL**=quality of life; **RCS**=retrospective cohort study; **RCT**=randomized controlled trial; **SMWT**=standard moist wound therapy; **SR**=systematic review; **SWC**=standard wound care

Table A3.2: Summary of Study Characteristics of Included Economic Analyses

Type of Economic Evaluation, Perspective, Time	Patient Population	Comparison	Outcomes	Assumptions
Driver et al., 2014[17]				
CEA Public health sector perspective, USA 12 week therapy course	DFU- Wagner grades 2 and 3 (n=324) Based post-hoc retrospective analysis of RCT from 2008	NPWT (n=162) vs AMWT (n=162) Costs divided into ulcer therapy costs and non-therapy ulcer treatment costs	• Total average cost per patient • Total average cost per closed ulcer patient • Total average cost per patient with persistent ulcer • Total average cost per closed ulcer patient for non-therapy ulcer treatment • Total average cost per persistent ulcer patient for non-therapy ulcer treatment • Breakdown of non-therapy ulcer costs associated with patients	Costs calculated retrospectively
Hutton et al., 2011[18]				
CEA Medicare and private payer perspectives, USA 16 week treatment course	DFU	NPWT vs SNaP™ wound care system (Spiracur, Inc., Sunnyvale, CA) vs SWC	• Total Costs per patient • Breakdown of cost components per patient	Based on economic modelling Modelled exponential healing rates Model based on 'best' available data Equal efficacy between SNaP™ and NPWT systems

Type of Economic Evaluation, Perspective, Time	Patient Population	Comparison	Outcomes	Assumptions
				SNaP™ does not require home healthcare costs Assumptions about efficacy based on preliminary studies
Whitehead et al., 2011[19]				
CUA Payer perspective in France One year time horizon	DFU (28% infected, 75% of which are gangrenous) Modelled 1000 patients over 12 months	NPWT (V.A.C. Therapy system, KCI Medical Ltd., England) vs AMWT (Algosteril®, alginate with Adaptic®)	• Total Costs per 1000 patients • Breakdown of cost components per patient • QALYs	Based on economic modelling Long-term outcomes extrapolated Some cost equivalent assumptions made between treatment arms
AMWT=advanced moist wound therapy; **CEA**=cost-effectiveness analysis; **CUA**=cost-utility analysis; **DFU**=diabetic foot ulcer; **NPWT**=negative pressure wound therapy; **QALY**=quality-adjusted life-year; **RCT**=randomized controlled trial; **SWC**=standard wound care				

Table A3.3: Summary of Study Characteristics of Included Guidelines

Origin, Publication Year	Interventions of Interest	Grading (See Appendix 3)	Target Population
CDA 2013[3]			
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Canada, 2013	NPWT	Levels of Evidence 1A – 4 Recommendations Graded A - D	Healthcare professionals
AHRQ 2012[20]			
Wound, Ostomy, and Continence Nurses Society, Agency for Healthcare Research and Quality USA, 2012	NPWT	Levels of Evidence I – VI Recommendations Graded A - C	Advanced practice nurses Allied Health Personnel Dietitians Health Care providers Nurses Physical Therapists Physician Assistants Physicians Podiatrists
IDSA 2012[21]			
Infectious Diseases Society of America, USA, 2012	NPWT	Levels of Evidence High, Moderate, Low and Very Low quality evidence ratings Recommendations Graded Strong or Weak	Clinicians Healthcare organizations
NHMRC 2011[7]			
National Health and Medical Research Council, Melbourne, Australia, 2011	NPWT	Levels of Evidence I – IV Recommendations Graded A -D	Broad range of Health Professionals and Healthcare Workers in urban and rural/remote primary care and specialist foot centres
NICE 2011[22]			
National Health Service, National Institute for Health and	NPWT	GRADE evidence profiles	Hospital staff who care for patients with diabetic foot problems

Origin, Publication Year	Interventions of Interest	Grading (See Appendix 3)	Target Population
Clinical Excellence, London, UK, 2011			
International Expert Panel on NPWT 2011[9]			
International Expert Panel of NPWT, Hamburg, Germany, 2011	NPWT	SIGN classification Levels of Evidence 1 – 4 Recommendation Grades A - D	Healthcare professionals
SIGN 2010[23]			
National Health Service Quality Improvement Scotland, Scottish Intercollegiate Guidelines Network, Scotland, 2010	NPWT	SIGN classification Levels of Evidence 1 – 4 Recommendation Grades A - D	All healthcare professionals involved in the care of people with diabetes Diabetic Patients Diabetic Caregivers

AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **GRADE=**Grading of Recommendations Assessment, Development and Evaluation; **IDSA**=Infectious Diseases Society of America; **NHMRC**= National Health and Medical Research Council; **NPWT**=negative pressure wound therapy; **SIGN**=Scottish Intercollegiate Guidelines Network; **UK**=United Kingdom; **USA**=United States of America

APPENDIX 4: Summary of Guideline Grading and Recommendations and Levels of Evidence

Table A4: Guideline Grading of Recommendations and Levels of Evidence

Recommendation	Levels of Evidence
CDA 2013[3]	
A Evidence from Level **1** **B** Evidence from Level **2** **C** Evidence from Level **3** **D** Evidence from Level **4** or consensus	**1A** SR or MA of high quality RCTs **1B** non-RCT or cohort study with indisputable results **2** moderate quality RCT or SR **3** non-RCT or cohort study or SR, MA of Level 3 studies **4** Other
AHRQ 2012[20]	
A Two or more supporting RCTs (Level **I** or **II**), an MA of RCTs, or Cochrane SR of RCTs **B** One or more supporting controlled trials (n≥10), or two or more supporting non-RCTs (n≥10) (Level **III**) **C** Two supporting case series (n≥10) or expert opinion	**I** Statistically significant difference (p<0.05) from an RCT **II** An RCT not meeting Level I criteria **III** A non-RCT **IV** Retrospective cohort or case series (n≥10) **V** Case series (n≥10) with no controls **VI** Case report (n≤10)
IDSA 2012[21]	
Strong Desirable effects clearly outweigh undesirable effects, or vise versa **Weak** Desirable effects closely balanced with undesirable effects, or uncertainty in estimates	**High-quality** Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies **Moderate-quality** Evidence from moderate quality RCTs or exceptionally strong evidence from unbiased observational studies **Low-quality** Evidence for at least one critical outcome from observational studies or indirect evidence or poor quality RCTs or indirect evidence **Very low-quality** One critical outcome evident in clinical observations or very indirect evidence
NHMRC 2011[7]	
A Level **I** (n≥1) or Level **II** (n≥2) with a low risk of bias **B** Level **II** (n≤2) with a low risk of bias or SR or several level **III** studies with low bias risk **C** Level **III** (n≤2) with low bias risk or Level **I** or **II** studies with moderate bias risk **D** Level **IV** (n≥1) or Level **I** – **III**, SRs with high bias risk	**I** SR of Level **II** **II** RCT **III-1** pseudo-randomized controlled trial **III-2** non-RCT, cohort study, case-control study, interrupted time series with control group **III-3** historical control study, two or more single arm studies, or interrupted time series without parallel control group **IV** Case series
NICE 2011[22]	
N/A	GRADE evidence profile **High** - RCT **Moderate** **Low** **Very Low** – Observational study

Recommendation	Levels of Evidence
	Level decreases one category for: Study limitations Inconsistency Indirectness Imprecision Publication bias Level increases one category for: Large magnitude of effect Evidence of dose-response All plausible confounding factors are accounted for
International Expert Panel on NPWT 2011[9]	
A At least one relevant MA, SR, or RCT rated as **1++**, or multiple overall consistent relevant studies rated as **1+** **B** Relevant consistent studies rated as **2++** or extrapolated evidence from studies rated as **1++** or **1+** **C** Relevant consistent studies rated as **2+** or extrapolated evidence from studies rated as **2++** **D** Evidence level **3** or **4** or Extrapolated evidence from studies rated as **2+**	**1++** High quality MAs, SRs of RCTs, or RCTs - very low risk of bias **1+** Well conducted MAs, SRs, or RCTs - low risk of bias **1 -** MAs, SRs, or RCTs - high risk of bias **2++** High quality SRs of case control or cohort studies or high quality case control or cohort studies - very low risk of confounding or bias and a high probability of a causal relationship **2+** Well conducted case control or cohort studies - low risk of confounding or bias and a moderate probability of a causal relationship **2 -** Case control or cohort studies - high risk of confounding or bias and a significant risk that the relationship is not causal **3** Non-analytic studies, e.g. case reports, case series **4** Expert opinion
SIGN 2010[23]	
A At least one relevant MA, SR, or RCT rated as **1++**, or multiple overall consistent relevant studies rated as **1+** **B** Relevant consistent studies rated as **2++** or extrapolated evidence from studies rated as **1++** or **1+** **C** Relevant consistent studies rated as **2+** or extrapolated evidence from studies rated as **2++** **D** Evidence level **3** or **4** or Extrapolated evidence from studies rated as **2+**	**1++** High quality MAs, SRs of RCTs, or RCTs - very low risk of bias **1+** Well conducted MAs, SRs, or RCTs - low risk of bias **1 -** MAs, SRs, or RCTs - high risk of bias **2++** High quality SRs of case control or cohort studies or high quality case control or cohort studies - very low risk of confounding or bias and a high probability of a causal relationship **2+** Well conducted case control or cohort studies - low risk of confounding or bias and a moderate probability of a causal relationship **2 -** Case control or cohort studies - high risk of confounding or bias and a significant risk that the relationship is not causal **3** Non-analytic studies (e.g. case reports, case series) **4** Expert opinion
AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **GRADE=**Grading of Recommendations Assessment, Development and Evaluation; **IDSA**=Infectious Diseases Society of America; **MA**=meta-analysis; **NHMRC**= National Health and Medical Research Council; **NPWT**=negative pressure wound therapy; **SIGN**=Scottish Intercollegiate Guidelines Network; **RCT**=randomised controlled trial; **SR**=systematic review; **UK**=United Kingdom; **USA**=United States of America	

APPENDIX 5: Summary of Critical Appraisal

Table A5.1: Critical Appraisal Summary for SRs/MAs/HTAs using AMSTAR tool[10]

Strengths	Limitations
Braun et al., 2014[14]	
• COI statement • Literature search selection/inclusion/exclusion methodology outlined • PRISMA flowchart • Study quality assessed (ACP criteria) • Data extraction methodology outlined • Tabulated study conclusions	• One author with financial COI • Lacks pre-defined research questions • No mention of COI statements of included studies • Unquantified conclusions • No assessment of publication bias • No assessment of patient characteristics • No mention of adverse events
Zhang et al., 2014[1]	
• Statement of no financial COI • Literature search selection/inclusion/exclusion methodology detailed • PRISMA flowchart • Defined research objective • Study quality assessed (Jadad scale) • Data extraction methodology described • Statistical methods outlined • Publication bias examined (Begg funnel plot) • Statistical heterogeneity tested • Sensitivity analyses conducted • Used ITT analysis • Quantified conclusions • Examination of reported adverse events	• No mention of COI statements of included studies
Dumville et al., 2013[2]	
• COI statement • Literature search selection/inclusion/exclusion methodology detailed • PRISMA flowchart • Defined research objective • Study quality discussed • Data extraction methodology described • Statistical heterogeneity tested • Mention of COI statements of included studies • Quantified conclusions • Risk of study bias examined • Patient characteristics of included studies outlined • Table of excluded study characteristics • Examination of reported adverse events	• Some industry support for one author • No examination of publication bias
Xie et al., 2010[15]	
• Statement of no COI • Literature search selection/inclusion/exclusion methodology described •Formulated objective	• No patient characteristic analysis • No list of excluded studies • Study quality assessment did not penalize for failing to blind

Strengths	Limitations
• Study quality assessed quantitatively • Study heterogeneity mentioned • Detailed tabulated study characteristics and results • Discussion of industry funding in the literature • Tabulated study conclusions • Discussion of publication bias • Adverse event occurrence mentioned	
NHS QIS 2010[5]	
• Literature search selection/inclusion methodology detailed • PRISMA flowchart • Excluded studies tabulated with reason for exclusion • Defined objective • Patient perspectives provided • COI of included studies discussed and tabulated • Mention of publication bias • Detailed tabulation of study characteristics/quality and results • Patient characteristics tabulated with study characteristics • Includes data and analysis of three relevant economic studies	• No COI statement • No assessment of study heterogeneity • Conclusions not quantitative • Adverse event outcomes mentioned without quantification
ACP=American College of Physicians; **COI**=conflict of interest; **ITT**=intention to treat; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses;	

Table A5.2: Critical Appraisal Summary for included RCT using Downs and Black checklist[11]

Strengths	Limitations
Ravari et al., 2013[16]	
• Patient and ulcer characteristics tabulated • Randomization method outlined • Statistical methods described • Defined patient eligibility, intervention and outcomes • Statement of no COI	• No allocation concealment • No blinding • Small single centre study • No adverse event outcomes presented • Trial setting (Iran) may limit applicability to Canadian setting • No evidence of efficacy in control arm – inconsistent with other trials • Statistically significant difference between groups in the number of patients receiving prior ulcer treatment

Table A5.3: Critical Appraisal Summary for Economic Studies using Drummond checklist12

Strengths	Limitations
Driver et al., 2014[17]	
• Well defined analysis • Explicit purpose • Relevant comparator • Economic evaluation of an RCT • Comprehensive cost breakdown derived from published sources • Statement of no COI • Some incremental cost data • Patient demographics tabulated	• Limited long term data and endpoints • RCT has a moderate risk of bias • No sensitivity analysis performed
Hutton et al., 2011[18]	
• Sensitivity analysis performed • Analysis done from two perspectives • Relevant comparators	• Assumptions about efficacy based on preliminary studies • Modelled only short term endpoint • Industry funded study • Capital costs estimated from manufacturer • Selection methods for literature unclear • Assumption regarding rental structure of comparator system
Whitehead et al., 2011[19]	
• Explicit objective • Sensitivity analysis performed • Consultation to establish relevant comparator • Patient demographics described • Utility values presented with citation • Based on a published economic model for NPWT in a different setting • Model incorporates incremental costs	• Industry funded study • Based upon limited long term data
AMWT=advanced moist wound therapy; **DFU**=diabetic foot ulcer; **NPWT**=negative pressure wound therapy; **QALY**=quality-adjusted life-year; **RCT**=randomized controlled trial;	

Table A5.4: Critical Appraisal Summary for Guidelines using AGREE II tool[13]

Strengths	Limitations
CDA 2013[3]	
• Graded recommendations explicitly linked to evidence level • Guideline development methodology described • Statement regarding avoidance of potential COIs • Guideline update process outlined • Target audience described • Canadian perspective	• Very broad focus • Literature search methodology lacks specificity to NPWT • No detailed description of stakeholder representation • No statement of limitations
AHRQ 2012[20]	
• Graded recommendations • Grades of recommendations linked to a level of evidence • Statement of no COIs • Explicit scope • Benefits and harms of guideline implementation outlined	• Broad focus • Literature search methodology lacks specificity to NPWT, inclusion and exclusion criteria • No description of stakeholder representation • No statement of limitations
IDSA 2012[21]	
• Graded recommendations explicitly linked to evidence level • COI statement	• Broad focus • Full text of methodology not available • No description of stakeholder representation • No statement of limitations
NHMRC 2011[7]	
• Graded recommendations • Grades of recommendations linked to a level of evidence • Literature search methodology provided in separate source • Quality of supporting literature evaluated and discussed • Explicit scope and purpose • Guideline development methodology described • Guideline update process outlined • Guidance for guideline implementation • Suggestions for needed future research	• Broad focus • COI statement only available in external document • No procedure for limiting potential COIs • No statement of limitations
NICE 2011[22]	
• Explicit scope • Guideline update process outlined • Guidance for guideline implementation • Stakeholder involvement in guideline development • Literature search methodology described in separate source	• Broad scope • Recommendations not graded • Evidence quality evaluated only for individual studies •Evidence quality not presented with recommendations • No COI statement available • No statement of limitations

Strengths	Limitations
International Expert Panel on NPWT 2011[9]	
• Focused scope • Graded recommendations explicitly linked to evidence level • Statement of COIs • Guideline development methodology described • Literature search methodology outlined	• No statement of limitations • Limited stakeholder representation • Guidelines funded by vendor of NPWT products
SIGN 2010[23]	
• Explicit purpose • Graded recommendations • Grades of recommendations linked to a level of evidence • Guideline development methodology described • Guidance for guideline implementation • Guideline update process outlined • Suggestions for needed future research • Stakeholder involvement in guideline development	• Very broad scope • Statement of COIs available upon request • Literature search methodology vague
AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **COI**=conflict of interest; **GRADE=**Grading of Recommendations Assessment, Development and Evaluation; **IDSA**=Infectious Diseases Society of America; **MA**=meta-analysis; **NHMRC**=National Health and Medical Research Council; **NPWT**=negative pressure wound therapy; **SIGN**=Scottish Intercollegiate Guidelines Network; **RCT**=randomised controlled trial; **SR**=systematic review; **UK**=United Kingdom; **USA**=United States of America	

APPENDIX 6: Summary of Findings

Table A6.1: Summary of Main Findings and Author's Conclusions of SRs/MAs/RCTs

Main Findings	Author's Conclusions
Braun et al., 2014[14]	
OHTA, 2010[36] 2 RCTs (n=342) 1) "Proportion of patients who achieved complete ulcer closure in NPWT was significantly greater than in controls in both studies" (pp. 271) 2) "Time to complete healing was significantly shorter in NPWT groups vs. controls" (pp. 271) *Noble-Bell and Forbes, 2008*[37] 4 RCTs (n=206) 1) "Proportion of patients who achieved complete ulcer closure in NPWT was significantly greater than in controls in the two studies that evaluated this outcome" (pp. 271) 2) "Time to complete healing was significantly shorter in NPWT groups vs. controls" (pp. 271) *International Expert Panel on NPWT 2011*[9] 9 studies 1) "NPWT should be considered in an attempt to prevent amputation or re-amputation" (pp. 271) 2) "NPWT must be considered as an advanced wound care therapy for postoperative Texas grade 2 and 3 diabetic feet without ischemia" (pp. 271) 3) "NPWT must be considered to achieve healing by secondary Intention" (pp. 271) 4) "NPWT should be stopped when wound has progressed suitably to be closed by surgical means" (pp. 271) *Hinchliffe et al., 2008*[38] 3 RCTs "Significant improvements in healing rate and healing time associated with NPWT (included chronic DFUs and postamputation wounds in diabetic patients)" (pp. 271) *Game et al., 2012*[35] 6 studies 1) "Two methodologically sound RCTs reported reduced healing time, increased incidence of healing (at 16 weeks) and reduced risk of minor amputation in participants using NPWT" (pp. 271)	"Moderate-quality evidence suggests that NPWTs improve healing of DFUs and non-healing post amputation wounds compared with standard wound care. Many questions remain regarding ideal patient population and cost effectiveness." (pp. 277)
Zhang et al., 2014[1]	
Clinical Effectiveness **Proportion of DFU Healing (3 RCTs)** RR>1 favours NPWT RR (95%CI (*p*)): 1.52 (1.23, 1.89 (*p*<0.001)) (I^2=0.0%)	"In summary, negative-pressure wound therapy appears to be a more effective

Main Findings	Author's Conclusions
DFU Area Reduction (4 RCTs) SMD>0 favours NPWT SMD (95%CI (*p*)): 0.89 (0.41, 1.37 (*p*=0.003)) (I^2=0.0%) **DFU Healing Time (2 RCTs)** SMD<0 favours NPWT SMD (95%CI (*p*)): -1.10 (-1.83, -0.37 (*p*=0.003)) (I^2=0.0%) **Secondary Amputation (2 RCTs)** RR<1 favours NPWT RR (95%CI (*p*)): 0.35 (0.17, 0.74 (*p*=0.006)) (I^2=0.0%) **Major Amputation (2 RCTs)** RR<1 favours NPWT RR (95%CI (*p*)): 0.14 (0.04, 0.51 (*p*=0.003)) (I^2=0.0%) **Minor Amputation (2 RCTs) - No Significant Difference** RR<1 favours NPWT RR (95%CI (*p*)): 0.37 (0.18, 0.76 (*p*=0.837)) (I^2=0.0%) **Adverse Events** **Treatment-Related Adverse Events (3 RCTs) - No Significant Difference** RR>1 favours NPWT RR (95%CI (*p*)): 1.12 (0.66, 1.89 (*p*=0.683)) (I^2=0.0%)	treatment for diabetic foot ulcers, with a similar safety profile, compared with non–negative-pressure wound therapy. Future well-designed clinical trials that should overcome the existing limitations and incorporate economic evaluation and patient satisfaction, when necessary, are required to provide more convincing evidence for clinical practice." (pp. 150)
Dumville et al., 2013[2]	
Clinical Effectiveness **Proportion of DFU Healing (2 RCTs)** RR>1 favours NPWT vs AMWT RR (95%CI (*p*)): 1.47 (1.18, 1.84 (*p*<0.001)) (I^2=0.0%) **Proportion of DFU Healing (1 RCTs)** RR>1 favours NPWT vs Gauze RR (95%CI (*p*)): 0.38 (0.05, 2.59 (*p*<0.00001)) **DFU Healing Time (2 RCTs)** HR>1 favours NPWT vs AMWT HR (95%CI (*p*)): 1.85 (1.40, 2.45 (*p*<0.001)) (I^2=0.0%) **Secondary Amputation (2 RCTs)** RR<1 favours NPWT vs AMWT RR (95%CI (*p*)): 0.35 (0.17, 0.74 (*p*=0.006)) (I^2=0.0%) **Adverse Events** **Treatment-Related Adverse Events (1 RCT) – No Significant Difference** RR>1 favours NPWT vs AMWT	"Data from the two largest included studies suggested that NPWT may be an effective treatment in terms of healing debrided foot ulcers and post-operative amputation wounds in people with DM. However, these studies could be at risk of bias. Thus, any potential change in practice

Main Findings	Author's Conclusions
RR (95%CI (*p*)): 0.90 (0.40, 2.06 (*p*>0.05) **All Adverse Events (1 RCT) – No Significant Difference** RR>1 favours NPWT vs AMWT RR (95%CI (*p*)): 0.96 (0.72, 1.28 (*p*>0.05)	regarding the use of NPWT would need to be informed by clinical experience and acknowledge the uncertainty around this decision due to the quality of data." (pp.25)
Xie et al., 2010[15]	
Quality of Included studies was evaluated as: A - High B - Moderate C - Low **Ratings based upon:** Selection Bias including Randomization Method and Baseline Equality Detection Bias including Blinding Attrition Bias including handling of dropouts Sample Size and Statistical Analysis **Statistically Significant Level A Quality Evidence (2 RCTs)** NPWT evidence for: 1 RCT - Less time to 90% granulation 1 RCT - Greater proportion healing by 112 days 1 RCT - Less time to complete ulcer closure **Statistically Significant Level B Quality Evidence (3 RCTs)** NPWT evidence for: 2 RCTs - Greater reduction in ulcer size 1 RCT - Greater proportion with ulcer improvement 1 RCT - Greater proportion healing by 112 days 1 RCT - Less time to >76% granulation 1RCT - Less time to almost granulation **Statistically Significant Level C Quality Evidence (2 RCTs)** NPWT evidence for: 1 RCT - Greater reduction in ulcer depth 1 RCT - Greater reduction in ulcer volume	"There is now sufficient evidence to conclude that the healing of diabetes-associated chronic lower extremity wounds can be accelerated with the use of NPWT." (pp. 495)
Ravari et al., 2014[16]	
Clinical Effectiveness **Proportion of DFU Healing** Percent healed completely NPWT: 70% Moist dressing: 30.76%	"Although the number of patients in this study was limited, the results

Main Findings	Author's Conclusions
Change in Ulcer Surface Area Surface area before (± SD) - surface area after (± SD) (*p*) NPWT: 39.5 (± 9.1) cm^2 - 28.8 (± 8.5) cm^2 (*p* = 0.02) Moist dressing: 36.9 (± 10.4) cm^2 - 54.2 (± 12.5) cm^2 (*p* = 0.1) Difference between groups *p* = 0.03 **Change in Ulcer Depth** Depth before (± SD) - depth after (± SD) (*p*) NPWT: 19 (± 7) mm - 12 (± 4) mm (*p* = 0.007) Moist dressing: 17 (± 6) mm - 20 (± 8) mm (*p* = 0.5) Difference between groups *p* = 0.02 **Patient Satisfaction** Percent satisfied (*p* = 0.004) NPWT: 76.9% Moist dressing: 23.1% **Amputation** Percent Major, Minor amputation NPWT: 0%, 0% Moist dressing: 38.5%, 7.69% Difference between groups *p* = 0.03	obtained from this study and satisfaction of the patients allowed us to conclude that V.A.C. is a suitable treatment modality in the management of diabetic foot ulcers." (pp. 7 of 9)

AMWT=advance moist wound therapy; **CI**=confidence interval; **DFU**=diabetic foot ulcer; **HR**=hazard ratio; **NPWT**=negative pressure wound therapy; **OHTA**=Ontario Health Technology Assessment; **RCT**=randomized controlled trial; **RR**=relative risk; **SMD**=standardized mean difference

Table A6.2: Main Study Findings and Author's Conclusions of Economic Studies

Main Findings	Author's Conclusions
Driver et al., 2014[17]	
TOTAL COST - 12 weeks therapy **Mean Cost per patient ±SD(95%CI)** NPWT (n=162): **$11 984.40** ±$19 423.76($8 970.69, $14 998.10) AMWT (n=162): **$13 557.51** ±$21 923.21($10 156.00, $16 959.01) **Mean Cost per patient achieving DFU closure ±SD(95%CI)** NPWT (n=67): **$10 172.38** ±$13 692.47($6 832.52, $13 512.23) AMWT (n=44): **$9 505.23** ±$20 289.99($3 336.51, $15 673.95) **Mean Cost per patient not achieving DFU closure ±SD(95%CI)** NPWT (n=95): **$13 262.34** ±$22 595.76($8 659.35, $17 865.34) AMWT (n=118): **$15 068.52** ±$22 396.32($10 985.34, $19 151.71) **DFU TREATMENT COSTS - 12 weeks therapy** NPWT (n=67): **$4 718.47** AMWT (n=44): **$2 312.34** **DFU NON-TREATMENT - 12 weeks therapy** NPWT (n=95): **$7 265.93** AMWT (n=118): **$11 245.17** **MEDIAN COST PER CM^2 REDUCTION** NPWT= $1 460.42 AMWT= $2 566.17	"Our results show greater cost effectiveness with NPWT versus AMWT in recalcitrant wounds that didn't close during a 12-week period, due to lower expenditures on procedures and use of health-care resources." (pp. 147)
Hutton et al., 2011[18]	
TOTAL COSTS DFU treatment (16 weeks) includes long term costs of treatment failure **Model from Higher efficacy NPWT literature** Modern dressings: $23 079 NPWT Private payer: $16 154 NPWT Medicare: $15 676 SNaP^{TM} Wound Care System: $10 878 **Model from Lower efficacy NPWT literature** Modern dressings: $22 575 NPWT Private payer: $26 084 NPWT Medicare: $24 356 SNaP^{TM} Wound Care System: $22 156	"For any given level of effectiveness, modern dressings have lower total costs. However, if negative pressure wound therapies are sufficiently more effective, they can have lower overall total costs." (pp. 202)
Whitehead et al., 2011[19]	
TOTAL COST per patient over 12 months (QALYs) V.A.C.® Therapy: €24 881.23 (0.787) AMWT: €28 854.98 (0.784) If unhealed V.A.C.® Therapy. treated patients remain on V.A.C.® Therapy for 12 months instead of switching to AMWT after 3 months, V.A.C.® Therapy costs increase to €27 133.00 per patient	"• V.A.C.® Therapy results in less amputations, at a lower cost • V.A.C.® Therapy results in more ulcers healed, at a lower cost

Main Findings	Author's Conclusions
per year	• V.A.C.® Therapy results in more QALYs, at a lower cost" (pp. 27)
NHS QIS 2010[43]	
1 CEA % DFU healed NPWT: 55% AMWT: 38.8% Incremental cost per patient to achieve 100% DFU healing -$9 915 using NPWT **1 CEA** %DFU healed NPWT: 46.3% SWC: 32.8% 20-week cost of care per patient NPWT: $16 733 SWC and one nurse visits/day: $15 258 SWC and two nurse visits/day: $28 691 **1 CUA** Average total costs 1 year per patient (QALYs) NPWT: $57 944.37 (0.531) Traditional dressings: $79 950.69 (0.523) NPWT: $52 829.89 (0.540) AMWT: $61 756.76 (0.534)	"Evidence on the cost effectiveness of TNP is necessarily limited, because of the lack of robust clinical effectiveness evidence. It was confined to diabetic foot wounds and related to only one manufacturer's product. Further, the evidence base identified included only one full economic evaluation, was based on small sample sizes in non-UK care settings and was sponsored by the manufacturer. Consequently, there is currently insufficient cost-effectiveness evidence to support routine use of [NPWT] technology in NHSScotland." (pp. 36)

AMWT=advanced moist wound therapy; **CI**=confidence interval; **CUA**=cost-utility analysis; **DFU**=diabetic foot ulcer; **NPWT**=negative pressure wound therapy; **QALY**=quality-adjusted life-year; **RCT**=randomized controlled trial; **SD**=standard deviation; **SWC**=standard wound care

Table A6.3: Summary of Recommendations by Source (see Appendix 3 for grading schemes).

CDA 2013[3]
No relevant recommendations "There is also insufficient evidence to make any recommendation about the role of negative pressure wound therapy (NPWT) in the routine management of neuropathic wounds. There is, however, some evidence to support NPWT as a postoperative intervention after extensive debridement" (pp. S146)
AHRQ 2012[20]
Recommendation: "Consider use of negative pressure wound therapy which may increase complete wound closure compared to standard wound dressings and is associated with lower risk of secondary infections." **Level of Evidence = C**
IDSA 2012[21]
Recommendation: "No adjunctive therapy has been proven to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak, moderate), growth factors (weak, moderate), granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low)." (pp. 1684)
NHMRC 2011[7]
Recommendation: "Topical negative pressure therapy may be considered for foot ulcers in specialist centres, as part of a comprehensive wound management program." **Grade B** (pp. 30)
NICE 2011[22]
Recommendation: "Negative pressure wound therapy should not be routinely used to treat diabetic foot problems, but may be considered in the context of a clinical trial or as rescue therapy (when the only other option is amputation)." Based upon **LOW quality** evidence. (pp. 129)
International Expert Panel on NPWT 2011[9]
Recommendation: NPWT must be considered as an advanced wound care therapy for postoperative Texas Grade 2 and 3 diabetic feet without ischaemia. **Grade A** **Recommendation:** NPWT must be considered to achieve healing by secondary intention. **Grade A** **Recommendation:** Alternatively NPWT should be stopped when wound has progressed suitably to be closed by surgical means. **Grade B** **Recommendation:** NPWT should be considered in an attempt to prevent amputation or re-amputation. **Grade B**
SIGN 2010[23]
Recommendation: Negative pressure wound therapy should be considered in patients with active diabetic foot ulcers or postoperative wounds. **Grade B**
AHRQ=Agency for Healthcare Research and Quality; **CDA**=Canadian Diabetes Association; **COI**=conflict of interest; **GRADE=**Grading of Recommendations Assessment, Development and Evaluation; **IDSA**=Infectious Diseases Society of America; **MA**=meta-analysis; **NHMRC**= National Health and Medical Research Council; **NPWT**=negative pressure wound therapy; **SIGN**=Scottish Intercollegiate Guidelines Network; **RCT**=randomised controlled trial; **SR**=systematic review; **UK**=United Kingdom; **USA**=United States of America