

Negative Pressure Wound Therapy – Home Use

Draft Evidence Report

August 17, 2016

Health Technology Assessment Program (HTA)

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Negative Pressure Wound Therapy – Home Use

A Health Technology Assessment

Prepared for Washington State Health Care Authority

DRAFT REPORT

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Acknowledgement

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Table of Contents

EVIDENCE SUMMARY..... 1

 Summary of Clinical Background 1

 Wound Types of Interest 1

 Negative Pressure Wound Therapy 1

 Policy Context 2

 Summary of Review Objectives and Methods 2

 Review Objectives 2

 Key Questions 2

 Methods..... 3

 Search Strategy and Selection Criteria..... 3

 Inclusion Criteria 3

 Exclusion Criteria..... 4

 Quality Assessment..... 4

 Summary of Search Results..... 5

 Findings 5

 Practice Guidelines..... 17

 Selected Payer Policies..... 19

 Aetna 19

 Centers for Medicare & Medicaid Services (CMS)..... 19

 Group Health Cooperative 20

 Oregon Health Evidence Review Commission (HERC) 20

 Regence..... 20

 Overall Summary and Discussion..... 20

 Evidence-Based Summary Statement..... 20

 Gaps in the Evidence..... 22

TECHNICAL REPORT 23

 Clinical Background..... 23

 Wound Types of Interest 23

 Negative Pressure Wound Therapy 24

 Washington State Agency Utilization and Costs 29

| | |
|--|----|
| Review Objectives..... | 30 |
| Scope..... | 30 |
| Key Questions | 30 |
| Search Strategy and Selection Criteria..... | 30 |
| Quality Assessment..... | 33 |
| Search Results | 34 |
| Included Studies..... | 35 |
| Excluded Studies | 35 |
| Literature Review..... | 36 |
| Key Question #1a: What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of chronic wounds (i.e., venous leg ulcers, arterial leg ulcers, diabetic foot ulcers, pressure ulcers, and mixed etiology chronic wounds)?..... | 36 |
| Key Question #1b: What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of nonhealing closed or open surgical wounds (i.e., incisions expected to heal by primary intention or incisions expected to heal by secondary intention)? | 41 |
| Key Question #2: What are the harms associated with NPWT?..... | 44 |
| Key Question #3: Does the effectiveness of NPWT or incidence of adverse events vary by clinical history (e.g., diabetes), wound characteristics (e.g., size, chronicity), duration of treatment, types of devices, or patient characteristics (e.g., age, sex, prior treatments, smoking, or other medications)? | 48 |
| Key Question #4: What are the cost implications and cost-effectiveness of NPWT? | 51 |
| Practice Guidelines..... | 53 |
| Selected Payer Policies..... | 55 |
| Aetna..... | 56 |
| Centers for Medicare & Medicaid Services (CMS)..... | 56 |
| Group Health Cooperative | 57 |
| Oregon Health Evidence Review Commission (HERC) | 57 |
| Regence..... | 58 |
| References | 59 |
| APPENDICES | 63 |
| APPENDIX I | 63 |
| SEARCH STRATEGY | 63 |
| APPENDIX II..... | 66 |

| | |
|---|----|
| THE ASSESSMENT OF MULTIPLE SYSTEMATIC REVIEWS (AMSTAR) TOOL | 66 |
| APPENDIX III | 67 |
| OVERVIEW OF EVIDENCE QUALITY ASSESSMENT METHODS | 67 |
| APPENDIX IV | 71 |
| EXCLUDED STUDIES..... | 71 |
| APPENDIX V..... | 74 |
| EVIDENCE TABLES | 74 |
| APPENDIX Va..... | 74 |
| STUDIES OF CHRONIC WOUNDS..... | 74 |
| APPENDIX Vb..... | 91 |
| STUDIES OF SURGICAL WOUNDS..... | 91 |
| APPENDIX VI..... | 97 |
| SUMMARY OF PRACTICE GUIDELINES | 97 |

List of Figures

[Figure 1.](#) Negative Pressure Wound Therapy System

[Figure 2.](#) Summary of Search Results

List of Tables

[Table 1.](#) Summary of Findings, Key Question 1a – Diabetic Foot Ulcers

[Table 2.](#) Summary of Findings, Key Question 1a – Arterial Ulcers

[Table 3.](#) Summary of Findings, Key Question 1a – Pressure Ulcers

[Table 4.](#) Summary of Findings, Key Question 1a – Venous Insufficiency Ulcers

[Table 5.](#) Summary of Findings, Key Question 1a – Mixed Ulcer Populations

[Table 6.](#) Summary of Findings, Key Question 1b – Surgical Wounds

[Table 7.](#) Summary of Findings, Key Question #2, Harms

[Table 8.](#) Summary of Practice Guideline Recommendations

[Table 9.](#) Negative Pressure Wound Therapy Technologies Commercially Available in the United States

[Table 10.](#) Inclusion/Exclusion Criteria

[Table 11.](#) Study Characteristics of Studies Included for KQ1a

[Table 12.](#) Randomized Controlled Trials Included for KQ1b

[Table 13.](#) Study Characteristics of Studies Included for KQ2 (Harms) – Chronic Wounds

List of Abbreviations

AMWT Advanced moist wound therapy

DFU Diabetic foot ulcer

NPWT Negative pressure wound therapy

PU Pressure ulcer

SNaP Smart Negative Pressure Wound Care System

VAC Vacuum-assisted closure negative pressure wound therapy (generic term)

V.A.C. Vacuum-Assisted Closure Negative Pressure Wound Therapy System (brand name)

VLU Venous leg ulcer

EVIDENCE SUMMARY

The **EVIDENCE SUMMARY** summarizes background information, the methods and search results for this report, findings with respect to the Key Questions, and payer policies and practice guidelines. The **EVIDENCE SUMMARY** also includes conclusions and an assessment of the quality of the evidence for each Key Question. In general, references are not cited in the **EVIDENCE SUMMARY**. The **EVIDENCE SUMMARY** ends with an **Overall Summary and Discussion**. The **TECHNICAL REPORT** provides additional detail, with full citation, regarding background information, study results, and payer policies and guidelines, but does not include conclusions or quality assessment.

Summary of Clinical Background

Wound Types of Interest

Chronic wounds, defined within this report by type or etiology and not by duration, include venous insufficiency ulcers, diabetic foot ulcers (DFUs), and pressure ulcers. Although the causes for chronic wounds vary, in all cases, at least one of the phases of wound healing is altered and the pathway to healing is impaired. Patients with chronic wounds may experience a range of severity, including substantial limitations in mobility and poor health-related quality of life. Chronic wounds account for an estimated \$25 billion dollars in healthcare expenditures per year.

Surgical wounds are defined for this report as incisions made to initially closed skin and tissue in the course of a patient's care for an underlying health concern requiring surgical intervention. Surgical wounds that are closed by means such as sutures, staples, tape, or glue that hold the wound edges together are referred to as surgical wounds expected to heal by primary intention. Surgical wounds may also be left open for the healing process; these are referred to as surgical wounds healing by secondary intention. The scope of this report encompasses both types of wounds but does not include surgical repair of wounds related to trauma, fractures, burns, or skin grafting.

Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT), also referred to as subatmospheric pressure wound therapy or vacuum-assisted wound therapy, involves the application of subatmospheric pressure to the surface of a wound. The technology was introduced in the 1990s and is used for treatment of chronic and acute wounds. NPWT is thought to promote wound healing by providing a warm, moist wound bed while removing wound fluid. The device may remove molecular factors that inhibit cell growth, improve blood flow to the wound, enhance wound oxygenation, and improve the flow of nutrients to the wound. NPWT may also create mechanical forces that draw the wound edges together, and induce cell proliferation, cell migration to the wound, and angiogenesis.

NPWT consists of the application of a foam or gauze type dressing sealed with an adhesive film and connected via tubing to a vacuum pump. Continuous or intermittent controlled negative pressure

(suction) is applied across the wound. Wound effluent is collected in a canister. Figure 1 shows a generalized NPWT system.

Policy Context

NPWT is used in the treatment of slow or nonhealing wounds. Home use of NPWT includes use of a portable device. Concerns are considered medium for safety, medium/high for efficacy, and medium for cost-effectiveness. An evidence-based assessment of the comparative effectiveness, safety, and cost is warranted to guide coverage policy.

Summary of Review Objectives and Methods

Review Objectives

Population: Patients diagnosed with chronic wounds (defined as venous leg ulcers, arterial leg ulcers, diabetic foot ulcers, pressure ulcers, and mixed etiology chronic wounds) or nonhealing surgical wounds

Interventions: NPWT

Comparisons: Other wound care methods; comparison of NPWT devices

Outcomes: Clinical outcomes (complete wound healing; time to complete wound healing; time to surgical readiness of the wound bed or time to wound closure; proportion of wounds closed; seroma/hematoma; reoperation; mortality; wound healing rate for healed wounds); patient-centered outcomes (return to prior level of functional activity; pain; health-related quality of life); safety (infection rates; extremity amputation; emergency room visits related to the NPWT or treated wound; unplanned hospitalizations or surgeries related to the NPWT or treated wound; blood transfusions/bleeding)

Settings: Home or outpatient setting

Key Questions

- 1a. What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of chronic wounds (i.e., venous leg ulcers, arterial leg ulcers, diabetic foot ulcers, pressure ulcers, and mixed etiology chronic wounds)?
- 1b. What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of nonhealing closed or open surgical wounds (i.e., incisions expected to heal by primary intention or incisions expected to heal by secondary intention)?
2. What are the harms associated with NPWT?
3. Does the effectiveness of NPWT or incidence of adverse events vary by clinical history (e.g., diabetes), wound characteristics (e.g., size, chronicity), duration of treatment, types of device, or patient characteristics (e.g., age, sex, prior treatments, smoking, or other medications)?
4. What are the cost implications and cost-effectiveness of NPWT?

Methods

See the **Methods** section of the **TECHNICAL REPORT**, [Appendix I](#), [Appendix II](#), and [Appendix III](#) for additional detail.

Search Strategy and Selection Criteria

Core databases, PubMed, and the websites of relevant specialty societies were searched for systematic reviews, meta-analyses, economic evaluations, and practice guidelines. Systematic reviews were selected if they were of good quality and pertained to 1 or more of the key questions. Three such systematic reviews were identified and used as the source of primary studies and the foundation for update literature searches for this report. Update literature searches and study selection processes were done to update the existing systematic reviews with more recent primary evidence. The PubMed (searched on May 17, 2016) and OVID-Embase (searched on July 1, 2016) databases were searched for primary studies designed to answer the Key Questions. Additional update searches will be conducted prior to publication of the final health technology assessment (HTA) to ensure the inclusion of the most up-to-date evidence.

Inclusion Criteria

- Studies conducted in patients diagnosed with chronic wounds (venous, arterial, diabetic, pressure, or mixed) or nonhealing surgical wounds.
- NPWT was intervention.
- Comparative study (randomized controlled trials [RCTs] only for nonhealing surgical wound types; other comparative study designs accepted for chronic wounds as long as the number of participants was ≥ 20).
- Studies conducted in the home or outpatient setting (studies were included that were described as in “outpatient setting” if it was reported (or we interpreted) that patients were not in assisted living, skilled, or maintenance nursing homes)
- Studies that evaluated 1 of the following outcomes:
 - Clinical outcomes (complete wound healing; time to complete wound healing; time to surgical readiness of the wound bed or time to wound closure; proportion of wounds closed; seroma/hematoma; reoperation; mortality; wound healing rate for healed wounds)
 - Patient-centered outcomes (return to prior level of functional activity; pain; health-related quality of life)
 - Safety (infection rates; extremity amputation; emergency room visits related to the NPWT or treated wound; unplanned hospitalizations or surgeries related to the NPWT or treated wound; blood transfusions/bleeding)

More details of these criteria, the rationale for these criteria, and the rationale for using existing systematic reviews to identify primary studies are presented in the **METHODS** section of the **TECHNICAL REPORT**.

Exclusion Criteria

- Patients with traumatic wounds, fractures, skin grafts, or burns
- Fewer than 20 patients with chronic wounds (studies with ≤ 10 patients per group would not be adequately powered to detect meaningful differences in clinical outcomes); any-size RCT accepted for nonhealing surgical wounds
- Studies that evaluated an NPWT that is not commercially available and approved for use in the United States
- Studies with no comparison with other wound treatments or other NPWT devices
- Studies that reported wound healing rates without also reporting complete wound healing (wound healing rate is considered a surrogate outcome measure because chronic wounds may not heal in a linear fashion, and cannot be used to accurately predict complete healing)
- Conference abstracts, posters, or presentations
- Nonhuman studies
- No original data (e.g., editorials, letters, non-systematic reviews)

More details of these criteria and the rationale for these criteria are presented in the **METHODS** section of the **TECHNICAL REPORT**.

Quality Assessment

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was employed to determine the quality of selected systematic reviews. The process used by Hayes for assessing the quality of primary studies and bodies of evidence is in alignment with the methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as the Agency for Healthcare Research and Quality (AHRQ), use the phrase *strength of evidence*. A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors, was used to assess the

quality of practice guidelines. See the **Methods** section of the **TECHNICAL REPORT** and [Appendix II](#) and [Appendix III](#) for details on quality assessment methods.

Summary of Search Results

A total of 21 articles representing 14 primary studies met inclusion criteria. Eleven articles representing 9 primary studies were carried forward from the 3 selected systematic reviews, and 10 additional articles meeting inclusion criteria for this HTA were identified from recent literature searches and manual searches of key references. These 10 articles represent 5 newly included studies and 2 recent publications from studies included in the previously published systematic reviews.

See [Appendix IV](#) for a list of the 38 studies that were excluded from analysis after full-text review.

Five practice guidelines published in the last 10 years were identified.

Findings

Summary of Findings tables follow each Key Question. See **EVIDENCE SUMMARY, Methods, Quality Assessment** and the corresponding section in the **TECHNICAL REPORT**, as well as [Appendix II](#) and [Appendix III](#), for details regarding the assessment of bodies of evidence. See [Appendix V](#) for full evidence tables.

Key Question #1a: What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of chronic wounds (venous leg ulcers, arterial leg ulcers, diabetic foot ulcers, pressure ulcers, and mixed etiology chronic wounds)?

Six primary studies meeting inclusion criteria were identified that address KQ1a. There were 2 RCTs and 4 observational studies. The RCTs ranged in size from 28 to 341 patients. The observational studies ranged in size from 78 to 2677 patients. All 6 studies compared NPWT therapy with other types of wound treatment, there was variation across the studies in the types and the level of detail provided about comparison treatments. Wound types in the study populations varied. Patients with diabetic foot ulcers were the focus of 3 studies. One study included only patients with pressure ulcers. The remaining 2 studies included patients with lower extremity ulcers of different etiologies. Half of the studies (3 out of 6) included for KQ1a were rated as poor quality. Two RCTs and 1 retrospective cohort study were rated as fair quality. Overall, the quality of the evidence regarding *the clinical effectiveness of the home use of NPWT for treating chronic wounds* was considered to be low due to insufficient evidence for many direct outcomes, methodological limitations of available studies, few available studies for specific types of chronic wounds, and obvious or potential heterogeneity within the body of evidence with respect to several aspects such as treatment delivery, comparators, and methods.

Diabetic Foot Ulcers

A total of 4 studies (2 poor-quality and 2 fair-quality) met inclusion criteria for key question 1a and evaluated NPWT for treating DFUs. Three studies assessing NPWT for treating chronic DFUs found benefit with NPWT for complete wound healing or wound closure. Time to wound closure was shorter for patients receiving NPWT in 1 study. No other clinical outcomes eligible for this HTA were reported in

these studies. Provision of pain medication as a surrogate measure for pain was reported in 1 study of DFU. Results suggest no difference between groups. The evidence for each of these 3 outcomes for this indication was considered to be of low to very low quality because of lack of studies, quality of the individual studies, and mixed or uncertain applicability to 1 or more PICOS (population, intervention, comparator, outcomes, setting) elements. No studies reporting on other clinical or patient-centered outcomes were identified; therefore, the evidence is insufficient for these outcomes with respect to the home use of NPWT for treating DFUs. See **Table 1** for a summary of findings from the included studies for DFUs.

Table 1. Summary of Findings, Key Question 1a – Diabetic Foot Ulcers

Key: AMWT, advanced moist wound therapy; DFU(s), diabetic foot ulcer(s); HR, hazard ratio; NPWT, negative pressure wound therapy; NS, not significant; PICOS, population, intervention, comparator, outcomes, setting; RCT, randomized controlled trial; tx, treatment

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|--|--|-----------------------|--|
| KQ #1a. DFUs – clinical outcomes: complete wound healing/closure | | | |
| 3 studies (n=3361) Lavery, 2007 (retrospective cohort, poor) Blume, 2008 (RCT, fair) Yao, 2012 (retrospective cohort, fair) | OVERALL: LOW Study quality: Poor-Fair Quantity and precision: Few studies, moderate to large sample sizes Consistency: Consistent results in 3 studies in favor of NPWT Applicability to PICOS: Mixed Publication bias: Unknown | Results favor NPWT | Lavery, 2007 (n=2677) Complete wound healing at 12 wks and 20 wks (NPWT matched; Controls): 12 wks (all population): 39.5%; 23.9%; P<0.001 12 wks (small ulcers <2 cm ²): 43.1%; 29.4%; P<0.05 12 wks (medium ulcers 2-4 cm ²): 43.7%; 17.9%; P<0.05 12 wks (large ulcers >4 cm ²): 37.8%; 13.8%; P<0.05 20 wks (all population) 46.3%; 32.8%; P<0.001 20 wks (small ulcers <2 cm ²): 50.3%; 38.9%; P<0.05 20 wks (medium ulcers 2-4 cm ²): 46.1%; 48.5%; 25.2%; P<0.05 20 wks (large ulcers >4 cm ²): 45.3%; 44.9%; 22.4%; P<0.05 Blume, 2008 (n=342) (NPWT, AMWT) Complete closure during active tx phase: 73/169 (43%); 48/166 (29%); P=0.007 Complete closure at end of active tx phase: 73/120 (61%); 48/120 (40%), P=0.001 Surgical closure by split-thickness skin grafts, flaps, sutures, or amputations: 16 (10%); 14 (8%), P=NR Yao, 2012 (n=342 total, includes pts with different types of lower extremity ulcers and/or multiple ulcers) Incidence of wound healing for DFU Non-NPWT as reference group Unadjusted HR: 2.38 (95% CI, 1.75-3.23) Adjusted HR: 3.26 (95% CI, 2.21-4.83) |

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|--|--|-----------------------|--|
| KQ #1a. DFUs – clinical outcomes: time to complete wound healing/closure: | | | |
| 1 study (n=342) Blume, 2008 (multicenter RCT, fair) | OVERALL: LOW Study quality: Fair Quantity and precision: Single study Consistency: Single study Applicability to PICOS: Uncertain Publication bias: Unknown | Results favor NPWT | Blume, 2008 (n=342) <i>Kaplan-Meier median estimate for 100% ulcer closure was 96 days (95% CI, 75.0-114.0) for NPWT and not determinable for AMWT (P=0.001)</i> |
| KQ1a. DFUs – patient-centered outcomes: pain | | | |
| 1 study (n=1331) Fife, 2008 (Retrospective cohort, poor) | OVERALL: VERY LOW Study quality: Poor Quantity and precision: Single study Consistency: Single study Applicability to PICOS: ✓ Publication bias: Unknown | No difference | Fife, 2008 (n=1331) <i>Provision of pain medication as a surrogate measure for pain: P=NS</i> |
| KQ1a. DFUs – other clinical and patient-centered outcomes: Insufficient, no studies | | | |

Arterial Ulcers

One fair-quality study reported incidence of wound healing for patients with arterial ulcers; results favored NPWT. The evidence for this outcome was considered to be of **very low quality** because of the availability and quality of only 1 study. No studies reporting on other clinical or any patient-centered outcomes were identified; therefore, the evidence is insufficient for these outcomes with respect to the home use of NPWT for treating arterial ulcers. See **Table 2** for a summary of the findings.

Table 2. Summary of Findings, Key Question 1a – Arterial Ulcers

Key: HR, hazard ratio; NPWT, negative pressure wound therapy; PICOS, population, intervention, comparator, outcomes, setting; pts, patients

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|---|---|-----------------------|---|
| KQ #1a. Arterial ulcers – clinical outcomes: complete wound healing | | | |
| 1 study (n=342) Yao, 2012 (retrospective cohort, fair) | OVERALL: VERY LOW Study quality: Fair Quantity and precision: Single study Consistency: Single study Applicability to PICOS: Uncertain Publication bias: Unknown | Favors NPWT | Yao, 2012 (n=342 total, includes pts with different types of lower extremity ulcers and/or multiple ulcers) <i>Incidence of wound healing for arterial ulcers Non-NPWT as reference group Unadjusted HR: 2.33 (95% CI, 1.57-3.48) Adjusted HR: 2.27 (95% CI, 1.56-3.78)</i> |
| KQ #1a. Arterial ulcers - other clinical and patient-centered outcomes: Insufficient, no studies | | | |

Pressure Ulcers

Two fair-quality studies provided results for complete wound healing with NPWT for patients with pressure ulcers compared with other wound treatments. Both studies suggest a benefit for NPWT, however the differences between the groups were not statistically significant in either study. The evidence for this outcome was considered to be of very low quality because of imprecision, uncertain applicability to 1 or more PICOS elements, and lack of data. No studies reporting on other clinical or any patient-centered outcomes were identified; therefore, the evidence is insufficient for these outcomes with respect to the home use of NPWT for treating pressure ulcers. See **Table 3** for a summary of the findings.

Table 3. Summary of Findings, Key Question 1a – Pressure Ulcers

Key: HR, hazard ratio; NPWT, negative pressure wound therapy; NS, not significant; PICOS, population, intervention, comparator, outcomes, setting; pts, patients; RCT, randomized controlled trial

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Result |
|---|--|---|--|
| KQ #1a. Pressure ulcers – clinical outcomes: complete wound healing | | | |
| 2 studies (n=364) Ford, 2002 (RCT, fair) Yao, 2012 (retrospective cohort, fair) | OVERALL: VERY LOW Study quality: Fair Quantity and precision: Few studies, small sample sizes Consistency: Consistent Applicability to PICOS: Mixed Publication bias: Unknown | Trend in favor of NPWT, however difference NS | Ford, 2002 (n=22 pts, 35 wounds; results analyzed per wound) NPWT, Control: 2/20 (10%); 2/15 (13%) (risk difference 3% (95% CI, -18%-25%) [calculated by Rhee (2014)]) Yao, 2012 (n=342 total, includes pts with different types of lower extremity ulcers and/or multiple ulcers) Incidence of wound healing for pressure ulcers: Non-NPWT as reference group: Unadjusted HR: 2.19 (95% CI, 1.03-4.66) Adjusted HR: 1.72 (95% CI, 0.43-6.95) |
| KQ #1a. Pressure ulcers - other clinical and patient-centered outcomes: Insufficient, no studies | | | |

Venous Insufficiency Ulcers

One fair-quality study reported complete wound healing for patients with venous ulcers. Results suggest that venous ulcers were more likely to heal among patients who received NPWT than among those who did not receive NPWT. The evidence for this outcome was considered to be of very low quality because of the availability and quality of only 1 study. No studies reporting on other clinical or any patient-centered outcomes were identified; therefore, the evidence is insufficient for these outcomes with respect to the home use of NPWT for treating venous insufficiency ulcers. See **Table 4** for a summary of the findings.

Table 4. Summary of Findings, Key Question 1a – Venous Insufficiency Ulcers

Key: HR, hazard ratio; NPWT, negative pressure wound therapy; PICOS, population, intervention, comparator, outcomes, setting; pts, patients

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|---|--|-----------------------|--|
| KQ #1a. Venous insufficiency ulcers – clinical outcomes: complete wound healing | | | |
| 1 study (n=342) Yao, 2012 (retrospective cohort, fair) | OVERALL: VERY LOW Study quality: Fair Quantity and precision: Single study, small sample size Consistency: Single study Applicability to PICOS: Uncertain Publication bias: Unknown | Favors NPWT | Yao, 2012 (n=342 total, includes pts with different types of lower extremity ulcers and/or multiple ulcers) <i>Incidence of wound healing for venous ulcers: Non-NPWT as reference group: Unadjusted HR: 4.90 (95% CI, 1.72-13.59) Adjusted HR: 6.31 (95% CI, 1.49-26.6)</i> |
| KQ #1a. Venous insufficiency ulcers – other clinical and patient-centered outcomes: Insufficient, no studies | | | |

Mixed Ulcer Populations

For populations of patients with different wound types, results from 1 fair-quality and 1 poor-quality study favor NPWT compared with other wound treatments. Both studies suggest that more wounds healed in the NPWT groups than in the non-NPWT groups, and 1 study suggests that wounds healed faster among patients who received NPWT than among those who did not. The evidence for each of these outcomes was considered to be of low to very low quality because of lack of studies, quality of the individual studies, and mixed or uncertain applicability to 1 or more PICOS elements. No studies reporting on other clinical or any patient-centered outcomes were identified; therefore, the evidence is insufficient for these outcomes with respect to the home use of NPWT for treating ulcers of mixed etiology. See **Table 5** for a summary of the findings.

Table 5. Summary of Findings, Key Question 1a – Mixed Ulcer Populations

Key: CND, cannot determine; HR, hazard ratio; NPWT, negative pressure wound therapy; NR, not reported; PICOS, population, intervention, comparator, outcomes, setting; pts, patients

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|--|---|--|--|
| KQ #1a. Mixed ulcer populations – clinical outcomes: complete wound healing | | | |
| 2 studies (n=342) Lerman, 2010 (prospective cohort with matched historical controls, poor) Yao, 2012 (retrospective) | OVERALL: LOW Study quality: Poor-Fair Quantity and precision: Few studies, small sample sizes Consistency: <u>C</u> ND Applicability to PICOS: Mixed Publication bias: Unknown | 1 study favors NPWT; trend favors NPWT in 1 study, statistical significance <u>N</u> R | Lerman, 2010 (n=78) <i>Complete wound healing NPWT, Control (statistical significance <u>N</u>R): 1 month: 0%; 0% 2 months: 20%; 7.1% 3 months: 66.2%; 21.4%, 4 months: 83.1%; 35.7%</i> Yao, 2012 (n=342 total, includes pts with different types of lower extremity ulcers and/or multiple ulcers) |

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|--|--|-----------------------|--|
| cohort, fair) | | | <i>Incidence of wound healing for mixed ulcers: Non-NPWT as reference group: Unadjusted HR: 2.25 (95% CI, 1.73-3.96) Adjusted HR: 2.63 (95% CI, 1.87-3.70)</i> |
| KQ #1a. Mixed ulcer populations – clinical outcomes: time to complete wound healing | | | |
| 1 study (n=78) Lerman, 2010 (prospective cohort with matched historical controls, poor) | OVERALL: VERY LOW Study quality: Poor Quantity and precision: Single study, small sample size Consistency: Single study Applicability to PICOS: ✓ Publication bias: Unknown | Favors NPWT | Lerman, 2010 (n=78) <i>Time to complete wound healing (mean ± SD), days: NPWT, Control (analysis based on pts with healed wounds): 74.25±20.1; 148.73±63.1 (P<0.0001), represents 50% absolute reduction in time to healing</i> |
| KQ #1a. Mixed ulcer populations – other clinical and patient-centered outcomes: <i>Insufficient, no studies</i> | | | |

Key Question #1b: What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of nonhealing closed or open surgical wounds (i.e., incisions expected to heal by primary intention or incisions expected to heal by secondary intention)?

Three fair-quality RCTs were identified for Key Question 1b, all 3 assessed the use of NPWT in patients with surgical wounds healing by secondary intention; no eligible studies investigating home use of NPWT for surgical wounds healing by primary intention were identified. Each of the studies of surgical wounds includes a unique population. The studies included patients with deep infected wounds, patients requiring surgical treatment for a pilonidal sinus, and patients with wounds from diabetic foot wound-related amputations. In all 3 studies, wound care started in an acute care setting and was continued at home after discharge. Study sizes ranged from 20 to 162. One study was a multicenter RCT conducted in the United States, and the other 2 were single-center studies conducted in Europe. Vacuum-assisted closure (VAC) was compared with alginate dressing in 1 study, compared with silicone dressing in another, and compared with various dressings (moist wound care with alginates, hydrocolloids, foams, or hydrogels) in the third study.

Two studies conducted in Europe among patients who received different surgical interventions reported conflicting results with respect to median time to wound healing. One study found no difference between NPWT and silicone dressing for patients being treated for pilonidal sinus, and 1 study found that the median number of days to complete wound healing was statistically significantly shorter in the NPWT group compared with a group receiving alginate dressing for deep perivascular wound infections. It should be noted that these studies included different patient populations and evaluated NPWT therapy against different comparisons. The third study was conducted in the United States among patients with diabetic foot wound-related amputations. Results from this study suggest that a higher proportion of wounds were healed in the NPWT therapy group than in the standard moist wound therapy group, and the NPWT group healed faster. Patient-centered outcomes were reported in 2 of the 3 studies. These results suggest no difference between NPWT and alginate dressing for quality of life,

return to prior level of activity, and pain outcomes. The quality of the evidence for each of these outcomes was considered to be of low to very low quality because of lack of studies for specific wound types, quality of the individual studies, small sample sizes, and some inconsistencies in the findings. See **Table 6** for a summary of the findings from the 3 studies.

The overall quality of the body of evidence for the *clinical effectiveness of NPWT in the home or outpatient settings for treatment of surgical wounds healing by secondary intention* is considered to be low because of insufficient evidence for some direct outcomes, methodological limitations of available studies, heterogeneity within the body of evidence with respect to populations, methods, and comparators, and few available studies.

Table 6. Summary of Findings, Key Question 1b – Surgical Wounds

Key: EQ(-5D), European Quality of Life (5 Dimensions); IQR, interquartile range; NPWT, negative pressure wound therapy; NR, not reported; NS, not significant; PICOS, population, intervention, comparator, outcomes, setting; tx, treatment; VAS, visual analog scale (or score)

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|--|---|------------------------------|--|
| Key Question 1b. Surgical wounds – clinical outcomes: complete wound healing/closure | | | |
| 1 study (n=162) Armstrong, 2005, Apelqvist, 2008 (RCT, fair) | OVERALL: VERY LOW Study quality: Fair Quantity and precision: Single study Consistency: Single study Applicability to PICOS: ✓ Publication bias: Unknown | Favors NPWT | Armstrong, 2005; Apelqvist, 2008 (n=162) NPWT, standard tx Proportion of wounds healed: 43 (56%), 33 (39%); P=0.04 Difference in proportions = 0.1702 (95% asymptotic CI, 0.0184-0.322) Wounds healed by secondary intention: 31 (40%), 25 (30%); P=NR Wounds healed after surgical closure: 12 (16%), 8 (9%); P=0.244 |
| Key Question 1b. Surgical wounds – clinical outcomes: time to complete wound healing | | | |
| 3 studies (n=231) Armstrong, 2005, Apelqvist, 2008 (RCT, fair) Biter, 2014 (RCT, fair) Monsen, 2014; Acosta, 2013, Monsen, 2015 (RCT, fair) | OVERALL: LOW Study quality: Fair Quantity and precision: Few studies, small sample sizes Consistency: Inconsistent Applicability to PICOS: ✓ Publication bias: Unknown | No difference or favors NPWT | Armstrong, 2005; Apelqvist, 2008 (n=162) Time to complete wound healing (median [IQR]), days: NPWT, standard tx 56 days (26-92), 77 (40-112); P=0.005 Biter, 2014 (n=49) Time to complete wound healing (median [range]), days: NPWT, silicone dressing 84 (34-349), 93 (43-264); P=0.44 Monsen, 2014, Acosta, 2013, Monsen, 2015 (n=20) Time to complete wound healing (median [range]), days: NPWT, alginate dressing 57 (25-115) (for n=9); 104 (57-175) (for n=7); P=0.026 |
| Key Question 1b. Surgical wounds – patient-centered outcomes: pain | | | |
| 2 studies (n=69) | OVERALL: VERY LOW Study quality: Fair | No difference | Biter, 2014 (n=49) Pain (VAS, median): |

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|---|---|-----------------------|--|
| Biter, 2014 (RCT, fair) Monsen, 2014; Acosta, 2013, Monsen, 2015 (RCT, fair) | Quantity and precision: Few studies, small sample sizes Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown | | <i>NPWT, silicone dressing</i> <i>Day of surgery: 1.5; 1.7; P=0.24</i> <i>14 days after surgery: 2.2; 2.5; P=0.29</i> Monsen, 2014; Acosta, 2013, Monsen, 2015 (n=20 at study start, n=17 at 4 weeks) <i>No difference was shown between the NPWT and the alginate group, in pain intensity or influence on daily life at study start or after 4 weeks of tx.</i> |
| KQ #1b. Surgical wounds – patient-centered outcomes: return to prior level of activity | | | |
| 1 study (n=49) Biter, 2014 (RCT, fair) | OVERALL: VERY LOW Study quality: Fair Quantity and precision: Single study, small sample size Consistency: Single study Applicability to PICOS: ✓ Publication bias: Unknown | No difference | Biter, 2014 (n=49) <i>Time to return to work or school (median [range]), days:</i> <i>NPWT, silicone dressing</i> <i>27 (7-126); 29 (6-63); P=0.92</i> |
| KQ #1b. Surgical wounds – patient-centered outcomes: quality of life | | | |
| 1 study (n=20) Monsen, 2014; Acosta, 2013, Monsen, 2015 (RCT, fair) | OVERALL: VERY LOW Study quality: Fair Quantity and precision: Single study, small sample sizes Consistency: Single study Applicability to PICOS: ✓ Publication bias: Unknown | No difference | Monsen, 2014; Acosta, 2013, Monsen, 2015 (n=20) <i>Quality of life, EQ-5D Index, and EQ-VAS (health status):</i> <i>NPWT n=6 with healed wound; alginate dressing n=6 with healed wound</i> <i>EQ-5D Index: 0.69 (0.30-0.80), 0.66 (0.52-0.86); P=NS</i> <i>EQ-VAS (median [q1-q3]): 70 (63.75-750), 55 (35-85.5)</i> <i>Neither scale was statistically significantly different between groups either before or after tx.</i> |
| KQ #1b. Surgical wounds – other clinical and patient-centered outcomes: insufficient, no studies | | | |

Key Question #2: What are the harms associated with NPWT?

Safety outcomes sought for this HTA were infection rates; extremity amputation; emergency room visits related to the NPWT or treated wound; unplanned hospitalizations or surgeries related to the NPWT or treated wound; and blood transfusions/bleeding. Six studies were identified that reported on adverse events in patients with chronic wounds. These studies evaluated NPWT compared with other wound treatments in patients with DFUs, pressure ulcers, and mixed ulcers. No studies comparing NPWT with other wound treatments reporting adverse events for patients with arterial ulcers or venous insufficiency ulcers were identified. Results from 2 studies favored NPWT with respect to rates of amputation and a third study favored NPWT with respect to rates of infection among patients with DFUs. For patients with pressure ulcers, 1 study reported statistically significant results in favor of NPWT

for emergent care and hospitalization. The study reporting adverse events among a mixed ulcer population did not report data for the comparison group. The evidence for harms associated with the home use of NPWT to treat chronic wounds was considered to be of low quality because of the quality of the individual studies, few studies for specific wound types, and uncertain applicability to 1 or more of the PICOS elements.

Adverse events were reported in 3 studies evaluating NPWT compared with other wound treatments for surgical wounds. None of the studies reported statistically significant differences between groups for the adverse events described in the publications. The evidence for harms associated with the home use of NPWT to treat surgical wound healing by secondary intention was considered to be of very low quality because of the quality of the individual studies, few studies for specific wound types, and small sample sizes.

The quality of the overall body of evidence for *harms associated with home use of NPWT for chronic or surgical wounds healing by secondary intention is considered to be low* because of methodological limitations of available studies, few available studies for specific types of wounds, and uncertain applicability of some of the studies to the home setting. See **Table 7** for a summary of the evidence.

Table 7. Summary of Findings, Key Question #2, Harms

Key: AMWT, advanced moist wound therapy; DFU(s), diabetic foot ulcer(s), NPWT, negative pressure wound therapy; NR, not reported; NS, not significant; PICOS, population, intervention, comparator, otcomes, setting; pts, patients; PU, pressure ulcers; RCT, randomized controlled trial; RR, risk ratio; tx, treatment

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|---|--|------------------------------|---|
| KQ #2: Chronic wounds | | | |
| 6 studies (n=20,445) Blume, 2008 (RCT, fair) Fife, 2008 (retrospective observational, poor) Ford, 2002 (RCT, poor) Frykberg, 2007 (retrospective observational, fair) Lerman, 2010 (retrospective observational, poor) Schwien, 2005 (retrospective | OVERALL: LOW Study quality: Poor-Fair Quantity and precision: Few studies for each wound type, small to large study sizes Consistency: Consistent Applicability to PICOS: Mixed Publication bias: Unknown | No difference or favors NPWT | Blume, 2008 (n=341) - DFUs <i>Complications (NPWT group; AMWT group) n (%):</i> <i>Secondary amputations: 7 (4%); 17 (10%); P=0.035</i> <i>Edema: 5 (3%); 7 (4%); P=NS</i> <i>Wound infection: 4 (2%); 1 (<1%); P=NS</i> <i>Cellulitis: 4 (2%); 1 (<1%); P=NS</i> <i>Osteomyelitis: 1 (<1%); 0; P=NS</i> <i>Staphylococcus infection: 1 (<1%); 0; P=NS</i> <i>Infected skin ulcer: 1 (<1%); 2 (1%); P=NS</i> Fife, 2008 (n=1331) - DFUs <i>Complications (NPWT group; Control group):</i> <i>Bleeding (discontinued NPWT due to bleeding): No DFU pts with the V.A.C. required the discontinuation of the V.A.C. because of bleeding.</i> <i>Bleeding (sanguineous drainage): No cases found in either group</i> <i>Infection (antibiotics): V.A.C. pts had fewer antibiotic prescriptions (numbers NR); P<0.05</i> <i>Infection (culture): V.A.C. pts had fewer cultures taken (numbers NR); P<0.05</i> Ford, 2002 (n=28) – Pressure ulcers |

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|---|---|-------------------------------------|---|
| <p>observational, poor)</p> | | | <p><i>Complications (VAC group; Control group) n (%):</i> <i>Sepsis: 1 (0.5); 0 (0); P= NR</i> <i>Extremity amputation: 1 (0.5); 0 (0); P=NR</i> Frykberg, 2007 (n=16,319) - DFUs <i>Complications:</i> <i>Amputations – Overall, NS differences without stratification or risk adjustment</i> <i>Amputations – Overall, cost-based risk adjustment analysis:</i> <i>Commercial dataset: Control group 21.4% vs NPWT group 14.1%; P=0.0951</i> <i>Medicare dataset: Control group 16.6% vs NPWT group 10.8%; P=0.0077</i> <i>Amputations – Overall, debridement-based risk adjustment analysis:</i> <i>Commercial dataset: Control group 21.4% vs 18.3%; P=0.5221</i> <i>Medicare dataset: Control group 16.6% vs NPWT group 11.2%; P=0.0128</i> Lerman, 2010 (n=78) – Mixed ulcers <i>7 NPWT pts had complications related to the study protocol requiring withdrawal: allergic skin reaction to the hydrocolloid dressing (n=1), wound infection (n=1), bleeding post debridement (n=1), worsening lower extremity edema (n=1), and maceration to periwound skin (n=3)</i> <i>NOTE: Data for these and 8 other pts who withdrew were not included in the final analysis.</i> Schwieh, 2005 (n=2348) – Pressure ulcers <i>Complications (NPWT group; Control group):</i> <i>Emergency room visits, all pts: 0/60 (0%); 189/2288 (8%); P<0.01</i> <i>Stage III PU: 0 (0%), 126 (7%); P<0.01</i> <i>Stage IV PU: 0 (0%), 63 (11%); P<0.01</i> <i>Wound-related hospitalization, all pts: 3/60 (5%); 310/2288 (14%); P<0.01</i> <i>Stage III PU: 1 (3%), 194 (11%); P<0.01</i> <i>Stage IV PU: 2 (7%), 116 (20%); P<0.01</i></p> |
| <p>KQ #2: Surgical wounds</p> | | | |
| <p>3 studies (n=231) Armstrong, 2005, Apelqvist, 2008 (RCT, fair) Biter, 2014 (RCT, fair) Monsen, 2014;</p> | <p>OVERALL: VERY LOW Study quality: Fair Quantity and precision: Few studies, small sample sizes Consistency: Consistent Applicability to PICOS: ✓ Publication bias: Unknown</p> | <p>No difference or favors NPWT</p> | <p>Armstrong, 2005; Apelqvist, 2008 (n=162) <i>Complications (NPWT group; Standard tx group):</i> <i>Second amputation: 2 (3%); 9 (11%); P=0.060; RR 0.225 (95% CI, 0.05-1.1)</i> <i>5 (6%) of standard tx group received high-level (above foot) amputation—2 above knee, 3 below knee; no high-level amputations were done in the NPWT group.</i> <i>Infections and infestations: 25 (32%); 27 (32%); P=1.000</i></p> |

| Number, Size, and Quality of Studies | Quality of Evidence | Direction of Findings | Key Study Results |
|--|---------------------|-----------------------|--|
| Acosta, 2013, Monsen, 2015 (RCT, fair) | | | <p>Wound infection: 13 (17%); 5 (6%) In the NPWT group, 3 infections were classified as mild, 6 as moderate, 4 as severe; none were deemed related to tx. In the Standard tx group, 2 were classified as mild, 1 as moderate, and 2 as severe; 2 of the 5 events were deemed to be related to the tx, 1 of which was serious. Tx-related adverse events: 9 (12%); 11 (13%) 1 event in the NPWT group was classified as serious; 5 events in the Standard tx group were classified as serious.</p> <p>Biter, 2014 (n=49) Complications (NPTW group; Silicone dressing group) n (%): Wound infection/abscess: 2 (8%); 2 (8%); P=1.00</p> <p>Monsen, 2014, Acosta, 2013, Monsen, 2015 (n=20) Complications (NPWT group; dressing group) n (%): Amputation: 3 (30%); 2 (20%) Mortality, in-hospital: 0; 1 (10%) Mortality, total: 2 (20%); 5 (50%) by end of follow-up (P=0.35)</p> |

Key Question #3: Does the effectiveness of NPWT or incidence of adverse events vary by clinical history (e.g., diabetes), wound characteristics (e.g., size, chronicity), duration of treatment, types of device, or patient characteristics (e.g., age, sex, prior treatments, smoking, or other medications)?

Four studies were identified providing information pertaining to KQ3 with respect to patients with chronic wounds. One was a fair-quality RCT, 1 was a fair-quality observational study, and 2 were poor-quality observational studies. Two of these studies compared different NPWT devices. An RCT conducted by Armstrong et al. provides a comparison of the V.A.C. Therapy System (KCI Inc.), and the SNaP Wound Care System (Spiracur Inc.), and the Law et al. study provides a comparison of the V.A.C. Therapy System with non-KCI models. The studies by Lavery et al. and Yao et al. provide information about the role of wound size and chronicity when NPWT is compared with other wound treatments. However, the Yao et al. study does not provide information about chronicity for the alternative wound treatment group, therefore the results are shown here for information only and are not considered in the overall body of evidence. No studies looked at comparative effectiveness in relation to clinical history, duration of treatment, or patient characteristics.

Overall, evidence of varying clinical effectiveness or rates of harms is considered to be very low because of a lack of studies for specific wound types and comparisons, methodological limitations of the few available individual studies, and lack of direct evidence for some outcomes.

Different Types of NPWT Devices Compared with Each Other (SNaP Versus V.A.C.)

In a fair quality RCT enrolling 162 patients with DFUs or venous leg ulcers (VLUs) and evaluating treatment with SNaP compared with V.A.C. for up to 16 weeks, complete wound healing was assessed at 4, 8, 12, and 16 weeks. A Kaplan-Meier survival analysis showed no significant difference between the SNaP and V.A.C. groups for the proportion of wounds healed over time ($P=0.9620$); analyses adjusting for baseline wound size were also not statistically significant. Time to surgical readiness of the wound bed and mortality were not reported. Although percentage decrease in the wound area was reported, the wound healing rate for healed wounds was not reported. Information about return to prior level of activity and pain were also evaluated in this RCT through responses to exit interviews from 105 patients who completed the study. Patients who were treated with the SNaP device were more likely to agree or strongly agree that they were able to perform their normal daily activities than patients treated with the V.A.C. device (79% and 58%, respectively). A higher percentage of SNaP-treated subjects than V.A.C.-treated subjects reported that their activity level either increased or stayed the same (83% and 48%, respectively). P values were calculated for these outcomes by Rhee and colleagues, authors of an AHRQ systematic review. The results were statistically significant. The level of pain was examined by a summation of pain scores, as compared with what would be the expected sum of scores. It is unclear how the expected summary score number was obtained, and further description of the definition of the pain scores is not provided. Patient-reported pain scores were not statistically significantly different between the 2 NPWT devices. In a subanalysis of 40 patients (V.A.C. $n=21$; SNaP $n=19$) with VLUs from this same RCT, Kaplan-Meier estimates suggest no significant difference in the proportion of VLU patients who completely healed over time ($P=0.3547$ unadjusted for baseline wound size; $P=0.4656$ adjusted for baseline wound size). Rates of adverse events reported in this RCT for the full patient population were similar between the groups. The rate of clinically determined infection was 3.1% in the SNaP ($n=2$) and 7.4% in the V.A.C. group ($n=5$) ($P=0.28$; P -value calculated by Rhee et al.). In the subanalysis of VLUs, the rate of infection was found to be 5.3% in the SNaP group ($n=1$) and 9.5% in the V.A.C. group ($n=2$) ($P=1.000$).

Different Types of NPWT Devices Compared with Each Other (V.A.C. Versus non-KCI Models)

In a publication of findings from a poor-quality retrospective national claims database analysis comparing V.A.C. NPWT to non-KCI NPWT devices for patients with chronic and acute wounds ($n=13,556$), investigators reported hospital readmission rates for the period following an initial NPWT claim in an outpatient setting. At 3 months and 6 months, wound-related readmission rates were statistically significantly lower for the V.A.C. group compared with the non-KCI device group across all wound types. At 3 months, the rates in each group were 5% and 8%, respectively, for the V.A.C. ($n=12,843$) and non-KCI device ($n=713$) groups ($P\leq 0.01$). The rates at 6 months were 6% and 11%, respectively, for the V.A.C. ($n=11,073$) and non-KCI device ($n=601$) groups ($P\leq 0.01$). Significant differences in favor of V.A.C. were also reported for mean per-patient inpatient stays and emergency room visits at 3 months and 6 months for all wound types. When mean per-patient inpatient stays and emergency room visits at 3 months and 6 months were analyzed by wound category (nonhealing surgical wounds, open wounds, and pressure ulcers) statistical significance did not persist for inpatient

stays at 3 months and at 6 months for nonhealing surgical wounds or emergency room visits for pressure ulcers at 3 months and at 6 months.

NPWT Compared with Other Wound Treatments: Wound Size and Chronicity

One poor-quality study among patients with DFUs (n=2677) examined healing in relation to ulcer size and wound duration at 12 and 20 weeks. The authors reported that wounds of all sizes treated with NPWT were more likely than those treated with standard wound care to achieve successful treatment endpoint (closure through secondary intention or through surgical intervention, or if adequate granulation tissue was present) ($P < 0.05$). Moreover, at 12 weeks, wounds in the NPWT group that were less than 6 months duration and those greater than 12 months duration were more likely to achieve closure than those treated with standard wound care. At 20 weeks, NPWT healed significantly more wounds compared with standard wound care only among wounds older than 12 months ($P < 0.05$).

One fair-quality study among patients with mixed etiology chronic wounds (n=342) evaluated whether the timing of NPWT application had an effect on healing. The ulcers in the early NPWT treatment group had higher incidence of wound closure compared with those in which NPWT was used later (adjusted hazard ratio [HR], 3.38; 95% CI, 1.68 to 6.82).

Key Question #4: What are the cost implications and cost-effectiveness of NPWT?

Five studies were found that provided information about the cost of NPWT compared with usual care or other NPWT devices. One study compared the cost of mechanical NPWT (SNaP) with electrically powered NPWT devices and standard of care. Four studies compared the cost of NPWT using V.A.C. with other wound therapies or other NPWT devices. All studies found that the primary NPWT device of interest (SNaP or V.A.C.) resulted in cost savings over usual care or alternative NPWT devices. Cost analyses are limited by the limitations of the available evidence base described within this HTA.

Practice Guidelines

The search of the core sources and relevant specialty groups identified 5 guidelines regarding NPWT and published within the past 10 years. The general recommendations provided by the guidelines are summarized in **Table 8**. Additional details, by guideline, are presented in [Appendix VI](#). See also **Practice Guidelines** in the **TECHNICAL REPORT** for additional background information on guidelines.

Table 8. Summary of Practice Guideline Recommendations

Key: DFU(s), diabetic foot ulcer(s); FDA, Food and Drug Administration; GL(s), guideline(s); NPWT, negative pressure wound therapy; PU(s), pressure ulcer(s); VLU(s), venous leg ulcer(s)

| Quantity of Individual GLs | Individual GL Quality | Recommendations |
|--|-----------------------|--|
| Multiple Wound Types | | |
| 1 International Expert Panel on Negative Pressure Wound Therapy (NPWT-EP) (2011) | Fair | <p>PU:</p> <ul style="list-style-type: none"> NPWT may be used until surgical closure is possible/desirable. Alternatively, NPWT should be considered to achieve closure by secondary intention. NPWT should be used to reduce wound dimensions. NPWT should be used to improve the quality of the wound bed. <p>DFUs:</p> <ul style="list-style-type: none"> NPWT must be considered as an advanced wound care therapy for postoperative Texas grade 2 and 3 diabetic feet without ischemia. NPWT must be considered to achieve healing by secondary intention. Alternatively, NPWT should be stopped when wound has progressed suitably to be closed by surgical means. NPWT should be considered in an attempt to prevent amputation or re-amputation. <p>Ischemic lower limb wounds:</p> <ul style="list-style-type: none"> The cautious use of NPWT in chronic limb ischemia when all other modalities have failed may be considered in specialist hands but never as an alternative for revascularization. NPWT may be considered as an advanced wound care therapy for lower limb ulceration after revascularization. The use of NPWT is NOT indicated in acute limb ischemia. <p>VLUs:</p> <ul style="list-style-type: none"> If first-line therapy (compression) is not efficacious, NPWT should be considered to prepare the wound for surgical closure as part of a clinical pathway. Use of gauze may be considered to reduce pain during dressing changes in susceptible patients. |
| Diabetic Foot Ulcers | | |
| 1 International Working Group on the Diabetic Foot (2016) | Good | <p>Topical NPWT may be considered in postoperative wounds, even though the effectiveness and cost-effectiveness of the approach remain to be established. (weak; moderate)</p> <p>It is not possible to make a recommendation on the use of NPWT in nonsurgical wounds because of the lack of available evidence.</p> |
| Pressure Ulcers | | |
| 2 National Pressure Ulcer Advisory Panel (2014) Association for the Advancement of | 1, Good 1, Fair | <p>Consider NPWT as an early adjuvant for the treatment of deep, Category/Stage III and IV pressure ulcers. (Strength of Evidence = B; Strength of Recommendation = Weak positive recommendation)</p> <p>ADVANCED OR ADJUNCTIVE INTERVENTIONS IF PU IS UNRESPONSIVE TO A-LEVEL MANAGEMENT: NPWT – No consistent effect on PU healing. Increased granulation, less fibrin compared to Redon drain, earlier use</p> |

| Quantity of Individual GLs | Individual GL Quality | Recommendations |
|--|-----------------------|---|
| Wound Care (2010) | | may shorten home care stays. Lower cost than gauze. The FDA has advised caution in selecting patients for this therapy due to serious, occasionally fatal, complications. |
| Venous Ulcers | | |
| 1 Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) (2014) | Good | Guideline 4.24: NPWT – The GL suggests against routine primary use of NPWT for venous leg ulcers [GRADE = 2; LEVEL OF EVIDENCE = C] There is currently not enough information to support the primary use of NPWT for VLUs. Evidence supports positive effects with the use of negative pressure therapy for wound healing in general. Tissue granulation, area and volume reduction, and reductions in bioburden have all been reported. There have been few studies specifically studying negative pressure therapy for VLUs, with most studies reporting on mixed wound causes. There has been an increase in the use of NPWT for wound bed preparation to augment skin graft healing. |

Selected Payer Policies

At the direction of WA State HCA, the coverage policies for the following organizations were reviewed: Aetna, Centers for Medicare & Medicaid Services (CMS), Oregon Health Evidence Review Commission (HERC), Group Health Cooperative, and Regence Blue Cross/Blue Shield.

See **Selected Payer Policies** in the **TECHNICAL REPORT** for additional details and links to policy documents.

Aetna

Aetna considers NPWT pumps medically necessary for ulcers and wounds encountered in an inpatient setting or in the home setting when the criteria are met. An NPWT pump and supplies are considered not medically necessary if any contraindication for use (as identified in the policy) is present.

Centers for Medicare & Medicaid Services (CMS)

No CMS National Coverage Determination (NCD) for NPWT was identified on July 25, 2016 (search National Coverage Documents by keywords *negative pressure* or *wound* or *ulcer* or *e2402* in all documents at: <https://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx>). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. There is a Local Coverage Determination (LCD) for NPWT pumps (L33821) that was effective July 1, 2016. The LCD was issued by Noridian Healthcare Solutions LLC, a Medicare contractor in the state of Washington.

The LCD states that an NPWT pump and supplies are covered when ulcers and wounds are encountered in an inpatient setting or in the home setting when the criteria are met.

Group Health Cooperative

Group Health Cooperative covers NPWT pumps and supplies for wound edema, exudate management, and stimulation of granulation for an initial 14-day course when the criteria are met for ulcers and wounds encountered in an inpatient setting or in the home setting, there is a goal of therapy clearly stated, and there are no contraindications for use (as identified in the policy).

Oregon Health Evidence Review Commission (HERC)

No coverage guidance for NPWT was identified on the Oregon HERC website.

Regence

No coverage policy for NPWT was identified on the Regence Group website (Regence Group Medical Policies).

Overall Summary and Discussion***Evidence-Based Summary Statement***

The availability and use of NPWT devices for treating a variety of wounds has been increasing across the care spectrum. The focus of this HTA was specified as home use of NPWT for chronic and nonhealing surgical wounds. The aim of this HTA was to identify, assess, and summarize the best available evidence applicable to the topic. In recognition of the substantial volume of published literature on the topic of NPWT in general, and recent work by the Agency for Healthcare Research and Quality and the Cochrane Collaboration it was decided to identify recent systematic reviews with a similar scope and purpose in order to identify relevant primary studies. Subsequently, update literature searches and manual searches of key references were conducted to find additional primary literature meeting inclusion criteria. Ultimately, 14 primary studies meeting inclusion criteria were identified.

Overall, the quality of the evidence regarding the clinical effectiveness of the home use of NPWT for treating chronic wounds was considered to be low. For the effectiveness of home use of NPWT to treat chronic wounds, studies were organized based on the type of wound investigated. Low to very low quality evidence from 3 studies assessing NPWT compared with other wound therapies for treating chronic DFUs suggests benefit with NPWT for complete wound healing or wound closure (3 studies) and time to wound closure (1 study). No other clinical outcomes eligible for this HTA were reported in these studies. Very low quality evidence from 1 study found no difference between groups for provision of pain medication as a surrogate measure for pain. Evidence for the home use of NPWT for treating arterial ulcers or venous ulcers was considered to be of very low quality, as there was only one study for each wound type. The study suggests that complete wound healing is more likely among arterial or venous ulcer patients who receive NPWT than those who do not. Two studies focused on patients with pressure ulcers; evidence for this indication was also considered to be of very low quality. The studies suggest a trend favoring NPWT over other wound therapies for complete wound healing, however the results were not statistically significant in either study. Low quality evidence from 2 studies that evaluated mixed etiology wounds suggests that NPWT heals a higher proportion of wounds than other wound therapies, and very low quality evidence from 1 study indicates a shorter time to complete

wound healing with the use of NPWT. There is insufficient evidence to determine the effect of NPWT on other direct clinical outcomes or patient-centered outcomes.

The overall quality of the body of evidence for the clinical effectiveness of NPWT in the home or outpatient settings for treatment of surgical wounds healing by secondary intention is considered to be low. There was considerable heterogeneity among the 3 studies included for this key question. Each of the 3 RCTs enrolled patients undergoing different surgical procedures and they compared different alternative wound therapies. Overall, the results favored NPWT for the clinical outcomes reported: complete wound healing (1 study) and time to complete wound healing (3 studies). No differences between groups were found for patient-centered outcomes: pain (2 studies), return to prior level of activity (1 study), and quality of life (1 study).

The quality of the overall body of evidence for harms associated with home use of NPWT for chronic wounds and surgical wounds healing by secondary intention is considered to be low. Six studies evaluated NPWT compared with other wound treatments in patients with DFUs, pressure ulcers, and mixed ulcers. No studies comparing NPWT with other wound treatments reporting adverse events for patients with arterial ulcers or venous insufficiency ulcers were identified. Results from 2 studies favored NPWT with respect to rates of amputation and a third study favored NPWT with respect to rates of infection among patients with DFUs. For patients with pressure ulcers, 1 study reported statistically significant results in favor of NPWT for emergent care and hospitalization. The study reporting adverse events among a mixed ulcer population did not report data for the comparison group. Adverse events were reported in 3 studies evaluating NPWT compared with other wound treatments for surgical wounds. None of the studies reported statistically significant differences between groups for the adverse events described in the publications.

Overall, evidence of varying clinical effectiveness or rates of harms from 4 studies is considered very low quality. This body of evidence is also heterogeneous. One study compared the V.A.C. Therapy System (KCI Inc.) with the SNaP Wound Care System (Spiracur Inc.), another compared the V.A.C. Therapy System with unspecified non-KCI models. Two other studies compared NPWT with other wound therapies and evaluated outcomes based on wound size or chronicity. No studies looked at comparative effectiveness in relation to clinical history, duration of treatment, or patient characteristics. In the study comparing V.A.C. with SNaP, no differences were found for proportion of wounds healed over time or patient reported pain scores. However, patients in the SNaP group were statistically significantly more likely to agree or strongly agree that they were able to perform their normal daily activities than patients treated with the V.A.C. device. Also, higher percentage of SNaP-treated subjects than V.A.C.-treated subjects reported that their activity level either increased or stayed the same. Rates of adverse events reported in this RCT for the full patient population were similar between the groups. In a comparison of hospital readmission rates for V.A.C. patients compared with patients using a non-KCI NPWT device, readmission rates were lower for the V.A.C. group at 3 and 6 months. Analyses of wound size and chronicity in 1 study favored NPWT over other wound therapies. The remaining study did not provide comparative data between NPWT and other wound treatments.

Five studies were found that provided information about the cost of NPWT compared with usual care or other NPWT devices. One study compared the cost of mechanical NPWT (SNaP) with electrically powered NPWT devices and standard of care. Four studies compared the cost of NPWT using V.A.C. with other wound therapies or other NPWT devices. All studies found that the primary NPWT device of interest (SNaP or V.A.C.) resulted in cost savings over usual care or alternative NPWT devices.

Gaps in the Evidence

The following evidence is needed to better answer the Key Questions of this report:

- Future work needs to include larger, more rigorous prospective studies conducted by independent researchers designed to evaluate direct evidence of NPWT compared with consistent comparators for treatment of specific wound types in the home setting. Consistent definitions and measurements for outcomes across studies would also be helpful.
- Publications with better reporting of study protocols, including settings and details about who changes wound dressings and details about interventions, comparators, and concomitant treatments are needed. Clear descriptions of inpatient and outpatient care would help identify studies applicable to the questions relevant to home use.
- Study methods need to include more details about collecting and analyzing clinical, patient-centered, and harms outcomes.
- There is a need for more studies examining response to treatment according to patient characteristics such as comorbidities, smoking status, and age.

TECHNICAL REPORT

Clinical Background

The purpose of this HTA is to assess the evidence on the use of negative pressure wound therapy (NPWT) in the home setting. The types of wounds of most interest are those likely to be managed in the home setting. These include common chronic wounds such as venous insufficiency ulcers, diabetic foot ulcers (DFUs), and pressure ulcers (Rhee et al., 2014). Also of interest to the Washington State Health Technology Assessment program is the use of NPWT in the home setting to treat surgical wounds.

Wound Types of Interest

Chronic wounds, defined within this report by type or etiology and not by duration, include venous insufficiency ulcers, DFUs, and pressure ulcers. Although the causes for chronic wounds vary, in all cases, at least one of the phases of wound healing is altered and the pathway to healing is impaired. Patients with chronic wounds may experience a range of severity, including substantial limitations in mobility and poor health-related quality of life. Chronic wounds account for an estimated \$25 billion dollars in healthcare expenditures per year (Rhee et al., 2014).

Surgical wounds are defined for this report as incisions made to initially closed skin and tissue in the course of a patient's care for an underlying health concern requiring surgical intervention. Surgical wounds that are closed by means such as sutures, staples, tape, or glue that hold the wound edges together are referred to as surgical wounds expected to heal by primary intention. Surgical wounds may also be left open for the healing process; these are referred to as surgical wounds healing by secondary intention. The scope of this report encompasses both types of wounds but does not include surgical repair of wounds related to trauma, fractures, burns, or skin grafting.

Diabetic Foot Ulcers

Complications of diabetes include neuropathy and ischemia affecting the feet. These conditions contribute to the formation of 2 types of DFUs—neuropathic and neuroischemic ulcers (Edmonds and Foster, 2006). A DFU is a full-thickness wound penetrating through the skin. DFUs may lead to infection of surrounding tissue and subsequently to foot and lower limb amputations (Frykberg and Williams, 2007). The Centers for Disease Control and Prevention (CDC) reports that approximately 73,000 lower limb amputations were done in adults with diabetes in 2010 (CDC, 2014). A near 50 percent decrease in the rate of amputations among patients with diabetes from 2010 to 2014 is attributed to advances in clinical care, increased availability of preventive healthcare, control of risk factors, and increased awareness of the potential complications of diabetes. However, the number of people affected by complications of diabetes, including DFUs, is still high and is expected to remain high (CDC, 2015).

Venous Insufficiency Ulcers

A venous leg ulcer (VLU) is an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension and poor blood circulation. Risk factors include older age, obesity, previous leg

injuries, deep venous thrombosis, and phlebitis. Open ulcers may persist for a long period of time (Collins and Seraj, 2010). VLUs account for approximately 70 percent of all leg ulcers. Estimates suggest that more than 2 million people in the United States have chronic venous insufficiency, 20 percent of whom may develop VLUs. The recurrence rate of VLUs within 10 years is approximately 50 percent (O'Donnell et al., 2014). Pain, disability, and psychosocial effects from VLUs may be substantial.

Pressure Ulcers

The National Pressure Ulcer Advisory Panel (NPUAP) defines a pressure ulcer (or pressure injury) as "...localized damage to the skin and/or underlying soft tissue usually over a bony prominence or related to a medical or other device. The injury can present as intact skin or an open ulcer and may be painful. The injury occurs as a result of intense and/or prolonged pressure or pressure in combination with shear. The tolerance of soft tissue for pressure and shear may also be affected by microclimate, nutrition, perfusion, co-morbidities and condition of the soft tissue." (NPUAP, 2016) Those most at risk for pressure ulcers include diabetic, obese, and elderly patients, and those who have a medical condition limiting their ability to change positions. The prevalence of pressure ulcers varies between 0.31 to 0.70 percent per year (Rhee et al., 2014). Between 1995 and 2008, the incidence of pressure ulcers increased by as much as 80 percent (Sullivan and Schoelles, 2013).

Surgical Wounds

Surgical incisions are often closed by means such as sutures, staples, tape, or glue that hold the wound edges together. This is called healing by primary intention. Some closed surgical wounds may be slow to heal or fail to heal because of infection or other factors such as the patient's age or presence of co-occurring medical conditions (e.g., diabetes, malnutrition, obesity, cardiovascular disease). Failure to heal may also be caused by separation of the wound edges (dehiscence) because of broken sutures, sutures cutting through the skin, or slipped knots. Infection may also contribute to dehiscence (Webster et al., 2014).

Healing by secondary intention is when wounds are intentionally left open after surgical intervention. Healing by secondary intention can be an intended part of postsurgical care, or it can be an approach implemented after the failure of wound closure, such as when there is dehiscence caused by inflammation and edema. A recent systematic review by the Cochrane Collaboration stated that good data on the incidence, prevalence, healthcare expenditures, and quality of life effects related to surgical wounds healing by secondary intention are not readily available (Dumville et al., 2015a).

Negative Pressure Wound Therapy

NPWT, also referred to as subatmospheric pressure wound therapy or vacuum-assisted wound therapy, involves the application of subatmospheric pressure to the surface of a wound. The technology was introduced in the 1990s and is used for treatment of chronic and acute wounds. NPWT is thought to promote wound healing by providing a warm, moist wound bed while removing wound fluid. The device may remove molecular factors that inhibit cell growth, improve blood flow to the wound, enhance wound oxygenation, and improve the flow of nutrients to the wound. NPWT may also create mechanical

forces that draw the wound edges together, and induce cell proliferation, cell migration to the wound, and angiogenesis.

NPWT comprises the application of a foam or gauze type dressing sealed with an adhesive film and connected via tubing to a vacuum pump. Continuous or intermittent controlled negative pressure (suction) is applied across the wound. Wound effluent is collected in a canister. Figure 1 shows a generalized NPWT system.

Figure 1. Negative Pressure Wound Therapy System

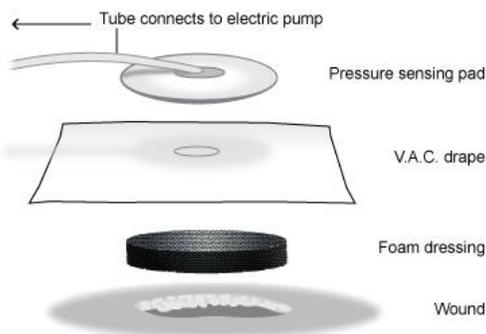


Figure 1. Negative Pressure Wound Therapy System

The V.A.C. Therapy System, manufactured by Kinetic Concepts Inc. (KCI), was the first Food and Drug Administration (FDA)-approved NPWT device available in the United States. Many other NPWT devices produced by other manufacturers now have FDA clearance. Stationary and portable NPWT systems are available, and recently, a system (SNaP Wound Care System; Spiracur Inc.) that does not require electric or battery power has been developed. **Table 9** lists NPWT devices commercially available in the United States. Dressing changes are typically performed every 48 to 72 hours during NPWT therapy and no less than 3 times per week for most models. Infected wounds may require more frequent dressing changes. Target pressures and treatment cycling and duration vary according to the type of wound being treated (Argenta and Morykwas, 1997; Mooney et al., 2000; KCI Licensing Inc., 2014). The devices range in price and in type and offer a variety of options, including the ability to: add instillation fluids, vary the negative pressure settings, vary the dressing applied to the wound base from foams to gauzes, and use multiple types of overlying wound dressings. In traditional systems, the electronic pump is continually used and the dressings are disposable. There are also systems in which both the pump and dressings are disposable. NPWT devices are usually applied by a variety of clinicians, but patients can apply some of the newer technologies (Rhee et al., 2014).

Among the potential benefits of NPWT are symptom management, reduced frequency of dressing changes, and cost-effectiveness compared with alternative wound therapies because of faster healing times that may lead to lower overall treatment costs (Ousey and Milne, 2014). There are also potential harms associated with NPWT. These include pain, retention of foreign bodies from the dressing, bleeding, infection, death from infection or bleeding, and complications stemming from loss of

electricity (Rhee et al., 2014). Safety concerns, particularly those related to home use of NPWT devices, prompted the FDA to issue a preliminary Public Health Notification and Advice for Patients communication in November 2009 (FDA, 2009a; FDA, 2009b). An updated safety communication was issued in 2011, and included recommendations to clinicians regarding patient selection, monitoring, contraindications, and risk factors. The agency also endorsed patient and caregiver education (FDA, 2011; Rhee et al., 2014). Contraindications for NPWT include: inadequately debrided wounds; necrotic tissue with eschar; untreated osteomyelitis; cancer in the wound; untreated coagulopathy; nonenteric and unexplored fistulas; and exposed vital organs (Rock, 2014).

Table 9. Negative Pressure Wound Therapy Technologies Commercially Available in the United States^a

Key: NPWT, negative pressure wound therapy; SNaP, Smart Negative Pressure Wound Care System

| Manufacturer/Company | Model | Care Setting |
|--|--|--|
| Atmos | Wound RX S 041 Wound pump | Hospital and home |
| ConvaTec | See IRB/Boehringer | - |
| Cardinal Health | Cardinal Health™ NPWT PRO | Acute and skilled care |
| | Cardinal Health™ NPWT PRO to GO | Home |
| | Cardinal Health™ NPWT PRO at Home | Home |
| | Sved® Wound Treatment System | Hospital and home |
| Cork Medical Products LLC (Creo Quality LLC) | Nisus NPWT | Hospital, long-term care, home |
| Devon Medical Products | Extricare® 2400 NPWT | Ambulatory/outpatient |
| | Extricare® 3600 NPWT | Acute, postacute, and skilled nursing facilities |
| Foryou Medical Electronics Co. Ltd. | ForYou NPWT Pro | Setting not specified |
| | ForYou NPWT Home | Hospital and home |
| Genadyne Biotechnologies Inc. | Genadyne A4 Wound Vacuum System | Hospital and home |
| | XLR8 | Hospital and home |
| Innovative Therapies | SVED™ Wound Treatment System | Hospital and home |
| | SVEDMAN™ Wound Treatment System | Setting information not found |
| Invacare | MobIVac® | Hospital and home |
| IRB Medical Equipment/ Boehringer Wound Systems/ConvaTec | Engenex® Advanced NPWT System | Hospital and home |
| IVT Medical Ltd. | Vcare α | Setting not specified |
| Kalypto Medical (acquired by Smith & Nephew) | NPD 1000™ Negative Pressure Wound Therapy System | Home |

| Manufacturer/Company | Model | Care Setting |
|---|---|--|
| KCI (Kinetic Concepts Inc.) (KCI, LifeCell, and Systagenix are now Acelity) | V.A.C. Via™ Therapy | Hospital and home |
| | V.A.C. Ultra™ Therapy | Hospital |
| | ActiV.A.C.® Therapy | Hospital and home |
| | V.A.C. ATS® Therapy | Hospital and home |
| | V.A.C. Freedom® Therapy | Hospital and home |
| | V.A.C. Instill® Wound Therapy | Hospital |
| | InfoV.A.C.® Therapy | Hospital and home |
| | ABThera™ Open Abdomen Negative Pressure Therapy (open abdominal wounds) | Hospital |
| | Prevena™ Incision Management System | Hospital and home |
| MediTop BV/The Medical Company | Exusdex® wound drainage pump | Primarily hospital use but may be used at home |
| Medela | Invia® Liberty™ | Hospital and home |
| | Invia® Vario | Setting for Vario not found |
| | Invia® Motion | Hospital and home |
| | Invia® Motion™ - Endure | Hospital and home |
| | Vario 8 and Vario 18 | Hospital and home |
| Haromed Medical Products (cleared for MediTop BV) | Exsudex® | Hospital and home |
| Molnlycke Health Care, US LLC Note: 510(k)s under these product names were not found | Avance® NPWT | Hospital and home |
| | Avance® Solo | Hospital and home |
| Premco Medical Systems | Prodigy™ NPWT System (PMS-800 and PMS-800V) | Hospital and home |
| Prospera | PRO-I™ (stationary) | Hospital and home |
| | PRO-II™ (portable) | Home |
| | PRO-III™ | Hospital and home |
| Smith & Nephew (includes subsidiary Blue Sky Medical) | Renasys EZ Plus | Hospital and home |
| | Renasys Go | Hospital and home |
| | PICO | Hospital and home |
| | V1STA (previously by Blue Sky Medical Group) | Hospital and home |
| | EZCare (previously by Blue Sky Medical Group) | Hospital and home |
| Spiracur | SNaP® | Hospital and home |

| Manufacturer/Company | Model | Care Setting |
|--|--|---|
| (SNaP® Therapy System acquired by Acelity in 2015) | | |
| Talley Group Ltd. | Venturi™ Negative Pressure Wound Therapy | Hospital and home |
| Wound Rx Medical LLC | Whisper Pump system | Hospital, transitional, or nursing facility |

^aThe table from Rhee et al. (2014) titled “Negative Pressure Wound Therapy Technologies Commercially Available in the U.S.” was updated using the following strategy: After confirming that NPWT does not require a premarket authorization (PMA), the term “negative pressure wound therapy” was used to search <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmnsimplesearch.cfm>. Supplemental information was obtained from manufacturers’ websites.

Washington State Agency Utilization and Costs

Review Objectives

Scope

The scope of this report is defined as:

Population: Patients diagnosed with chronic wounds, defined specifically as venous leg ulcers, arterial leg ulcers, diabetic foot ulcers (DFUs), pressure ulcers, and mixed etiology chronic wounds; or nonhealing surgical wounds (either closed or open)

Interventions: Negative pressure wound therapy (NPWT)

Comparisons: Other wound care methods; comparison of NPWT devices

Outcomes: Clinical outcomes (complete wound healing; time to complete wound healing; time to surgical readiness of the wound bed or time to wound closure; proportion of wounds closed; seroma/hematoma; reoperation; mortality; wound healing rate for healed wounds); patient-centered outcomes (return to prior level of functional activity; pain; health-related quality of life); safety (infection rates; extremity amputation; emergency room visits related to the NPWT or treated wound; unplanned hospitalizations or surgeries related to the NPWT or treated wound; blood transfusions/bleeding)

Settings: Home or outpatient setting

Key Questions

The following key questions will be addressed:

- 1a. What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of chronic wounds (i.e., venous leg ulcers, arterial leg ulcers, DFUs, pressure ulcers, and mixed etiology chronic wounds)?
- 1b. What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of nonhealing closed or open surgical wounds (i.e., incisions expected to heal by primary intention or incisions expected to heal by secondary intention)?
2. What are the harms associated with NPWT?
3. Does the effectiveness of NPWT or incidence of adverse events vary by clinical history (e.g., diabetes), wound characteristics (e.g., size, chronicity), duration of treatment, types of devices, or patient characteristics (e.g., age, sex, prior treatments, smoking, or other medications)?
4. What are the cost implications and cost-effectiveness of NPWT?

Search Strategy and Selection Criteria

See [Appendix I](#) for additional search details.

Systematic Reviews and Guidelines

During the period of topic scoping, it was determined that the volume of available literature on NPWT was very large. To accommodate this large body of literature and in recognition of recent systematic review work conducted both by the Agency for Healthcare Research and Quality (AHRQ) and The Cochrane Collaboration, a decision was made to conduct a targeted search for high-quality systematic reviews to identify primary studies for inclusion in this report. In other words, the search strategy, inclusion and exclusion criteria, and the eligible included studies from the selected systematic reviews were included as primary data for the current report. A systematic search for additional primary data was conducted to ensure that all of the highest-quality available evidence was included in the report. All of the eligible studies (both from the selected systematic reviews and update searches) were abstracted, quality rated, and synthesized for this HTA. The following sources for systematic reviews were searched on March 15, 2016, and May 11, 2016, for systematic reviews:

- Core online databases such as AHRQ and the Centre for Reviews and Dissemination (York University)
- PubMed, using filters for systematic reviews

Systematic reviews were selected if they were of good quality and pertained to ≥ 1 of the key questions. Three such systematic reviews (Rhee et al., 2014; Webster et al., 2014; Dumville et al., 2015a) were identified and used as the source of some of the included primary studies and the foundation for update literature searches for this report.

Primary Studies and Practice Guidelines

The PubMed (searched on March 15, 2016, and May 17, 2016) and OVID-Embase (searched on March 15, 2016, and July 1, 2016) databases were searched for primary studies designed to answer the Key Questions. The searches were designed to be update literature searches of selected systematic reviews (Rhee et al., 2014; Webster et al., 2014; Dumville et al., 2015a). Beginning search dates were set to overlap slightly with the most recent search dates of selected systematic reviews to capture new evidence published since the last search of the reviews. Update searches will be conducted prior to completing the final HTA. The National Guidelines Clearinghouse (<https://guideline.gov/>) and websites of relevant professional societies were searched for practice guidelines. Specific search strings are documented in [Appendix I](#).

Inclusion/Exclusion Criteria

Detailed inclusion and exclusion criteria, along with their rationale, are presented in **Table 10**. The inclusion and exclusion criteria were derived from the previously published systematic reviews. Slight modifications were made to allow for the scope of this HTA that includes both chronic wounds and surgical wounds. Adopting the inclusion and exclusion criteria from the selected systematic reviews allowed for continuity in reviewing and selecting recent literature to add to the evidence base.

Table 10. Inclusion/Exclusion Criteria

Key: NPWT, negative pressure wound therapy; RCT(s), randomized controlled trial(s)

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Population: Patients diagnosed with chronic wounds defined as venous, arterial, diabetic, pressure, or mixed etiology chronic wounds; or patients with nonhealing surgical wounds | Patients with traumatic wounds, fractures, burns, or skin grafts |
| Intervention: NPWT | Studies that evaluated an NPWT device that is not commercially available and approved for use in the United States |
| Comparator: Other wound care methods; comparison of NPWT devices | Studies with no comparison with other wound treatments or other NPWT devices |
| <p>Outcomes:</p> <p><u>Clinical outcomes</u> – complete wound healing; time to complete wound healing; time to surgical readiness of the wound bed or time to wound closure; proportion of wounds closed; seroma/hematoma; reoperation; mortality; wound healing rate for healed wounds</p> <p><u>Patient-centered outcomes</u> – return to prior level of functional activity; pain; health-related quality of life</p> <p><u>Safety</u> – infection rates; extremity amputation; emergency room visits related to the NPWT or treated wound; unplanned hospitalizations or surgeries related to the NPWT or treated wound; blood transfusions/bleeding</p> | Studies that reported wound healing rates without also reporting complete wound healing (this is considered a surrogate outcome measure because chronic wounds may not heal in a linear fashion, and cannot be used to accurately predict complete healing) |
| <p>Study Design: Comparative studies (RCTs only for surgical wounds; other comparative study designs accepted for chronic wounds as long as the total number of participants was ≥ 20).</p> <p>Studies with mixed inpatient/outpatient populations that did not provide separate analyses for the different groups were included if they provided data on the proportion of patients and/or the proportion of therapy days treated in the inpatient versus outpatient/home setting, or if it can be interpreted that the majority of patients were treated in the outpatient/home setting.</p> | Fewer than 20 patients with chronic wounds (studies with ≤ 10 patients per group would not be adequately powered to detect meaningful differences in clinical outcomes); conference abstracts or posters; nonhuman studies; no original data (e.g., editorials, letters, non-systematic reviews) NOTE: Any size RCT was accepted for surgical wounds. |
| <p>Setting: Home or outpatient setting</p> <p>NOTE: Studies were included if they were described as in “outpatient setting” or if it was reported (or was interpreted) that patients were not receiving care in long-term care facilities, including assisted living, skilled, or maintenance nursing homes.</p> | Studies in which NPWT was applied only in inpatient (acute or long-term care) settings or that did not provide enough detail about the setting of care to determine whether outpatient or home-based care was provided during the study period. |

Quality Assessment

Clinical Studies

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was employed to determine the quality of selected systematic reviews (Shea et al., 2007; [Appendix II](#)). [Appendix III](#) outlines the process used by Hayes for assessing the quality of individual primary studies and the quality of bodies of evidence. This process is in alignment with the methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Quality checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *good*, *fair*, *poor*, or *very poor*.

Like the GRADE Working Group, Hayes uses the phrase *quality of evidence* to describe bodies of evidence in the same manner that other groups, such as AHRQ, use the phrase *strength of evidence*. The Hayes Evidence-Grading Guides ensure that assessment of the quality of bodies of evidence takes into account the following considerations:

- Methodological quality of individual studies, with an emphasis on the risk of bias within studies.
- Applicability to the population(s), intervention(s), comparator(s), and outcome(s) of interest, i.e., applicability to the PICO statement.
- Consistency of the results across studies.
- Quantity of data (number of studies and sample sizes).
- Publication bias, if relevant information or analysis is available.

NOTE: Two terms related to applicability are *directness* and *generalizability*. *Directness* refers to how applicable the evidence is to the outcomes of interest (i.e., health outcomes versus surrogate or intermediate outcomes) or to the comparator of interest (indirect comparison of 2 treatments versus head-to-head trials). *Generalizability* usually refers to whether study results are applicable to real-world practice. If the setting is not specified in a PICO (population-interventions-comparator-outcomes) statement, the issue of generalizability to real-world settings is not typically treated as an evidence quality issue. Another term used by some organizations is *imprecision*, which refers to findings based on such a small quantity of data that the CI surrounding a pooled estimate includes both clinically important benefits and clinically important harms, or such a small quantity of data that any results other than large statistically significant effects should be considered unreliable.

Bodies of evidence for particular outcomes are labeled as being of *high*, *moderate*, *low*, or *very low quality*. These labels can be interpreted in the following manner:

High: Suggests that we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.

Moderate: Suggests that we can have reasonable confidence that the results represent the true direction of effect but that the effect estimate might well change with the publication of new studies.

Low: We have very little confidence in the results obtained, which often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and possibly the direction of the results.

Very Low: Suggests no confidence in any result found, which often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Economic Evaluations

A tool created for internal use at Hayes was used to guide interpretation and critical appraisal of economic evaluations. The tool for economic evaluations was based on best practices as identified in the literature and addresses issues such as the reliability of effectiveness estimates, transparency of the report, quality of analysis (e.g., the inclusion of all relevant costs, benefits, and harms), generalizability/applicability, and conflicts of interest. Sources are listed in [Appendix III](#).

Guidelines

The Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool (AGREE Next Steps Consortium, 2013), along with a consideration of the items related to commercial funding and conflicts of interest among the guideline authors, was used to assess the quality of practice guidelines. Use of the AGREE tool was limited to these areas because they relate most directly to the link between guideline recommendations and evidence.

Search Results

The 14 studies included in this HTA consist of 9 primary studies identified from 3 previously published, good-quality systematic reviews, and 5 additional studies that were added through update searches of electronic databases and manual searches of key publications.

The authors of the previously published systematic reviews screened a large volume of literature and found few eligible publications for evidence synthesis. The literature search conducted for the AHRQ systematic review on NPWT technologies for wound care in the home yielded 5912 unique citations, and the final number of included studies was 7 (published in 8 articles) (Rhee et al., 2014). The literature search done for the Cochrane Collaboration systematic review on NPWT for surgical wounds healing by secondary intention yielded 586 records, and the final number of included studies was 2 (Dumville et al., 2015a). The systematic review on NPWT for surgical wounds healing by primary intention was an update of a 2012 review; the literature search done by the authors of the updated review yielded 177 new, unique records and resulted in a total of 9 included studies (5 of which were part of the 2012 review). Out of the 18 studies (published in 20 articles) in these 3 systematic reviews, 9 studies (11 articles) met inclusion criteria for this HTA. The remaining 9 studies were excluded because of ineligible setting.

In addition to identifying 9 studies (11 articles) from previously published systematic reviews, update literature searches and manual searches of key references yielded 1269 unique citations for review; 47

of these were selected for full-text review. Five studies (9 articles) were selected for inclusion. See **Figure 2** for a summary of the update literature search results.

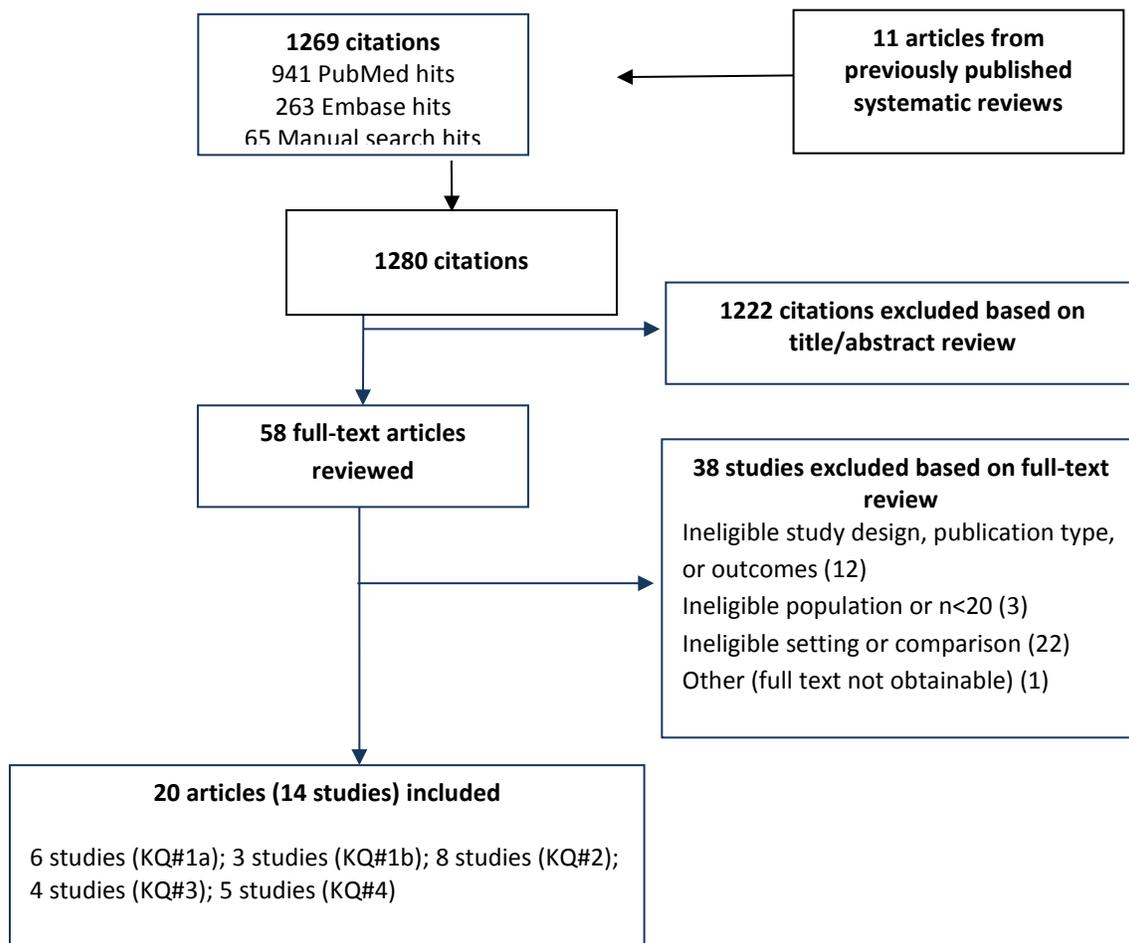
Included Studies

The 14 included primary studies consist of 11 studies (published in 14 articles) of populations with chronic wounds (Ford et al., 2002; Schwien et al., 2005; Frykberg and Williams, 2007; Lavery et al., 2007; Blume et al., 2008; Fife et al., 2008; Lerman et al., 2010; Armstrong et al., 2011; Hutton and Sheehan, 2011; Armstrong et al., 2012; Yao et al., 2012; Driver and Blume, 2014; Law et al., 2015; Marston et al., 2015) and 3 studies (6 articles) of populations with surgical wounds (Armstrong et al., 2005; Apelqvist et al., 2008; Acosta et al., 2013; Biter et al., 2014; Monsen et al., 2014; Monsen et al., 2015). The studies of chronic wounds include 3 randomized controlled trials (RCTs), 7 observational studies, and 1 economic modelling (decision analytic modelling) study. All 3 studies of surgical wounds were RCTs per the inclusion criteria. **Figure 2** shows the distribution of the included studies across the Key Questions. Some studies may apply to more than 1 Key Question.

Excluded Studies

See [Appendix IV](#) for a listing of the 38 studies that were excluded from analysis after full-text review.

Figure 2. Summary of Search Results



Literature Review

Key Question #1a: What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of chronic wounds (i.e., venous leg ulcers, arterial leg ulcers, diabetic foot ulcers, pressure ulcers, and mixed etiology chronic wounds)?

Study characteristics

A good-quality systematic review on NPWT for chronic wound care in the home setting (Rhee et al., 2014) was selected to identify primary studies for inclusion in this HTA. The search strategy by Rhee and colleagues was subsequently updated, through searches of electronic databases and manual searches of other relevant publications, to identify additional new studies since publication of the Rhee systematic review. In all, 6 primary studies meeting inclusion criteria were identified that address Key Question 1a; 5 of these were included in the review by Rhee and colleagues, and 1 additional study was identified for this HTA. **Table 11** includes brief descriptions of the study characteristics. See [Appendix V](#) for more details. There were 2 RCTs and 4 observational studies. The RCTs ranged in size from 28 to 341 patients (Ford et al., 2002; Blume et al., 2008). The observational studies ranged in size from 78 to 2677 patients (Lavery et al., 2007; Fife et al., 2008; Lerman et al., 2010; Yao et al., 2012). All 6 studies compared NPWT therapy with other types of wound treatment. One of the studies included both inpatients and outpatients and did not provide separate analyses for each group (Blume et al., 2008). This study was included in this HTA because the publication provided information about the proportion of home care days in each group (89.5% for the NPWT group and 95.3% for the comparison group) and it is one of the few RCTs identified (Blume et al., 2008). While the lack of separate analyses for patients who may have received only inpatient care while receiving NPWT is a limitation of this study, information that both groups received a majority of care in the home setting suggests some applicability to patient populations using NPWT at home.

Wound types in the study populations varied. Patients with DFUs were the focus of 3 studies (Lavery et al., 2007; Blume et al., 2008; Fife et al., 2008). One study included only patients with pressure ulcers (Ford et al., 2002). The remaining 2 studies included patients with lower extremity ulcers of different etiologies (Lerman et al., 2010; Yao et al., 2012).

Not all studies reported details of the NPWT devices used. The 1 study that did report details evaluated the SNaP (Spiracur) device (Lerman et al., 2010). The remaining studies reported the brand name only; in all cases this was the V.A.C. Therapy System (Kinetic Concepts Inc.). Details of comparison treatments were also lacking.

Studies were selected if authors reported, or it was possible to interpret with some certainty, that NPWT was utilized in the home setting. Studies of patients in acute or long-term care facilities such as hospitals, skilled or maintenance nursing facilities, or assisted living were excluded. Studies with patients recruited as inpatients but who received follow-up care in outpatient settings were eligible if all other eligibility criteria were met. The Blume et al. study includes both inpatients and outpatients; it reports proportion of outpatient days but does not report outcome results for each group of patients separately (Blume et al., 2008). In the remaining 5 studies, the setting was not explicitly described, but “outpatient

setting” was interpreted as home because it appeared that the patients were not in assisted living or skilled or maintenance nursing homes.

Study Quality

Half of the studies (3 out of 6) included for KQ1a were rated as poor quality (Lavery et al., 2007; Fife et al., 2008; Lerman et al., 2010). Two RCTs and 1 retrospective cohort study were rated as fair quality (Ford et al., 2002; Blume et al., 2008; Yao et al., 2012). The 3 fair-quality studies were limited by poor reporting and potentially meaningful differences between groups at baseline. The observational study (Yao et al., 2012) provided stratified and adjusted analyses, which contributed to its rating as fair quality. Poor-quality ratings were assigned because of methodological weaknesses, including potential for differential concomitant treatments between intervention and control groups (Fife et al., 2008; Lerman et al., 2010); inappropriate or poorly described control groups (Lavery et al., 2007; Fife et al., 2008); high overall attrition (Lerman et al., 2010); poor or selective reporting on comparative treatments, potential confounders, and outcomes (Fife et al., 2008); quality of data source not clear (Fife et al., 2008); and surrogate data used to assess outcomes (Fife et al., 2008). All studies were limited by the lack of blinding, and all of the observational studies were limited by the lack of randomization. The lack of blinding caregivers and patients to the treatment is primarily because of the nature and obvious differences between the treatments delivered and the unethical practice of delivering a sham or placebo treatment in this patient population (FDA, 2006). The Ford et al. study reported that personnel who measured wounds and obtained plaster impressions were blinded to treatment status. No other study reported blinding of outcome assessors.

Table 11. Study Characteristics of Studies Included for KQ1a

Key: DFU, diabetic foot ulcer; NPWT, negative pressure wound therapy; PU, pressure ulcer; RCT, randomized controlled trial

| Study Study Design (n), Quality | Wound Type | | | Comparisons | NPWT Devices | |
|--|------------|----|-------|--|--------------------|-----------------|
| | DFU | PU | Mixed | | SNaP (Spiracur) | V.A.C. (KCI) |
| Blume et al. (2008) RCT (341), Fair | X | | | Advanced moist wound therapy of primarily hydrogels and alginates consistent with standards of care | | X |
| Fife et al. (2008) Retrospective observational (1331), Poor | X | | | Unspecified wound care treatment either prior to the start of NPWT or among patients who never received NPWT | | X |
| Ford et al. (2002) RCT (28), Fair | | X | | Three gel products – Accuzyme, Iodosorb, and Panafil each targeted to optimize a particular macroscopic phase of wound healing | | X |

| Study Study Design (n), Quality | Wound Type | | | Comparisons | NPWT Devices | |
|--|------------|----|-------|--|--------------------|-----------------|
| | DFU | PU | Mixed | | SNaP (Spiracur) | V.A.C. (KCI) |
| Lavery et al. (2007) Retrospective observational (2677), Poor | X | | | Matched and unmatched groups of NPWT patients were compared with a control group receiving standard wound care; the control group was identified from a meta-analysis of 5 RCTs published between 1992 and 1998. | | X |
| Lerman et al. (2010) Retrospective observational (78), Poor | | | X | Matched controls treated at the same center with modern wound care protocols that included the use of Apligraf, Regranex, and skin grafting. | X | |
| Yao et al. (2012) Retrospective observational (342), Fair | | | X | Matched controls who did not receive NPWT. | | X |

Clinical and Patient-Centered Outcomes

For Key Question 1a, information on the following clinical outcomes were sought: complete wound healing; time to complete wound healing; time to surgical readiness of the wound bed or time to wound closure; proportion of wounds closed; mortality; and wound healing rate for healed wounds. In line with decisions made by Rhee and colleagues for inclusion in their systematic review, the surrogate outcome of wound healing rate (percent ulcer area reduction or other measurement) was not eligible as an outcome if studies did not also report complete wound healing. Chronic wounds may not heal in a linear fashion, becoming static at any time, and thus rate cannot be used to accurately predict complete healing (Rhee et al., 2014). Patient-centered outcomes of interest were: return to prior level of functional activity, pain, and health-related quality of life. Only 1 of the studies included for KQ1a reported an eligible patient-centered outcome (Fife et al., 2008).

Diabetic Foot Ulcers

Lavery et al. and Yao et al. reported results for complete wound healing. Blume et al. reported results for wound closure. One of these studies were rated poor quality (Lavery et al., 2007) and 2 (Blume et al., 2008; Yao et al., 2012) were rated fair quality. All 3 studies found benefit with NPWT for complete wound healing or wound closure (Lavery et al., 2007; Blume et al., 2008; Yao et al., 2012). Blume et al. also reported time to wound closure; results suggest that wounds treated with NPWT are closed sooner. None of the studies on DFU reported on other eligible clinical outcomes. Provision of pain medication as a surrogate measure for pain was reported in 1 study of DFU; results suggest no difference between groups (Fife et al., 2008). No other patient-centered outcomes were reported in the DFU studies.

Lavery et al. defined wound healing differently for each group. In the NPWT group, it was described as closure by secondary intention or by surgical intervention, or if adequate granulation for closure was documented. Surgical interventions included flaps, grafts, and primary closure. Wound healing in the control group was defined as wounds completely healed (no drainage or full epithelialization). The proportion of wounds achieving complete wound healing was compared at 12 and 20 weeks. The proportion of wounds reaching complete healing was statistically significantly greater in the matched NPWT group compared with the control group at 12 weeks (39.5% versus 23.9%) the results remained significant at 20 weeks (46.3% versus 32.8%) ($P < 0.001$) (Lavery et al., 2007).

Complete healing was not explicitly defined in the Yao et al. study, although it was analyzed as an event. Unadjusted and adjusted hazard ratio (HR) analyses suggest that patients with DFUs who received NPWT ($n=140$) had a higher incidence of wound healing than those who did not receive NPWT ($n=118$) (unadjusted HR, 2.38 [95% CI, 1.75 to 3.23] and adjusted HR, 3.26 [95% CI, 2.21 to 4.83]). Analyses were adjusted for comorbidities (including diabetes, peripheral arterial disease, coronary heart disease, chronic kidney disease, congestive heart failure, stroke, smoking) and “other variables associated with disease severity” (Yao et al., 2012).

Blume et al. defined complete ulcer closure as skin closure (100% re-epithelialization) without drainage or dressing requirements. During the 112-day active treatment phase, a higher proportion of patients who received NPWT achieved complete closure compared with those who received advanced moist wound therapy (AMWT) (NPWT, 73 out of 169 [43.2%]; AMWT, 48 out of 166 [28.9%]; $P=0.007$). Surgical closure was performed in 9.5% of the NPWT wounds and 8.4% of the AMWT wounds (statistical significance not reported). With respect to time to wound closure, the Kaplan-Meier median estimate for 100 percent ulcer closure was 96 days (95% CI, 75.0 to 114.0) for NPWT and not determinable for AMWT ($P=0.001$). The study investigators state that 89.5 percent of total therapy days for the NPWT group were home care days, and 95.3 percent of total therapy days were home care days for the AMWT group (Blume et al., 2008). Despite the fact that the vast majority of care was provided in the home setting, it should be noted that this study may have included patients who received care only in the inpatient setting, which may have somewhat confounded the results since the inpatient population may have received different levels of care.

Provision of pain medication as a surrogate measure for pain was reported in 1 study of DFU (Fife et al., 2008). This study was rated poor quality and found no difference between the NPWT and non-NPWT groups.

Arterial Ulcers

One fair-quality study reported incidence of wound healing for patients with arterial ulcers; results favored NPWT. Yao et al. found that patients with arterial ulcers who received NPWT ($n=114$) had a higher incidence of wound healing than those who did not receive NPWT ($n=59$) (unadjusted HR, 2.33 [95% CI, 1.57 to 3.48]; adjusted HR, 2.27 [95% CI, 1.56 to 3.78]) (Yao et al., 2012).

Pressure Ulcers

Two fair-quality studies represent inconsistent results for complete wound healing with NPWT for patients with pressure ulcers compared with other treatments. One showed no difference, and one suggests benefit with NPWT. Of note, in the Ford et al. study, 21 patients had 35 wounds and results are reported per wound and not per patient. Complete wound healing results from the Ford et al. and Yao et al. studies are summarized in the Rhee et al. systematic review as follows. In the Ford et al. study, 6 ulcers in the NPWT group (30%) and 6 ulcers in the control group (40%) underwent flap surgery. Two ulcers in each group completely healed (risk difference 3%; 95% CI, -18% to 25% [calculated by Rhee et al.]) (Ford et al., 2002; Rhee et al., 2014). Yao et al. reported that those treated with NPWT had a higher incidence of wound healing compared to those in the control group. The adjusted HR for wound healing was 1.72 (95% CI, 0.43 to 6.95) in the study by Yao et al. (Yao et al., 2012; Rhee et al., 2014).

Venous Insufficiency Ulcers

The fair-quality study by Yao et al. also reported complete wound healing for patients with venous ulcers. Similar to the DFU, arterial ulcer, and pressure ulcer patients evaluated in this study, patients with venous ulcers who received NPWT had a higher incidence of wound healing than those who did not receive NPWT (unadjusted HR, 4.90 [95% CI, 1.72 to 13.59]; adjusted HR, 6.31 [95% CI, 1.49 to 26.6]) (Yao et al., 2012).

Mixed Ulcer Populations

For populations of patients with different wound types, results from 1 fair-quality (Yao et al., 2012) and 1 poor-quality (Lerman et al., 2010) study favor NPWT compared with other wound treatments. When all wound types (DFUs, arterial ulcers, venous insufficiency ulcers, and pressure ulcers) were analyzed together in the Yao et al. study, patients in the NPWT therapy group had a greater likelihood of wound closure compared with patients who did not receive NPWT (unadjusted HR, 2.25 [95% CI, 1.73 to 3.96], adjusted HR, 2.63 [95% CI, 1.87 to 3.70]) (Yao et al., 2012). In the study by Lerman et al., estimates of wound healing at 1, 2, 3, and 4 months of treatment were 0%, 20%, 66.2%, and 83.1%, respectively, for the SNaP (NPWT) group, and 0%, 7.1%, 21.4%, and 35.7%, respectively, in the matched control group that received modern dressings. Time to complete healing was statistically significantly shorter in the NPWT group than the control group (50% absolute reduction; $P < 0.0001$). In those reporting wound healing, the SNaP (NPWT)-treated patients healed in an average of 74.25 ± 20.1 days from the start of SNaP treatment, and the matched controls healed in an average of 148.73 ± 63.1 days from the start of conventional treatment ($P < 0.0001$) (Lerman et al., 2010).

Key Question #1b: What is the clinical effectiveness of NPWT in the home or outpatient settings for treatment of nonhealing closed or open surgical wounds (i.e., incisions expected to heal by primary intention or incisions expected to heal by secondary intention)?

Study Characteristics

Two good-quality systematic reviews were found that assessed evidence from RCTs on the use of NPWT to treat surgical wounds. One of the systematic reviews evaluated NPWT for wounds healing by secondary intention (Dumville et al., 2015a) and the other (Webster et al., 2014) evaluated NPWT for wounds healing by primary intention. These systematic reviews did limit their evidence to studies within the home setting; primary studies included in these reviews were screened for eligibility for this HTA on home use of NPWT, and only those with information about outpatient treatment were selected. Update literature searches were conducted to find recently published primary literature to add to the RCT evidence included in these reviews. Three primary studies were identified for Key Question 1b. Two of the RCTs were included in the previously published systematic review on healing by secondary intention (Dumville et al., 2015a); no eligible studies were carried forward from the systematic review on wounds healing by primary intention because none of them were conducted in the home setting (Webster et al., 2014). See **Table 12** for a brief summary of study characteristics. Details of included studies are presented in [Appendix V](#).

Each of the studies of surgical wounds includes a unique population. Populations include patients with deep infected wounds (Acosta et al., 2013; Monsen et al., 2014; Monsen et al., 2015), patients requiring surgical treatment for a pilonidal sinus (Biter et al., 2014), and patients with wounds from diabetic foot wound-related amputations (Armstrong et al., 2005; Armstrong et al., 2007; Apelqvist et al., 2008). Two studies were single-center studies conducted in Europe (Sweden and the Netherlands) (Acosta et al., 2013; Biter et al., 2014; Monsen et al., 2014; Monsen et al., 2015), and 1 was a multicenter study conducted in the United States (Armstrong et al., 2005; Armstrong et al., 2007; Apelqvist et al., 2008). In all 3 studies, wound care started in an acute care setting and was continued at home after discharge. The specific brands and models of the devices used in the Monsen et al. and Biter et al. studies were not specified; it is unclear whether they are devices commercially available in the United States. Because of the relative dearth of information from home care/outpatient settings, these 2 studies were included in this HTA despite the lack of details about the specific devices used in order to capture potentially relevant information.

Study Quality

A fair-quality rating was assigned to all 3 studies included for Key Question 1b. Limitations of the Monsen et al. study included possible selection bias during recruitment, lack of adequate randomization technique, unclear method for calculating time to wound healing, use of different types of alginate dressings in comparison group, and unclear mean length of follow-up in each group (Acosta et al., 2013; Monsen et al., 2014; Monsen et al., 2015). The investigators in this study performed power calculations which determined that enrollment of 42 patients was needed; however, the investigators pre-planned an interim analysis with 20 patients, and if NPWT was shown to be superior to alginate dressings, they planned to discontinue the trial. Limitations of the Biter et al. (2014) study included lack of power

calculations and unclear data analysis methods for the primary outcome, time to complete wound healing. The Armstrong et al. study was limited by the use of different wound dressings in the comparison group based on provider discretion and potential for bias in treatment/assessment decisions due to lack of blinding of providers and outcome assessors.

Table 12. Randomized Controlled Trials Included for KQ1b

Key: NPWT, negative pressure wound therapy; N/S, not specified; VAC, vacuum-assisted closure

| Study n, Quality | Patient Population | Comparisons | NPWT Devices |
|---|---|---|---------------------------------|
| Monsen (2014); Acosta, (2013); Monsen, (2015) n=20, Fair | Patients with deep perivascular groin infections (Szilagyi grade III) that had been surgically revised and left open for healing by secondary intention | Vacuum-assisted wound closure (VAC) vs alginate (Sorbalgon or Melgisorb), a soft, highly absorbent dressing that quickly forms a hydrophilic gel | VAC (N/S) |
| Biter, (2014) n=49, Fair | Patients requiring surgical treatment for a pilonidal sinus | NPWT for 14 days, then regular wound care was started vs standard open wound therapy (a silicone wound dressing with an absorbent bandage on top) | VAC (N/S) |
| Armstrong, (2005); Apelqvist, (2008) n=162, Fair | Patients with a wound from a diabetic foot wound amputation to the transmetatarsal level, and evidence of adequate perfusion | NPWT vs standard care (moist wound care with alginates, hydrocolloids, foams, or hydrogels) | V.A.C. Therapy System KCI Inc.) |

Clinical and Patient-Centered Outcomes

All three of the studies included for Key Question 1B reported median time to wound healing, and one of the three also reported proportion of wounds healed. Two studies conducted in Europe among patients who received different surgical interventions reported conflicting results with respect to median time to wound healing. One study (Biter et al., 2014) found no difference between NPWT and silicone dressing for patients being treated for pilonidal sinus, and 1 study (Monsen et al., 2014) found that the median number of days to complete wound healing was statistically significantly shorter in the NPWT group compared with a group receiving alginate dressing for deep perivascular wound infections. It should be noted that these studies included different patient populations and evaluated NPWT against different comparisons. The third study was conducted in the United States among patients with diabetic foot wound-related amputations. Results from this study suggest that a higher proportion of wounds were healed in the NPWT therapy group than in the standard moist wound therapy group, and the NPWT group healed faster. Patient-centered outcomes were reported in 2 of the 3 studies; these results

suggest no difference between NPWT and alginate dressing for quality-of-life, return to prior level of activity, and pain outcomes.

In the Biter et al. trial comparing NPWT (n=24) to silicone dressings (n=25), time to complete wound healing was defined as the number of days until full skin closure was achieved. Median time to complete healing was similar between groups (median: NPWT 84 [range, 34-349] days, control 93 [range, 43-264] days; $P=0.44$). The number of wounds healed was not reported. The median time to resume work or school was also similar between groups (median: NPWT 27 [range, 7-126], control 29 [range, 6-63]; $P=0.92$). Pain was assessed by the visual analog scale (VAS) score on the day of surgery and at 14 days after surgery. The groups were similar at both time points. The scores were higher at postoperative day 14 than on the day of surgery in both groups; the statistical significance of the change from baseline was not reported (Biter et al., 2014).

Monsen et al. compared NPWT to alginate dressing in patients with deep perivascular groin infections subsequent to vascular surgery. Patients were treated in the hospital until the arterial reconstruction was covered with granulation tissue, then patients well enough to be discharged continued treatment at home. In this study, complete wound healing was defined as full skin epithelialization. Median number of days to complete wound healing was statistically significantly shorter in the NPWT group compared with the alginate group (median: NPWT 57 [range, 25-115], control 104 [range, 57-175]; $P=0.026$). The number of wounds healed was not analyzed, however the median number of days to complete wound healing was calculated using 9 patients in the NPWT group and 7 patients in the alginate dressing group. This does not completely agree with the analysis provided for the number of wounds not healed (defined as no-healed wounds in the groin after 4 months, visible graft material or femoral artery after 1 month of treatment, or amputation or death as a consequence of the groin infection), which was reported as 1 (10%) in the NPWT group and 5 (50%) in the control group ($P=0.034$). It is not clear how many patients in the control group achieved complete wound healing, therefore this result from this study was not considered in the body of evidence. The NPWT group had fewer in-hospital days (median: NPWT, 13 [range, 5-93], control 20 [range, 6-76]; $P=0.79$), and statistically significantly fewer wound treatment days outside the hospital (median: NPWT 42 [range, 18-81], control 79 [range, 32-171]) (Monsen et al., 2014). At the study start and when the wound was healed, quality of life was assessed via the European Quality of Life-5 Dimensions (EQ-5D) questionnaire, which included a VAS for health status (EQ-VAS). Pain was measured at study start, the day after surgical wound revision, and at 4 weeks of treatment (or sooner if wound healing happened before 4 weeks) using the short form of the Brief Pain Inventory (BPI). Six patients in each group completed the EQ-5D at the time of wound healing, and 9 patients in the NPWT group and 8 in the control group completed the BPI at 4 weeks. No difference was shown in EQ-5D and EQ-VAS between the 2 groups at study start or after wound healing; similarly, no difference was shown between the NPWT and the alginate group, in pain intensity or influence on daily life at study start or after 4 weeks of treatment (Monsen et al., 2015).

Patients received either NPWT or standard moist wound care after partial diabetic foot amputation in the study by Armstrong et al. (2005). The study enrolled 162 patients from 18 centers in the United States and treated wounds until they were closed or until the completion of the 112-day assessment. Complete wound closure was defined as 100 percent re-epithelialization without drainage. There was a

greater proportion of healed wounds in the NPWT group compared with the control group (NPWT 43 [56%] versus control 33 [39%]; $P=0.040$). Patients in the NPWT group healed faster than those in the control group ($P=0.005$). The median time to complete wound closure for 43 patients in the NPWT group was 56 days. For the 33 patients in the control group who reached complete wound closure, the median time was 77 days. No patient-centered outcomes were reported (Armstrong et al., 2005).

Key Question #2: What are the harms associated with NPWT?

Harms Reported in Studies of Chronic Wounds

Safety outcomes sought for this HTA were infection rates; extremity amputation; emergency room visits related to the NPWT or treated wound; unplanned hospitalizations or surgeries related to the NPWT or treated wound; and blood transfusions/bleeding. Six studies (Ford et al., 2002; Schvien et al., 2005; Frykberg and Williams, 2007; Blume et al., 2008; Fife et al., 2008; Lerman et al., 2010) were identified that reported on adverse events in patients with chronic wounds (See **Table 13**). These studies evaluated NPWT compared with other wound treatments in patients with DFUs, pressure ulcers, and mixed ulcers. No studies comparing NPWT with other wound treatments reporting adverse events for patients with arterial ulcers or venous insufficiency ulcers were identified. Results from two studies favored NPWT with respect to rates of amputation, and a third study favored NPWT with respect to rates of infection among patients with DFUs. For patients with pressure ulcers, one study reported statistically significant results in favor of NPWT for emergent care and hospitalization. The study reporting adverse events among a mixed ulcer population did not report data for the comparison group.

Diabetic Foot Ulcers

Adverse events were reported in three studies of patients with DFU (Frykberg and Williams, 2007; Blume et al., 2008; Fife et al., 2008). Study characteristics and quality ratings for the Blume et al. and Fife et al. studies are summarized under Key Question 1a; this information appears below for the Frykberg and Williams study.

Results from a fair-quality retrospective analysis of data from 2 administrative claims databases evaluating the incidence of lower extremity amputations in patients with DFUs suggest lower amputation rates among patients who received NPWT compared with those who received traditional wound therapies (Frykberg and Williams, 2007). Patients included in this analysis were a mix of inpatient and outpatient populations and they were not analyzed separately. This study was nonetheless included in the report because the authors suggest that patients who received NPWT in acute care settings but not in the outpatient setting are likely to be a small group within their study. It should be noted, however, that measured proportions of inpatients and outpatients or proportion of outpatient care days are not reported. This study employed stratified and adjusted analyses, which contributed to its fair-quality rating. Limitations of this study include retrospective analyses using administrative claims databases and potentially meaningful differences in patient demographics between the groups not accounted for in adjusted analyses.

Frykberg and Williams used a commercial payer database that provided 2 years of data, and a Medicare database that provided 1 year of data. Groups of patients who received NPWT therapy were compared with control groups for each database. No statistical difference was seen in amputation rates between groups in either dataset prior to stratifying by total cost of treatment and depth of debridement, and adjusting for these risk categories within the NPWT group. Comparisons within risk categories between the control group with the unadjusted NPWT group in the commercial dataset showed a trend toward lower amputation rates in the NPWT groups in most of the risk categories. The differences were statistically significantly in favor of the NPWT group for the highest total cost category (> \$150,000), with an amputation rate of 45.7 percent in the control group and 27.3 percent in the NPWT group ($P<0.0001$) and in the deepest debridement category (bone) with an amputation rate of 52.7 percent in the controls and 26.3 percent in the NPWT group ($P<0.0001$). Overall amputation rates in the control group compared with the risk-adjusted cost and debridement NPWT groups were not statistically significantly different in the commercial dataset (cost: control group 21.4% versus NPWT 14.1%; $P=.0951$; debridement: control group 21.4% versus 18.3%; $P=0.5221$). With respect to the Medicare dataset, there was also a trend toward lower amputation rates in the NPWT groups for most of the risk categories. In the deepest debridement category, NPWT was associated with a statistically significantly lower amputation rate than the control group (18.3% versus 53.3%; $P<0.0001$). The NPWT group also had a statistically significantly lower amputation rate compared with the controls in the highest cost category (9.1% versus 44.7%; $P<0.0001$). The overall amputation rate was also statistically significantly lower in the cost and debridement risk-adjusted NPWT groups compared with the control group (cost: control group 16.6% versus NPWT group 10.8% $P=0.0077$; debridement: control group 16.6% versus NPWT group 11.2%; $P=0.0128$).

Blume et al. reported significantly fewer amputations in the NPWT group in their study when compared with the group that received AMWT (NPWT, 7 out of 169 [4.1%]; AMWT, 17 out of 166 [10.2%]; $P=0.035$) (Blume et al., 2008). There were no statistically significant differences in other adverse events (edema, wound infection, cellulitis, osteomyelitis, *staphylococcus* infection, and infected skin ulcer) reported in this RCT. However, more patients in the NPWT group experienced wound infection (4 versus 1), cellulitis (4 versus 1), osteomyelitis (1 versus 0), and *staphylococcus* infection (1 versus 0) compared with the AMWT group. The AMWT group had more cases of edema (7 versus 5) and infected skin ulcers (2 versus 1) than the NPWT group.

The cohort study conducted by Fife et al. used surrogate measures such as antibiotic prescriptions and number of cultures taken for estimating rates of infection. Specific data were not reported; however, the investigators concluded that the NPWT therapy group experienced fewer infections based on significantly fewer antibiotic prescriptions ($P<0.05$) and cultures ($P<0.05$) found in the database for this group compared with the control group. Bleeding was not reported in either group, and none of the NPWT patients discontinued treatment because of bleeding (Fife et al., 2008).

Pressure Ulcers

Two studies reported adverse events for patients with pressure ulcers. Study characteristics and quality rating are summarized in Key Question 1a for the Ford et al. study; these are summarized below for the

Schwien et al study. In 1 RCT of patients with pressure ulcers, 28 patients with 41 full-thickness pressure ulcers were enrolled; however, 22 patients with 35 wounds completed the trial. Reasons for the 6 patients who did not complete the trial include 2 deaths, 3 lost to follow-up, and 1 noncompliant. It is not clear to which groups each of these patients were randomized; the final numbers for each group were 20 in the NPWT group and 15 in the comparison group. One case of sepsis requiring amputation was reported in the NPWT group (Ford et al., 2002).

Schwien et al. conducted a retrospective analysis of data from home health care agencies. This study was rated poor because of the following limitations: inappropriate or poorly described control groups; poor or selective reporting on comparative treatments, potential confounders, and outcomes. The investigators found a statistically significant difference between the NPWT group and the control group for emergent care visits for wound-related problems. No patients in the NPWT group (n=60) needed emergent care compared with 189 (8%) patients in the comparison group (n=2348) ($P<0.01$). However, 3 (5%) NPWT patients required hospitalization for a wound-related problem, but this was also significantly fewer than the 310 (14%) patients in the comparison group who required hospitalization ($P<0.01$). The results remained statistically significant when data were stratified by pressure ulcer grade (Schwien et al., 2005).

Mixed Ulcer Populations

Adverse events as they were related to study withdrawal were reported only for the NPWT group in the Lerman et al. article. Comparison with the control group is not possible as the data are not provided. Two subjects were removed due to hospitalizations not related to the wound and 6 subjects were noncompliant with the protocol. Seven subjects had complications related to the study protocol requiring withdrawal: allergic skin reaction to the hydrocolloid dressing (n=1), wound infection (n=1), bleeding post debridement (n=1), worsening lower extremity edema (n=1), and maceration to periwound skin (n=3). Data for these dropped patients were not included in the final analysis (Lerman et al., 2010).

Table 13. Study Characteristics of Studies Included for KQ2 (Harms) – Chronic Wounds

Key: DFU, diabetic foot ulcer; NPWT, negative pressure wound therapy; N/S, not specified; PU, pressure ulcer; RCT, randomized controlled trial

| Study Study Design (n), Quality | Wound Type | | | Comparisons | NPWT Devices | |
|---|------------|----|-------|---|--------------------|-----------------|
| | DFU | PU | Mixed | | SNaP (Spiracur) | V.A.C. (KCI) |
| Blume et al., (2008) RCT (341), Poor | X | | | Advanced moist wound therapy of primarily hydrogels and alginates consistent with standards of care | | X |
| Fife et al., (2008) Retrospective observational (1331), | X | | | Unspecified wound care treatment either prior to the start of NPWT or among | | X |

| Study Study Design (n), Quality | Wound Type | | | Comparisons | NPWT Devices | |
|--|------------|----|-------|---|--------------------|-----------------|
| | DFU | PU | Mixed | | SNaP (Spiracur) | V.A.C. (KCI) |
| Poor | | | | patients who never received NPWT | | |
| Ford et al., (2002) RCT (28), Fair | | X | | Three gel products – Accuzyme, Iodosorb, and Panafil each targeted to optimize a particular macroscopic phase of wound healing | | X |
| Frykberg et al. (2007) Retrospective observational (16,319), Fair | X | | | Non-NPWT controls identified from administrative claims databases | | X |
| Lerman et al., (2010) Retrospective observational (78), Poor | | | X | Matched controls treated at the same center with modern wound care protocols that included the use of Apligraf, Regranex, and skin grafting | X | |
| Schwieb et al., (2005) Retrospective observational (2348), Poor | | X | | Matched controls receiving any other wound care therapy | | X |

Harms Reported in Studies of Surgical Wounds

Adverse events were reported in 3 studies evaluating NPWT compared with other wound treatments for surgical wounds (Armstrong et al., 2005; Apelqvist et al., 2008; Acosta et al., 2013; Biter et al., 2014; Monsen et al., 2014; Monsen et al., 2015). Study characteristics are described in KQ1b (See **Table 12**). Study characteristics and quality ratings are summarized in Key Question 1b. None of the studies reported statistically significant differences between groups for the adverse events described in the publications.

Monsen et al. reported a total of 5 amputations during a median follow-up period of 14 months— 3 out of 10 in the NPWT group and 2 out of 10 in the alginate dressing group (no *P* value reported; the Cochrane Review authors calculated a risk ratio [RR] of 1.5 [95% CI, 0.32-7.14] in favor of alginate dressings) (Monsen et al., 2014; Dumville et al., 2015a). One death occurred in the alginate dressing group during in-hospital stay; no deaths occurred in the NPWT patients while they were in the hospital (the Cochrane Review authors calculated an RR of 0.33 [95% CI, 0.02-7.32] in favor of NPWT) (Monsen et al., 2014; Dumville et al., 2015a). Overall, there were 2 deaths in the NPWT group and 5 in the alginate dressing group (*P*=0.35) (Monsen et al., 2014).

Among patients requiring surgical treatment for a pilonidal sinus, Biter et al. reported no differences in wound infection rate between the NPWT group and the standard open wound care group. There were 2

(8%) events in each group (the Cochrane Review authors calculated an RR of 1.04 [95% CI, 0.16-6.81]) (Biter et al., 2014; Dumville et al., 2015b). One patient in the NPWT group visited the emergency room because of a malfunctioning device that needed to be reconnected properly. No other adverse events were reported (Biter et al., 2014).

Armstrong et al. evaluated NPWT compared with standard moist wound therapy in patients after partial diabetic foot amputation. The proportion of patients undergoing a second amputation was higher in the standard therapy group, but the difference was not statistically significant (NPWT 2 [3%], control 9 [11%]; $P=0.060$). Wound infection rates were 17 percent and 6 percent in the NPWT and control groups, respectively (P value not reported). In the NPWT group, 3 of the 13 wound infections were classified as mild, 6 were moderate, and 4 were severe. Out of the 5 wound infections in the control group, 2 were mild, 1 was moderate, and 2 were severe. The authors state that none of the 13 wound infections among patients who received NPWT were related to treatment, and 2 of the 5 among the control group were related to treatment. Treatment related adverse events occurred in 9 (12%) NPWT patients and 11 (13%) control patients. One treatment related adverse event in the NPWT was classified as serious, and 5 treatment-related adverse events in the control group were classified as serious in the control group (Armstrong et al., 2005).

Key Question #3: Does the effectiveness of NPWT or incidence of adverse events vary by clinical history (e.g., diabetes), wound characteristics (e.g., size, chronicity), duration of treatment, types of devices, or patient characteristics (e.g., age, sex, prior treatments, smoking, or other medications)?

Chronic Wounds

Four studies were identified providing information pertaining to KQ3 with respect to patients with chronic wounds, 1 was a fair-quality RCT (Armstrong et al., 2011; Armstrong et al., 2012; Marston et al., 2015), 1 was a fair-quality observational study (Yao et al., 2012), and 2 were poor-quality observational studies (Lavery et al., 2007; Law et al., 2015) Two of these studies compared different NPWT devices. An RCT conducted by Armstrong et al. provides a comparison of the V.A.C. Therapy System (KCI Inc.), and the SNaP Wound Care System (Spiracur Inc.), and the Law et al. study provides a comparison of the V.A.C. Therapy System with non-KCI models. The studies by Lavery et al. and Yao et al. provide information about the role of wound size and chronicity when NPWT is compared with other wound treatments. No studies looked at comparative effectiveness in relation to clinical history, duration of treatment, or patient characteristics.

Different Types of NPWT Devices Compared with Each Other (SNaP Versus V.A.C.)

The RCT conducted by Armstrong et al. is presented in three publications. The first was an interim analysis (Armstrong et al., 2011), the second is an analysis of the full study population (Armstrong et al., 2012), and the third (Marston et al., 2015) is a subanalysis of patients with venous leg ulcers. Treatment was evaluated for up to 16 weeks, and the full study enrolled 132 patients from 17 wound care centers and analyzed 115 patients (SNaP $n=59$; V.A.C $n=56$). Eighty-three patients completed the study with either healing or 16 weeks of therapy. Complete wound healing was a secondary outcome in this study;

the outcome was not defined. Adverse events and patient-centered outcomes were also assessed. The study was rated fair because of potentially meaningful differences in wound size between groups at baseline, the utilization of 2 different V.A.C. (KCI) systems in the comparison group without presenting separate analyses for each device, differential treatment between groups with respect to personnel who changed wound dressings, and patient outcome data were obtained from an exit interview and subject to recall and attrition bias, as well as the potential for bias because of the lack of blinding to which device was used. Complete wound healing was assessed at 4, 8, 12, and 16 weeks. A Kaplan-Meier survival analysis showed no significant difference between the SNaP and V.A.C. groups for the proportion of wounds healed over time ($P=0.9620$); analyses adjusting for baseline wound size were also not statistically significant. Time to surgical readiness of the wound bed and mortality were not reported. Though percent decrease in the wound area was reported, the wound healing rate for healed wounds was not reported (Armstrong et al., 2012).

Information about return to prior level of activity and pain were also evaluated in this RCT through responses to exit interviews. Additionally, rates of pain were reported by the authors as an adverse event; rates were similar between the groups (SNaP $n=1$ [1.6%]; V.A.C. $n=4$ [5.9%]). Rhee and colleagues summarized the results of the exit surveys as reported in the Armstrong et al. (2012) publication, and calculated P values for the between-group differences. Their summary and calculations are as follows. Exit surveys to assess user experiences were completed for the 105 subjects who finished the study ($n=52$ V.A.C. and $n=53$ SNaP). To examine the ability to return to their prior level of functional activity, subjects were asked about their level of activity both during and after device usage. Patients who were treated with the SNaP device were significantly more likely to agree or strongly agree that they were able to perform their normal daily activities than patients treated with the V.A.C. device (79% versus 58%; $P=0.004$ [calculated by Rhee et al.]). Additionally, a higher percentage of SNaP-treated subjects than V.A.C.-treated subjects reported that their activity level either increased or stayed the same (83% versus 48%; $P<0.05$ [calculated by Rhee et al.]) (Armstrong et al., 2012; Rhee et al., 2014).

The level of pain was examined by a summation of pain scores, as compared with what would be the expected sum of scores. It is unclear how the expected summary score number was obtained, and further description of the definition of the pain scores is not provided. Patient-reported pain scores were not statistically significantly different between the 2 NPWT devices (Armstrong et al., 2012; Rhee et al., 2014).

In a subanalysis of patients with venous leg ulcers (VLUs) from this same RCT, Marston et al. analyzed 40 patients (V.A.C. $n=21$; SNaP $n=19$) from 13 wound care centers who completed the study. VLUs were defined as those patients who had a leg ulcer in the gaiter region with evidence of venous disease on physical examination, and who were not diabetic. The authors did not state whether this was a pre-planned or post hoc analysis. There was a notable difference in wound size between the 2 groups at baseline (mean \pm SD: 4.85 ± 4.49 square centimeters [cm^2] for SNaP versus 11.6 ± 12.12 cm^2 for V.A.C.). Kaplan-Meier estimates suggest no significant difference in the proportion of patients who completely healed over time ($P=0.3547$ unadjusted for baseline wound size; $P=0.4656$ adjusted for baseline wound size) (Marston et al., 2015).

Rates of adverse events reported in the Armstrong et al. (2012) publication for the full patient population were similar between the groups. The rate of clinically determined infection was 3.1% in the SNaP (n=2) and 7.4% in the V.A.C. group (n=5) ($P=0.28$ [P value calculated by Rhee et al.]) (Armstrong et al., 2012; Rhee et al., 2014). In the subanalysis of VLUs, the rate of infection was found to be 5.3% in the SNaP group (n=1) and 9.5% in the V.A.C. group (n=2) ($P=1.000$) (Marston et al., 2015).

Different Types of NPWT Devices Compared with Each Other (V.A.C. Versus non-KCI Models)

In a publication of findings from a poor-quality retrospective national claims database analysis comparing V.A.C. NPWT with non-KCI NPWT devices, Law and colleagues evaluated hospital readmission rates for the period following an initial NPWT claim in an outpatient setting. This study was rated poor because of the following methodological limitations: retrospective analysis; heterogeneous patient population and separate analyses were provided for only some of the included wound types; potentially meaningful baseline differences in 3-month analysis group and patient demographic results not presented for 6- and 12-month populations; methods state that data were analyzed at 12 months, but results were not provided; different group sizes; and methods do not indicate that analyses were adjusted to control for confounding variables. Multiple wound types were included in the dataset. Patients with chronic wounds, defined as DFUs (with and without amputation), pressure ulcers, VLUs, and nonhealing surgical wounds, comprised 82.1 percent of the wounds; the remaining wounds were categorized as acute wounds and included open wounds, cellulitis, and necrotizing fasciitis.

Claims data were analyzed at 3 months, 6 months, and 12 months after the index date of the first NPWT claim (patients included at each analysis point changed over time). There was a statistically significant difference in age between the two groups for the study sample analyzed at 3 months. Patients in the V.A.C. group (n=12,843 at 3 months) were younger (mean age 59.2 years) than the group treated with non-KCI devices (n=713 at 3 months; mean age 63.6 years) ($P<0.01$). The statistical significance of differences in the rates of individual comorbid conditions was not reported. Instead, the mean Charlson Comorbidity Index score was reported. This was similar between groups (P value not significant [NS]). At 3 months and at 6 months, wound-related readmission rates were statistically significantly lower for the V.A.C. group compared with the non-KCI device group across all wound types. At 3 months the rates in each group were 5 percent and 8 percent, respectively, for the V.A.C. (n=12,843) and non-KCI device (n=713) groups ($P\leq 0.01$). The rates at 6 months were 6 percent and 11 percent, respectively, for the V.A.C. (n=11,073) and non-KCI device (n=601) groups ($P\leq 0.01$). Significant differences in favor of V.A.C. were also reported for mean per-patient inpatient stays and emergency room visits at 3 months and at 6 months for all wound types. When mean per-patient inpatient stays and emergency room visits at 3 months and 6 months were analyzed by wound category (nonhealing surgical wounds, open wounds, and pressure ulcers), statistical significance did not persist for inpatient stays at 3 months and 6 months for nonhealing surgical wounds and emergency room visits for pressure ulcers at 3 months and 6 months. Results at 12 months were not reported (Law et al., 2015).

NPWT Compared with Other Wound Treatments: Wound Size and Chronicity

In their systematic review of home use of NPWT for treating chronic wounds, Rhee and colleagues summarized the methods and findings with respect to wound size and chronicity from the Lavery et al. and Yao et al. studies as follows (Rhee et al., 2014). Lavery et al. examined healing in relation to ulcer size and wound duration at 12 and 20 weeks. Wounds were stratified according to wound size and duration. Wounds < 2 cm² were considered small, those 2 to 4 cm² were medium in size, and those > 4 cm² were considered large in size. Wounds that were < 6 months old were stratified as short duration, those 6 to 12 months old were considered medium duration, and those > 12 months old were considered long duration. The authors reported that wounds of all sizes treated with NPWT were more likely than those treated with standard wound care to achieve successful treatment endpoint (closure through secondary intention or through surgical intervention, or if adequate granulation tissue was present) ($P<0.05$). However, at 12 weeks, wounds in the NPWT group that were < 6 months duration and those > 12 months duration were more likely to achieve closure. At 20 weeks, NPWT healed significantly more wounds compared with standard wound care only among wounds older than 12 months ($P<0.05$) (Lavery et al., 2007; Rhee et al., 2014).

Yao et al. also evaluated whether the timing of NPWT application had an effect on healing; however, they did not examine timing with respect to other wound treatments, therefore no comparison between NPWT and other wound treatments is possible with the data provided. Because no comparison with alternative treatments is provided, these results are shown here for information only and were not considered in the overall body of evidence. The authors defined ulcer onset as the date the ulcer was first documented in a clinic note. Early NPWT use was defined as receiving NPWT within 3 months of ulcer onset, intermediate NPWT use was defined as receiving NPWT within 4 to 12 months of ulcer onset, and late NPWT was defined as receiving NPWT 1 year or later after ulcer onset. The ulcers in the early NPWT treatment group had higher incidence of wound closure compared with those in which NPWT was used later (adjusted HR, 3.38; 95% CI, 1.68 to 6.82).

Key Question #4: What are the cost implications and cost-effectiveness of NPWT?

Five studies were found that provided information about the cost of NPWT compared with usual care or other NPWT devices (Lavery, 2007; Apelqvist, 2008; Hutton and Sheehan, 2011; Driver and Blume, 2014; Law et al., 2015). One study compared the cost of mechanical NPWT (SNaP) with electrically powered NPWT devices and standard of care. Four studies compared the cost of NPWT using V.A.C. with other wound therapies or other NPWT devices. All studies found that the primary NPWT device of interest (SNaP or V.A.C.) resulted in cost savings over usual care or alternative NPWT devices.

Cost Comparison of Mechanical SNaP Wound Care System with Powered NPWT Devices and Usual Care from Medicaid and Private Payer Perspectives

Hutton and Sheehan (2011) used decision analytic modeling to compare the cost of the SNaP device with standard care and electrically powered NPWT devices over a 16-week therapy period. Authors assumed equal wound healing efficacy between SNaP and powered NPWT devices based on preliminary studies and ongoing clinical trials (both heal 83.1% of patients). Modern dressings were assumed to heal 35.7 percent of patients. Costs of treatment included direct costs and other healthcare costs for diabetic lower extremity wounds. Costs were based on the literature comparing NPWT with modern dressings

and Medicare reimbursement rates. SNaP cost \$4445 more for the equipment and supplies than modern dressings but saved \$1853 in dressing changes, \$1846 in additional healthcare costs, \$3425 in costs of complications, and \$7020 in long-term costs for patients who did not heal. The SNaP Wound Care System saved \$9699 (42%) over modern dressings, \$2774 (17%) over powered NPWT for a private payer, and \$2296 (15%) over powered NPWT for Medicare. Compared with powered NPWT devices, the SNaP system saves \$659 in wound dressings for a private payer, and \$2612 in dressings and home visits for Medicare. A sensitivity analysis assuming more conservative healing rates (37.9% for modern dressing and 53.7% for powered NPWT and SNaP) still resulted in cost savings in favor of SNaP of \$420 versus modern dressings, \$3928 versus powered NPWT for private payer, and \$2201 versus powered NPWT for Medicare. This economic evaluation was funded by the SNaP device manufacturer (Hutton and Sheehan, 2011).

Cost Comparison of Vacuum-Assisted Closure Therapy (V.A.C.) with Other Wound Therapies

Driver and Blume (2014) conducted a post-hoc analysis of patient records from an RCT (Blume et al., 2008) to compare healthcare costs between patients with DFUs receiving V.A.C. and those receiving AMWT. Data were obtained from the medical records of 324 (162 NPWT, 162 AMWT) out of the 335 patients with diabetic ulcers who were analyzed in the original RCT. Wound therapy costs included dressings and labor costs to change dressings. Non-wound therapy consisted of antibiotic therapy, inpatient services, extended care hospitalizations, and surgical procedures. Costs were calculated from patients' healthcare utilization, including hospital costs (Healthcare Cost and Utilization Project Nationwide Inpatient Sample), physical services for surgical procedures (Medicare Resource-Based Relative Value Scale 2007), and extended-care facility cost per day (Medicare reimbursement rate). The average cost per patient regardless of wound closure was \$11,984 for NPWT and \$13,557 for AMWT. For patients who achieved wound closure, average cost was \$10,172 for NPWT and \$9505 for AMWT. For patients who did not achieve wound closure, average cost was \$13,262 for NPWT and \$15,068 for AMWT. Non-wound treatment costs were higher for patients undergoing AMWT than NPWT. For patients who achieved wound closure, average non-wound treatment cost was \$10,716 for NPWT and \$13,525 for AMWT. For patients who did not achieve wound closure, average non-wound treatment cost was \$13,694 for NPWT and \$17,927 for AMWT (Driver and Blume, 2014).

Lavery et al. (2007) aimed to assess the differential cost of care in the outpatient setting between NPWT and wet-to-moist therapy to treat DFUs. The 20-week expected cost of care was calculated using weekly costs of nursing visits, supplies and physician costs. One to 2 nursing visits per day at a cost of \$112 per visit were assumed for the wet-to-moist therapy group. The cost of wet-to-moist therapy supplies was based on an estimated 3 dressing changes per day. Costs estimates for the NPWT group were based on dressing changes every 48 hours and 3 nursing visits per week with supply costs of \$3.50 per dressing and \$107 per day rental for the device. Physician costs in both groups were estimated at \$66 per visit with an expected visit every 2 weeks. Calculations included the probability of successful treatment in a specified number of weeks; information for this estimate came from outcomes obtained from the retrospective observational study conducted by the authors and reported in the same publication. The 20-week expected cost of care for the NPWT was \$16,733. Twenty-week expected cost for the wet-to-moist therapy group based on one nursing visit per day was \$15,258; based on 2 nursing visits per day

the expected cost was \$28,691. The expected 20-week costs for NPWT were similar to those for wet-to-moist therapy when one nursing visit per day was assumed. When 2 nursing visits per day were assumed for the wet-to-moist therapy group, the 20-week expected costs of NPWT were 42% less (Lavery, 2007).

In an economic analysis based on data from patients who completed at least 8 weeks of treatment in an RCT of diabetic patients with post-amputation wounds, investigators aimed to evaluate resource utilization and direct economic costs of care for patients treated with NPWT (V.A.C., KCI) compared with those who received moist wound therapy (Armstrong, 2005; Apelqvist, 2008). Clinical results from the RCT are summarized in key question 1b (Armstrong, 2005). Direct costs were calculated retrospectively using data on resource use for each patient. Costs included inpatient care, antimicrobial agents, outpatient treatment visits, surgical procedures, and topical dressing treatment of foot ulcers. The cost of each item or procedure were based on mean costs derived from a national commercial claims dataset (Milliman's Health Cost Guidelines™). The cost of the V.A.C. Therapy Unit was based on an average daily rate of \$70. Costs for V.A.C. dressing materials were based on \$40 material cost applied at each dressing change. All costs are quoted as 2005 figures. The cost analysis concluded that the average direct cost per patient treated for 8 weeks or longer (regardless of clinical outcome) was \$27,270 and \$36,096 in the NPWT and MWT groups, respectively. The average total cost to achieve healing was \$25,954 for patients treated with NPWT (n=43) compared with \$38,806 for the MWT group (n=33). Sensitivity analyses suggest consistency of the study results.

Cost Comparison of NPWT V.A.C. with Other NPWT Devices

Law et al. (2015) conducted a retrospective claims database analysis on all patients who had submitted a claim to a major insurance company (Optum Life Sciences) for NPWT in an outpatient setting in the United States at 3-month and 12-month treatment periods. Chronic wounds comprised the majority of wounds (81%); acute wounds were also assessed. NPWT with V.A.C. (KCI) (n=12,843 at 3 months, n=7860 at 12 months) was compared with non-KCI model NPWT devices (n=713 at 3 months, n=378 at 12 months). At 3 months, the per-patient cost for NPWT with V.A.C. (\$35,498) was \$4224 (11%) lower than NPWT with other devices (\$39,722) ($P=0.08$). At 12 months, the per-patient cost for NPWT with V.A.C. (\$80,768) was significantly lower (\$30,444 [27%]) than NPWT with other devices (\$111,212) ($P=0.03$) (Law et al., 2015). This economic evaluation was funded by the device manufacturer.

Practice Guidelines

Five practice guidelines with relevant recommendations were identified. [Appendix VI](#) presents the recommendations of each guideline.

International Expert Panel on Negative Pressure Wound Therapy (NPWT-EP)

An international panel assembled and funded by NPWT device manufacturer Smith & Nephew Co. met to develop international guidelines concerning NPWT without reference to any particular NPWT device. The group developed evidence-based recommendations using a systematic literature review process including grading of evidence. Draft recommendations were followed by a formal consultative consensus development program involving 422 healthcare professionals. Individual recommendations

do not specifically address home use of NPWT; however, the preamble to the recommendations discusses the use of NPWT as a bridge to surgical closure or for healing by secondary intention, and notes the potential for home use of NPWT for wounds such as chronic wounds that may take a long time to heal. Some disadvantages of using NPWT for long periods are also noted, such as potential detriment on patients' quality of life as the result of the devices limiting activity, making noise, being heavy, or causing self-consciousness. Thirteen evidence-based recommendations regarding the general use (regardless of setting) of NPWT were developed: 4 for pressure ulcers, 4 for DFUs, 3 for ischemic lower limb wounds, and 2 for VLUs.

- Pressure ulcers:
 - NPWT may be used until surgical closure is possible/desirable.
 - Alternatively, NPWT should be considered to achieve closure by secondary intention.
 - NPWT should be used to reduce wound dimensions.
 - NPWT should be used to improve the quality of the wound bed.
- DFUs:
 - NPWT must be considered as an advanced wound care therapy for postoperative Texas grade 2 and 3 diabetic feet without ischemia.
 - NPWT must be considered to achieve healing by secondary intention.
 - Alternatively, NPWT should be stopped when wound has progressed suitably to be closed by surgical means.
 - NPWT should be considered in an attempt to prevent amputation or re-amputation.
- Ischemic lower limb wounds:
 - The cautious use of NPWT in chronic limb ischemia when all other modalities have failed may be considered in specialist hands but never as an alternative for revascularization.
 - NPWT may be considered as an advanced wound care therapy for lower limb ulceration after revascularization.
 - The use of NPWT is NOT indicated in acute limb ischemia.
- VLUs:
 - If first line therapy (compression) is not efficacious, NPWT should be considered to prepare the wound for surgical closure as part of a clinical pathway.
 - Use of gauze may be considered to reduce pain during dressing changes in susceptible patients.

Association for the Advancement of Wound Care

The most recent guidelines on pressure ulcer therapy from the Association for the Advancement of Wound Care (AAWC), updated in October 2010, do not specifically mention home use of NPWT. Regarding general guidance on the use of NPWT, the AAWC places NPWT under advanced or adjunctive interventions for pressure ulcers not responsive to "A-level" care. The guidelines state that NPWT shows no consistent effect on pressure ulcer healing, although it may increase granulation. The document

includes a statement about the FDA notice issued in 2009 regarding patient selection (FDA, 2009a; AAWC, 2010).

National Pressure Ulcer Advisory Panel

In 2014, the National Pressure Ulcer Advisory Panel (NPUAP), the European Pressure Ulcer Advisory Panel (EPUAP), and the Pan Pacific Pressure Injury Alliance updated their guidelines on the treatment of pressure ulcers (NPUAP et al., 2014). The group recommended the following regarding the use of NPWT for the treatment of pressure ulcers:

1. Consider NPWT as an early adjuvant for the treatment of deep, stage III and IV pressure ulcers.
2. Debride the pressure ulcer of necrotic tissue prior to the use of NPWT.
3. Follow a safe regimen in applying and removing the NPWT system.
4. Evaluate the pressure ulcer with each dressing change.
5. If pain is anticipated or reported, consider placing a nonadherent interface dressing on the wound bed, underneath the foam; lowering the level of pressure, and/or changing type of pressure (continuous or intermittent); or using a moist gauze filler instead of foam.
6. Educate the patient and caregivers about NPWT when used in the community setting.

International Working Group on the Diabetic Foot

In its 2016 guidance, the International Working Group on the Diabetic Foot (IWGDF) concluded that it was not possible to make a recommendation on the use of NPWT with respect to chronic, nonsurgical wounds because of a lack of available evidence. Regarding postoperative wounds of the diabetic foot, the group recommends that NPWT may be considered even though the effectiveness and cost-effectiveness remain to be established. The group labeled the strength of this recommendation “weak” with moderate quality of evidence. No specific mention of the use of NPWT in the home setting is included in the guidance (Game et al., 2016).

Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)

The SVS/AVF Joint Clinical Practices Guidelines Committee published recommendations for the management of VLUs in 2014. The only recommendation specific to NPWT is a recommendation against the routine primary use of NPWT for VLUs. The committee cites a lack of evidence to support the primary use of NPWT for VLUs even though there is some evidence supporting positive effects of NPWT for wound healing in general. These clinical practice guidelines do not discuss home use of NPWT (O'Donnell et al., 2014).

Selected Payer Policies

At the direction of WA State HCA, the coverage policies for the following organizations were reviewed: Aetna, Centers for Medicare & Medicaid Services (CMS), Oregon Health Evidence Review Commission (HERC), GroupHealth, and Regence Blue Cross/Blue Shield.

The terms used in searching the payer databases were *negative pressure or wound or e2402*.

Aetna

Aetna considers NPWT pumps medically necessary for ulcers and wounds encountered in an inpatient setting or in the home setting when the criteria are met. An NPWT pump and supplies are considered not medically necessary if any contraindication for use (as identified in the policy) is present.

For ulcers and wounds in the home setting, the member has a chronic stage III or IV pressure ulcer, neuropathic ulcer (e.g., diabetic ulcer), venous or arterial insufficiency ulcer, or a chronic ulcer of mixed etiology, present for at least 30 days. A complete wound therapy program as applicable depending on the type of wound (outlined in the policy), has been tried or considered and ruled out prior to application of NPWT.

Criteria for continued medical necessity, discontinuation, and maximum supply coverage are outlined in the policy.

Aetna considers NPWT experimental and investigational for the treatment of deep sternal wound infection, partial-thickness burns, tibial fractures, for use following surgical excision of pilonidal sinus disease and for recurrent pilonidal disease, and all other indications, because its effectiveness for these indications has not been established.

Aetna considers the use of chemotherapeutic agents in continuous-instillation or intermittent-instillation NPWT experimental and investigational because its effectiveness has not been established.

Aetna considers the use of nonpowered (mechanical) NPWT devices (Smart Negative Pressure [SNaP] Wound Care System) experimental and investigational because their effectiveness has not been established.

Aetna considers the use of single-use NPWT devices (PICO Single Use Negative Pressure Wound Therapy System; Prevena Incision Management System) experimental and investigational for all indications because of insufficient evidence of their effectiveness.

See Negative Pressure Wound Therapy (Aetna Clinical Policy Bulletin No. 0334:

http://www.aetna.com/cpb/medical/data/300_399/0334.html.

Centers for Medicare & Medicaid Services (CMS)

No CMS National Coverage Determination (NCD) for NPWT was identified on July 25, 2016 (search National Coverage Documents by keywords *negative pressure or wound or ulcer or e2402* in all documents at: <https://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx>). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. There is a Local Coverage Determination (LCD) for NPWT pumps (L33821) that was effective July 1, 2016. The LCD was issued by Noridian Healthcare Solutions LLC, a Medicare contractor in the state of Washington.

The LCD states that an NPWT pump and supplies are covered when ulcers and wounds are encountered in an inpatient setting or in the home setting when the criteria are met.

For ulcers and wounds in the home setting, the beneficiary has a chronic stage III or IV pressure ulcer, neuropathic (e.g., diabetic) ulcer, venous or arterial insufficiency ulcer, or a chronic (present for at least 30 days) ulcer of mixed etiology. A complete wound therapy program as applicable depending on the type of wound (outlined in the LCD), has been tried or considered and ruled out prior to application of NPWT.

An NPWT pump and supplies will be denied at any time as not reasonable or necessary if 1 or more of the exclusions (as identified in the LCD) are present.

See LCD for Negative Pressure Wound Therapy Pumps (L33821): <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33821&ver=6&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCD&PolicyType=Final&s=All&Keyword=negative+pressure&KeyWordLookup=Doc&KeywordSearchType=Exact&kq=true&bc=IAAABAAAAAAAAA%3d%3d&>.

Group Health Cooperative

Group Health Cooperative covers NPWT pumps and supplies for wound edema, exudate management, and stimulation of granulation for an initial 14-day course when the criteria are met for ulcers and wounds encountered in an inpatient setting or in the home setting, there is a goal of therapy clearly stated, and there are no contraindications for use (as identified in the policy).

For ulcers and wounds in the home setting, the patient has a stage III or IV pressure ulcer, neuropathic/diabetic ulcer, venous insufficiency or arterial ulcer, or a chronic ulcer of mixed etiology. These wounds should have exudate, size, and depth to require this specialized therapy.

A complete wound therapy program as applicable depending on the type of wound (outlined in the policy), should have been tried for 30 days unless edema and/or exudate mandates NPWT.

Criteria for continued coverage, denied coverage, and maximum supply coverage are outlined in the policy.

Group Health Cooperative does not cover nonpowered NPWT (SNAP, PICO) because there is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

See Negative Pressure Wound Therapy: Clinical Review Criteria: https://provider.ghc.org/all-sites/clinical/criteria/pdf/negative_pressure_wound_therapy.pdf.

Oregon Health Evidence Review Commission (HERC)

No coverage guidance for NPWT was identified on the Oregon HERC website (Oregon HERC Coverage Guidances: <http://www.oregon.gov/oha/herc/Pages/CoverageGuidances.aspx>).

Regence

No coverage policy for NPWT was identified on the Regence Group website (Regence Group Medical Policies: <http://blue.regence.com/policy/>).

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APPENDICES

APPENDIX I

SEARCH STRATEGY

INITIAL SEARCH, SYSTEMATIC REVIEWS (conducted March 15, 2016, and May 11, 2016)

Initially, evidence for this report was obtained by searching for systematic reviews, meta-analyses, practice guidelines, and economic evaluations that had been published in the past 10 years. Searches were conducted in the following databases using the terms *negative pressure wound therapy*: Agency for Healthcare Research and Quality (AHRQ), Blue Cross Blue Shield TEC Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (CRD) (York University), Hayes Knowledge Center, Institute for Clinical Systems Improvement (ICSI), National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (UK), United States Preventive Services Task Force (USPSTF), National Institute for Health and Care Excellence (NICE), and Veterans Affairs Technology Assessment Program (VA TAP). (NOTE: The CRD search strategy includes a search for Cochrane Reviews.) Additional systematic reviews were sought from a search of the PubMed database using filters for Systematic Reviews.

SEARCH FOR PRIMARY CLINICAL STUDIES AND ECONOMIC EVALUATIONS

Three systematic reviews were identified that were relevant to the Key Questions for this report; these systematic reviews were used to identify primary studies for this HTA. Subsequent searches for additional primary studies were designed to update the literature searches from the selected systematic reviews.

PubMed search on May 17, 2016

| Search | Query |
|--------|---|
| #26 | Search #23 NOT #24 Filters: Publication date from 2013/12/01 to 2016/05/17 |
| #25 | Search #23 NOT #24 |
| #24 | Search (animals[MeSH Terms]) NOT humans[MeSH Terms] |
| #23 | Search #22 AND #9 |
| #22 | Search #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 |
| #21 | Search vacuum-sealed[Title/Abstract] |
| #20 | Search vacuum sealed[Title/Abstract] |
| #19 | Search vacuum-sealing[Title/Abstract] |
| #18 | Search sub-atmospheric[Title/Abstract] |
| #17 | Search subatmospheric[Title/Abstract] |
| #16 | Search vacuum-assisted[Title/Abstract] |
| #15 | Search vacuum assisted[Title/Abstract] |
| #14 | Search negative-pressure[Title/Abstract] |
| #13 | Search negative pressure[Title/Abstract] |

- #12 Search negative-pressure wound therapy[MeSH Terms]
- #11 Search suction[MeSH Terms]
- #10 Search vacuum[MeSH Terms]
- #9 Search #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
- #8 Search infections, surgical wound[MeSH Terms]
- #7 Search dehiscence, surgical wound[MeSH Terms]
- #6 Search ulcer*[Title/Abstract]
- #5 Search wound*[Title/Abstract]
- #4 Search (wounds and injuries[MeSH Terms])
- #3 Search skin ulcer[MeSH Terms]
- #2 Search wound healing[MeSH Terms]

OVID-Embase search on July 1, 2016

The following search was run in both the Embase and MEDLINE databases. Only nonduplicated search results were reviewed.

1. Wound healing. ab,kw,sh,ti.
2. Wound care. ab,kw,sh,ti.
3. Skin ulcer. ab,kw,sh,ti.
4. "ulcer". ab,kw,sh,ti.
5. Wound. ab,kw,sh,ti.
6. 1 or 2 or 3 or 4 or 5
7. Vacuum. ab,kw,sh,ti.
8. Vacuum assisted closure. ab,kw,sh,ti.
9. (negative pressure or negative-pressure). ab,kw,sh,ti.
10. (vacuum assisted or vacuum-assisted). ab,kw,sh,ti.
11. (subatmospheric or sub-atmospheric). ab,kw,sh,ti.
12. (vacuum sealing or vacuum sealed or vacuum-sealed). ab,kw,sh,ti.
13. 7 or 8 or 9 or 10 or 11 or 12
14. Surgical wound infection. ab,kw,sh,ti.
15. Surgical wound dehiscence. ab,kw,sh,ti.
16. 14 or 15

17. 6 or 16
18. 13 and 17
19. Limit to English language
20. Limit 19 to humans
21. Limit 20 to yr="2014-current"
22. Remove duplicates from 21

Searches 23-34 removed ineligible publication types (e.g., conference abstracts, reviews, letters, editorials)

SEARCH FOR GUIDELINES

The National Guidelines Clearinghouse (<https://guideline.gov/>) and websites of professional organizations were searched using the term *negative pressure wound therapy*. Professional organizations included Association for the Advancement of Wound Care, International Working Group on the Diabetic Foot, and the National Pressure Ulcer Advisory Panel.

Update Searches

Update searches will be conducted prior to drafting the final HTA.

APPENDIX II

THE ASSESSMENT OF MULTIPLE SYSTEMATIC REVIEWS (AMSTAR) TOOL

The following key steps describe the AMSTAR tool (Shea et al., 2007):

| | |
|---------------|--|
| Step 1 | <p><u>Systematic Review Appraisal</u></p> <p>a. Rate the quality of each systematic review using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). This step is only necessary when data synthesis such as meta-analysis is conducted within the review and used in addition to or in place of individual study data.</p> |
| Step 2 | <p><u>Individual Study Appraisal</u></p> <p>a. Initial rating according to study design <i>Good</i>: Randomized controlled trials <i>Fair</i>: Nonrandomized trial (controlled, parallel-group, quasirandomized) <i>Poor</i>: Observational analytic studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) <i>Very poor</i>: Descriptive uncontrolled studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data])</p> <p>b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist</p> <p>c. Repeat for each study</p> |
| Step 3 | <p><u>Evaluation of Each Body of Evidence by Outcome, Key Question, or Indication</u></p> <p>a. Initial quality designation according to <i>best</i> study design in a body of evidence</p> <p>b. Downgrade/upgrade <i>Downgrade factors</i>: Study weaknesses (Quality Checklists), lack of applicability, inconsistency of results, small quantity of data, publication bias (if adequate information is available) <i>Possible upgrade factors</i>: Strong association, dose-response effect, bias favoring no effect</p> <p>c. Assign final rating: High-Moderate-Low-Very Low</p> <p>d. Repeat for each outcome/question/application</p> |
| Step 4 | <p><u>Evaluation of Overall Evidence</u></p> <p>a. Rank outcomes by clinical importance</p> <p>b. Consider overall quality of the evidence for each <i>critical</i> outcome</p> <p>c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low</p> |
| Step 5 | <p><u>Evidence-Based Conclusion</u></p> <p>Overall quality of the evidence + balance of benefits and harms</p> |

APPENDIX III

OVERVIEW OF EVIDENCE QUALITY ASSESSMENT METHODS

Clinical Studies

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

| | |
|---------------|--|
| <p>Step 1</p> | <p><u>Individual study appraisal:</u></p> <ul style="list-style-type: none"> a. Initial rating according to study design <ul style="list-style-type: none"> <i>Good:</i> Randomized controlled trials <i>Fair:</i> Nonrandomized trial (controlled, parallel-group, quasirandomized) <i>Poor:</i> Observational analytic studies (prospective or retrospective trials involving historical controls, pretest-posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) <i>Very poor:</i> Descriptive uncontrolled studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist c. Repeat for each study |
| <p>Step 2</p> | <p><u>Evaluation of each body of evidence by outcome, key question, or application:</u></p> <ul style="list-style-type: none"> a. Initial quality designation according to <i>best</i> study design in a body of evidence b. Downgrade/upgrade <ul style="list-style-type: none"> <i>Downgrade factors:</i> Study weaknesses (Quality Checklists), small quantity of evidence, lack of applicability, inconsistency of results, publication bias <i>Possible upgrade factors:</i> Strong association, dose-response effect, bias favoring no effect c. Assign final rating: High-Moderate-Low-Very Low d. Repeat for each outcome/question/application |
| <p>Step 3</p> | <p><u>Evaluation of overall evidence:</u></p> <ul style="list-style-type: none"> a. Rank outcomes by clinical importance b. Consider overall quality of evidence for each <i>critical</i> outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low |
| <p>Step 4</p> | <p><u>Evidence-based conclusion:</u></p> <p>Overall quality of evidence + Balance of benefits and harms</p> |

Practice Guidelines (checklist taken from [AGREE Tool](#) and approach to scoring used in this report)

Rank each item on a scale of 1-7.

Decide on overall quality (1 = lowest to 7 = highest), giving strongest weight to items 7-14 (Rigor of Development Domain) and items 22-23 (Editorial Independence).

For qualitative labels:

Very poor = 1

Poor = 2-3

Fair = 4-5

Good = 6-7

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Economic Evaluations

A tool developed by Hayes for internal use guides interpretation and critical appraisal of economic evaluations. The tool includes a checklist of items addressing issues such as the reliability of effectiveness assumptions, transparency of reporting, quality of analysis, generalizability/applicability, and conflicts of interest. The following publications served as sources of best practice.

Brunetti M, Shemilt I, Pregno S, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol*. 2013;66(2):140-150. PMID: [22863410](#).

Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ*. 1996;313(7052):275-283. PMID: [8704542](#).

Drummond M, Sculpher M. Common methodological flaws in economic evaluations. *Med Care*. 2005;43(7 Suppl):5-14. PMID: [16056003](#).

Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care*. 2005;21(2):240-245. PMID: [15921065](#).

Gerkens S, Crott R, Cleemput I, et al. Comparison of three instruments assessing the quality of economic evaluations: a practical exercise on economic evaluations of the surgical treatment of obesity. *Int J Technol Assess Health Care*. 2008;24(3):318-325. PMID: [18601800](#).

Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. *Cost Eff Resour Alloc*. 2003;1(1):8. PMID: [14687420](#).

Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid Policy*. 2010;6(1):51-59.

Smith KA, Rudmik L. Cost collection and analysis for health economic evaluation. *Otolaryngol Head Neck Surg*. 2013;149(2):192-199. PMID: [23641023](#).

Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med*. 2003;163(14):1637-1641. PMID: [12885677](#).

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Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd Edition. Oxford, UK: Oxford University Press; 1997.

Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. 1996. Oxford, UK: Oxford University Press; 1996.

Other

Canadian Agency for Drugs and Technologies in Health (CADTH). *Guidelines for the Economic Evaluation of Health Technologies*. 3rd Edition. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2006. Available at:

http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf. Accessed January 26, 2015.

APPENDIX IV

EXCLUDED STUDIES

The following 38 studies were excluded during full-text review.

Ineligible study design, publication type, comparison, or outcomes (13)

1. Anthony H. Efficiency and cost effectiveness of negative pressure wound therapy. *Nurs Stand*. 2015;30(8):64-70.
2. Armstrong DG, Lavery LA, Boulton AJ. Negative pressure wound therapy via vacuum-assisted closure following partial foot amputation: what is the role of wound chronicity? *Int Wound J*. 2007;4(1):79-86.
3. Brinkert D, Ali M, Naud M, Maire N, Trial C, Teot L. Negative pressure wound therapy with saline instillation: 131 patient case series. *Int Wound J*. 2013;(10 Suppl 1):56-60.
4. Chatterjee A, Macarios D, Griffin L, et al. Cost-utility analysis: sartorius flap versus negative pressure therapy for infected vascular groin graft management. *Plast Reconstr Surg Glob Open*. 2015;3(11):e566.
5. Egemen O, Ozkaya O, Ozturk MB, Aksan T, Orman C, Akan M. Effective use of negative pressure wound therapy provides quick wound-bed preparation and complete graft take in the management of chronic venous ulcers. *Int Wound J*. 2012;9(2):199-205.
6. Hurd T, Trueman P, Rossington A. Use of a portable, single-use negative pressure wound therapy device in home care patients with low to moderately exuding wounds: a case series. *Ostomy Wound Manage*. 2014;60(3):30-36.
7. Jeffery SL. Non-adherent and flexible -using Cutimed Sorbact as a filler and liner with NPWT. *J Wound Care*. 2014;23(5 Suppl):S3-S15.
8. Lavery LA, La Fontaine J, Thakral G, Kim PJ, Bhavan K, Davis KE. Randomized clinical trial to compare negative-pressure wound therapy approaches with low and high pressure, silicone-coated dressing, and polyurethane foam dressing. *Plast Reconstr Surg*. 2014;133(3):722-726.
9. Pellino G, Sciaudone G, Candilio G, Campitiello F, Selvaggi F, Canonico S. Effects of a new pocket device for negative pressure wound therapy on surgical wounds of patients affected with Crohn's disease: a pilot trial. *Surg Innov*. 2014;21(2):204-212.
10. Selvaggi F, Pellino G, Sciaudone G, et al. New advances in negative pressure wound therapy (NPWT) for surgical wounds of patients affected with Crohn's disease. *Surg Technol Int*. 2014;24:83-89.
11. Serena TE, Buan JS. The use of a novel canister-free negative-pressure device in chronic wounds: A retrospective analysis. *Adv Skin Wound Care*. 2016;29(4):165-168.
12. Stapleton H; DRESSING Team. Wound healing in obese women following caesarean section. *Aust Nurs Midwifery J*. 2015;23(3):34.
13. Vassallo IM, Formosa C. Comparing calcium alginate dressings to vacuum-assisted closure: a clinical trial. *Wounds*. 2015;27(7):180-190.

Ineligible population or n < 20 (3)

1. Ashby RL, Dumville JC, Soares MO, et al. A pilot randomised controlled trial of negative pressure wound therapy to treat grade iii/iv pressure ulcers. *Trials*. 2012;13:119.
2. de Laat EH, van den Boogaard MH, Spauwen PH, van Kuppevelt DH, van Goor H, Schoonhoven L. Faster wound healing with topical negative pressure therapy in difficult-to-heal wounds: a prospective randomized controlled trial. *Ann Plast Surg*. 2011;67(6):626-631.
3. Ousey KJ, Milne J, Cook L, Stephenson J, Gillibrand W. A pilot study exploring quality of life experienced by patients undergoing negative-pressure wound therapy as part of their wound care treatment compared to patients receiving standard wound care. *Int Wound J*. 2014;11(4):357-365.

Ineligible setting or comparison (21)

1. Correa JC, Mejia DA, Duque N, J MM, Uribe CM. Managing the open abdomen: Negative pressure closure versus mesh-mediated fascial traction closure: a randomized trial. *Hernia*. 2016;20(2):221-229.
2. Dwivedi MK, Srivastava RN, Bhagat AK, et al. Pressure ulcer management in paraplegic patients with a novel negative pressure device: a randomised controlled trial. *J Wound Care*. 2016;25(4):199-200, 202-204, 206-207.
3. Fulco I, Erba P, Valeri RC, Vournakis J, Schaefer DJ. Poly-n-acetyl glucosamine nanofibers for negative-pressure wound therapies. *Wound Repair Regen*. 2015;23(2):197-202.
4. Ghatak PD, Schlanger R, Ganesh K, et al. A wireless electroceutical dressing lowers cost of negative pressure wound therapy. *Adv Wound Care (New Rochelle)*. 2015;4(5):302-311.
5. Gillespie BM, Rickard CM, Thalib L, et al. Use of negative-pressure wound dressings to prevent surgical site complications after primary hip arthroplasty: a pilot RCT. *Surg Innov*. 2015;22(5):488-495.
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**APPENDIX V
EVIDENCE TABLES**

**APPENDIX Va
STUDIES OF CHRONIC WOUNDS**

Key: DFU(s), diabetic foot ulcer(s); DM, diabetes mellitus; EE, economic evaluation; ER, emergency room; f/u, follow-up; grp(s), group(s); HCPCS, Healthcare Common Procedure Coding System; HIV, human immunodeficiency virus; HR, hazard ratio; hx, history; mmHg, millimeter of Mercury; NPWT, negative pressure wound therapy; NA, not applicable; NR, not reported; prep, preparation; pt(s), patient(s); PU(s), pressure ulcer(s); RCT, randomized controlled trial; tx, treatment (or therapy); VAC, vacuum-assisted closure

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|--|---|---|--|--|
| <p>Ford et al. (2002) Boston University School of Medicine; Boston, MA</p> <p>RCT</p> <p>F/u: 10 mos</p> <p>Time frame: NR</p> <p>Funding source: Supported in part by an Alpha Omega Alpha Student Research Fellowship. Plastic Surgery Education Foundation Scientific Essay Award Winner (CNF). Supported in part by grants from the Plastic Surgery Education Foundation and Kinetic Concepts, San Antonio, TX.</p> | <p>n=28 pts, 41 wounds (# of wounds treated NR) 22 pts with 35 wounds completed the trial</p> <p># wounds in NPWT grp: 20</p> <p># wounds in control group: 15</p> <p>Inclusion criteria: PU or pressure sores</p> <p>Exclusion criteria: Aged <21 or > 80 yrs; ulcer duration <4 wks; clinical infection; comorbid conditions (e.g., vasculitis, rheumatoid arthritis, severe kidney disease, heart disease); tx with corticosteroids; absence of stage III or IV ulcers</p> <p>Clinical hx/pt characteristics (VAC</p> | <p>Tx setting: Plastic surgery clinic and inpatient referral at Boston Medical Center</p> <p>VAC tx: Brand NR; dressing type NR; recommended changing interval – every 2 days; suction and pressure setting (mmHg) – NR; reusable – NR; instillation system – NR; duration of use (wks) – 6</p> <p>Comparator tx: HealthPoint System HP—Accuzyme, Iodosorb, and Panafil each targeted to optimize a particular macroscopic phase of wound healing; dressing type – NR; change interval – once or twice daily; suction and pressure (mmHg) – NA;</p> | <p>Clinical outcomes (VAC grp; Control grp) (% wounds): Complete wound healing: 2/20 (10%); 2/15 (13%) (risk difference 3%, 95% CI, -18% to 25% [calculated by Rhee et al.]</p> <p>Complications (VAC grp; Control grp) (# pts) (% pts): Sepsis: 1 (0.5%); 0 (0%) Extremity amputation: 1 (0.5%); 0 (0%)</p> | <p>Limitations: incomplete reporting for some of the outcomes, such as osteomyelitis, and incomplete reporting of DM status and control; wounds of the comparison grps were heterogeneous in nature; pts who dropped out were not included in final analysis; baseline differences in age.</p> <p>Study quality: Fair</p> <p>Conflicts of interest: NR for individual investigators; study partially funded by industry (KCI).</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|--|---|--|---|
| | <p><i>grp; Control grp):</i> Mean age (yrs): 41.7; 54.4 % men: NR % smoker: NR Wound etiology: PU Wound location (%): Leg (2.9%); foot (11.4%); ankle (11.4%); sacral (48.6%); other (25.7%) Mean wound age (wks): NR Mean wound size (cm²): NR Infection status (%): NR Wound prep prior to study txs: Debridement as necessary</p> | <p>reusable – NA; instillation system – NA; duration of use (wks) – 6</p> <p><i>Outcome measures:</i> Complete wound healing by secondary infection – PU</p> | | |
| <p>Schwien et al. (2005) Outcome Concept Systems, Inc., Seattle, WA</p> <p>Retrospective analysis of a database</p> <p>F/u: NR</p> <p>Time frame: 2003-2004</p> <p>Funding source: Industry</p> | <p>n=2348 pts</p> <p>NPWT: n=60 Control: n=2288</p> <p><i>Inclusion criteria:</i> PU or pressure sores</p> <p><i>Exclusion criteria:</i> Clinical infection; pts who died at home; enteral or parenteral nutrition tx; high risk factor of heavy smoking, alcohol dependency, or drug dependency; poor or unknown overall prognosis; secondary diagnoses of uncontrolled DM, cancer, systemic infections, or related to malnutrition/anemias/proteinemia</p> <p><i>Clinical hx/pt characteristics (NPWT grp; Control grp):</i> Mean age (yrs): 65.0; 71.4 % men: 47; 42</p> | <p>Tx setting: Home healthcare setting</p> <p>NPWT tx: Brand – Kinetic Concepts Inc. (KCI); dressing type – foam, open cell; recommended changing interval – every 2 days, suction and pressure (mmHg) - intermittent and continuous; reusable – NR; instillation system – NR; duration of use (wks) – NR</p> <p>Control tx: Any other wound care tx other than NPWT; brand – NA; dressing type – NR; recommended changing interval – NA; suction and pressure (mmHg) – NA; reusable – NA; instillation system – NA; duration of use – NA</p> | <p>No efficacy outcomes.</p> <p><i>Complications (NPWT grp, Control grp) (# pts) (% pts):</i> Emergency room visits, all pts: 0/60 (0%), 189/2288 (8%); <i>P</i><0.01 Stage III PU: 0 (0%), 126 (7%); <i>P</i><0.01 Stage IV PU: 0 (0%), 63 (11%); <i>P</i><0.01</p> <p>Wound-related hospitalization, all pts: 3/60 (5%); 310/2288 (14%) Stage III PU: 1 (3%), 194 (11%); <i>P</i><0.01 Stage IV PU: 2 (7%), 116 (20%); <i>P</i><0.01</p> | <p><i>Limitations:</i> Inappropriate or poorly described control grps; poor or selective reporting on comparative txs, potential confounders, and outcomes.</p> <p><i>Study quality:</i> Poor</p> <p><i>Conflicts of interest:</i> The authors disclose that Kinetic Concepts Inc. funded this study through data consulting arrangements with Outcome Concept Systems Inc.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|---|--|---|--|
| | % smoker: NR Wound etiology: Pressure (100%; 100%) Wound location: NR Mean wound age (wks): NR Mean wound size (cm ²): NR Infection status (%): NR Wound prep prior to study txs: NR; NA | <i>Outcome measures (NPWT grp; Control grp):</i> Adverse events | | |
| <p>Frykberg and Williams (2007) Carl T. Hayden Veterans Administration Medical Center, Phoenix, AZ.; Milliman Inc, Windsor, CT.</p> <p>Retrospective claims review</p> <p><i>F/u:</i> NR</p> <p><i>Time frame:</i> Medicare claims from 2003, private claims from 2002-2003 data</p> <p><i>Funding source:</i> Partial funding by Kinetic Concepts Inc., maker of the studied VAC system; source of remaining funding NR.</p> | <p>n=16,319</p> <p>NPWT: n=380 (281 Medicare, 99 commercial) Control: n=15,939 (12,514 Medicare, 3425 commercial)</p> <p><i>Inclusion criteria:</i> Identified in databases as NPWT or Control for DFU using ICD-9 codes and criteria presented in next column</p> <p><i>Exclusion criteria:</i> Pts in Medicare database who had NPWT and amputation in same quarter, as unclear which came first</p> <p><i>Clinical hx/pt characteristics (NPWT grp, Control grp):</i> Mean age (yrs): In commercial sample, 55; 56 (NR for Medicare) % men: In commercial sample: 61; 62; in Medicare sample: 47; 55 % smoker: NR Wound etiology: DM-related, per inclusion criteria Wound location: Foot, per</p> | <p>Tx setting: NR; pts included in this analysis were a mix of inpatient and outpatient populations and they were not analyzed separately. The authors suggest that pts who received NPWT in acute care settings but not in the outpatient setting are likely to be a small grp within their study; however, measured proportions of inpatients and outpatients or proportion of outpatient care days are NR.</p> <p>NPWT: Identified by scanning pt claims involving NPWT device or supplies, HCPCS code, and medical equipment charges. No information about administration available.</p> <p>Control: Identified as all other standard wound txs and no claim or code indicating use of NPWT.</p> | <p><i>Complications (Commercial NPWT grp; Commercial control grp; Medicare NPWT grp; Medicare control grp) (# pts) (% pts):</i> Amputations – Overall, without stratification or risk adjustment. Toes to foot: 66 (67%); 2466 (72%); 169 (60%); 6507 (52%) Ankle to knee: 25 (25%); 788 (23%); 79 (28%); 3504 (28%) Above knee: 8 (8%); 171 (5%); 34 (12%); 2503 (20%)</p> | <p><i>Limitations:</i> Retrospective analyses using administrative claims databases and potentially meaningful differences in pt demographics between the grps not accounted for in adjusted analyses.</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> One author has research funding and is a speaker for Kinetic Concepts Inc., maker of the studied VAC system.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|---|---|---|--|
| | inclusion criteria Mean wound age (wks): NR Mean wound size (cm ²): NR Infection status (%): NR Wound prep prior to study txs: NR | Controls selected after adjustment for risk for more severe cases (more comparable to NPWT cases) using cost of care and depth of debridement. No information about administration available. <i>Outcome measures:</i> Amputation | | |
| <p>Lavery et al. (2007) Texas A&M Health Science Center College of Medicine; Scott and White Hospital, Temple, TX</p> <p>Cohort</p> <p>F/u: NR</p> <p>Time frame: 1996-2004</p> <p>Funding source: Industry</p> | <p>n=2677 pts</p> <p>NPWT: n=2091 NPWT matched: n=1135 Control: n=586</p> <p><i>Inclusion criteria:</i> DFUs</p> <p><i>Exclusion criteria:</i> No pts with chronic wounds; no debridement of necrotic tissue; no comprehensive DM management included with the case plan; no reduction in pressure of affected ulcer; no description of wound size and duration prior to NPWT</p> <p><i>Clinical hx/pt characteristics (NPWT grp; Matched grp; Control grp):</i> Mean age (yrs): 65.2; 58.5; 58.0 % men: 64.5%; 64.5%; 73.2% % smoker: NR Wound etiology: DM (100%; 100%; 100%) Wound location: NR</p> | <p>Tx setting: Outpatient</p> <p>NPWT tx: VAC tx; brand – Kinetic Concepts Inc. (KCI); dressing type – NR; recommended changing interval – NR; suction and pressure setting (mmHg) – NR; reusable – NR; instillation system – NR; duration of use (wks) – NR</p> <p>NPWT matched tx: VAC tx; brand – Kinetic Concepts Inc. (KCI); dressing type – NR; recommended changing interval – NR; suction and pressure setting (mmHg) – NR; reusable – NR; instillation system – NR; duration of use (wks) – NR</p> <p>Comparator tx: Standard wet-to-moist wound tx; brand – NR; dressing type – NR;</p> | <p><i>Clinical outcomes (% pts):</i> Complete wound healing: <i>NPWT matched grp; Control grp</i> 12 wks (all population): 39.5%; 23.9%; P<0.001 20 wks (all population) 46.3%; 32.8%; P<0.001 <i>Unmatched NPWT grp; NPWT matched grp; Control grp</i> 12 wks (small ulcers <2 cm²):41.4%; 43.1%; 29.4%; P<0.05 20 wks (small ulcers <2 cm²): 46.6%; 50.3%; 38.9%; P<0.05 for matched NPWT vs. control 12 wks (medium ulcers 2-4 cm²): 40.1%; 43.7%; 17.9% 20 wks (medium ulcers 2-4 cm²): 46.1%; 48.5%; 25.2%; P<0.05 12 wks (large ulcers >4 cm²): 37.8%; 37.8%; 13.8% 20 wks: (large ulcers >4 cm²): 45.3%; 44.9%; 22.4%; P<0.05 12 wks (short duration <6 mos): 39.9%; 40.3%; 30.2% 12 wks (medium duration 6-12 mos): 36.2%; 39.6%; 28.4% 12 wks (long duration >12 mos): 35.3%; 35.8%;</p> | <p><i>Limitations:</i> Inappropriate or poorly described control grps.</p> <p><i>Study quality:</i> Poor</p> <p><i>Conflicts of interest:</i> Research was sponsored in part by Kinetic Concepts Inc. In addition, 2 investigators reported receiving grants from and 2 investigators reported professional relationships with Kinetic Concepts Inc.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|--|--|---|---|
| | <p>Mean wound age (wks): 22.9; 26.5; 30 Mean wound size (cm²): 13.5; 13.8; 1.61 Infection status (%): NR Wound prep prior to study txs: NR; NR; NA</p> | <p>recommended changing interval – NR; suction and pressure (mmHg) – NA; reusable – NA; instillation system – NA; duration of use – NA</p> <p><i>Outcome measures:</i> Complete wound healing by secondary intention</p> | <p>15.3%</p> <p><i>Economic analysis:</i> 20-week expected cost of care <i>NPWT grp; Control grp</i> One nursing visit per day for both groups: \$16,733;\$15,258 One nursing visit per day for NPWT compared with 2 nursing visits per day for wet-to-moist wound care grp: \$16,733;\$28,691</p> <p><i>Complications:</i> NR</p> | |
| <p>Blume et al. (2008) Multicenter (initiated at 37 diabetic foot and wound clinics; enrolled pts from 1 Canadian and 28 U.S. sites)</p> <p>RCT</p> <p><i>F/u:</i> 9 mos</p> <p><i>Time frame:</i> NR</p> <p><i>Funding source:</i> Industry (KCI USA International, manufacturer of the NPWT device studied)</p> | <p>n=342 pts enrolled n=341 randomized n=335 analyzed</p> <p>NPWT: n=169 AMWT: n=166</p> <p><i>Inclusion criteria:</i> Aged ≥18 yrs old; DM; stage 2 or 3 calcaneal, dorsal, or plantar foot ulcer ≥2 cm² after debridement; adequate blood perfusion</p> <p><i>Exclusion criteria:</i> Active Charcot disease or ulcers from electrical, chemical, or radiation burns; collagen vascular disease; ulcer malignancy; untreated osteomyelitis; cellulitis; uncontrolled hyperglycemia; inadequate lower extremity perfusion; ulcer tx with normothermic or hyperbaric</p> | <p>Tx setting: Pts treated in both acute and home care settings (about 90% of tx days in home care)</p> <p>NPWT: VAC tx brand – KCI USA; electrically powered; dressing type – open cell sterile polyurethane or dense open-pore polyvinyl alcohol foam dressing; recommended changing interval – NR; suction and pressure setting (mmHg) – NR; reusable – pump device is reusable; instillation system – NR; duration of use – mean 64 days</p> <p>AMWT: Advanced moist wound tx of primarily hydrogels and alginates consistent with standards of care; recommended changing</p> | <p><i>Clinical outcomes (NPWT grp; AMWT grp) (# ptw) (% pts):</i> Complete closure during active tx phase: 73/169 (43%); 48/166 (29%); P=0.007 Complete closure at end of active tx phase: 73/120 (61%); 48/120 (40%); P=0.001 Surgical closure by split-thickness skin grafts, flaps, sutures, or amputations: 16 (10%); 14 (8%); P=NR</p> <p>Time to closure, median days: 96 (95% CI, 75-114); not determinable for AMWT (P=0.001)</p> <p><i>Complications (NPWT grp; AMWT grp) (# pts) (% pts):</i> Secondary amputations: 7 (4%); 17 (10%); P=0.035 Edema: 5 (3%); 7 (4%); P=NS Wound infection: 4 (2%); 1 (<1%); P=NS Cellulitis: 4 (2%); 1 (<1%); P=NS Osteomyelitis: 1 (<1%); 0; P=NS <i>Staphylococcus</i> infection: 1 (<1%); 0 (0%); P=NS</p> | <p><i>Limitations:</i> Potentially meaningful baseline differences between grps; potential for differential concomitant txs between intervention and control grps; potential performance bias due to lack of blinding</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> Financial relationships with KCI International, including study support.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|--|---|---|---|---|
| | <p>oxygen tx; concomitant medication; recombinant or autologous growth factor products; skin and dermal substitutes within 30 days of study start; use of enzymatic debridement; pregnant or breastfeeding</p> <p><i>Clinical hx/pt characteristics (NPWT grp, AMWT grp):</i> Mean age (yrs): 58; 59 % men: 83%; 73% % smoker: 34%; 32% Wound etiology: DM-related, per inclusion criteria Wound location: Foot, per inclusion criteria Mean wound age (days before tx): 198; 206 Mean wound size (cm²): 13.5; 11.0 Infection status (%): 30%; 27% Wound prep prior to study txs: All debridement within 2 days to random allocation per study protocol</p> | <p>interval – NR; duration of use – mean 78 days</p> <p><i>Outcome measures:</i> Complete ulcer closure: 100% re-epithelization, without drainage or dressing requirements; time to closure; complications</p> | <p>Infected skin ulcer: 1 (<1%); 2 (1%); P=NS</p> | |
| <p>Fife et al. (2008) University of Texas Health Science Center, Houston, TX</p> <p>Cohort</p> <p>F/u: NR</p> <p>Time frame: 2001-2006</p> | <p>n=1331 pts</p> <p>NPWT: n=72 Control: n=1299</p> <p><i>Inclusion criteria:</i> DFU <i>Exclusion criteria:</i> Not treated in an outpatient setting</p> <p><i>Clinical hx/pt characteristics (NPWT</i></p> | <p>Tx setting: Outpatient</p> <p>NPWT tx: VAC tx; brand – Kinetic Concepts Inc. (KCI); dressing type – NR; recommended changing interval – NR; suction and pressure setting (mmHg) – NR; reusable – NR; instillation system – NR; duration of use</p> | <p><i>Efficacy outcomes:</i> NR</p> <p><i>Complications (NPWT grp; Control grp):</i> Bleeding (discontinued NPWT due to bleeding): No DFU pts with the V.A.C. required the discontinuation of the V.A.C. because of bleeding.</p> <p>Bleeding (sanguineous drainage): No cases found in either grp</p> | <p><i>Limitations:</i> Controls not matched; potential selection bias; retrospective data analysis; quality of data source not clear; surrogate/indirect data used to measure outcomes.</p> <p><i>Study quality:</i> Poor</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|--|---|---|---|---|
| <p><i>Funding source:</i> Industry</p> | <p><i>grp; Control grp):</i> Mean age (yrs): NR % men: NR % smoker: NR Wound etiology: DM (100%) Wound location: NR Mean wound age (wks): NR Mean wound size (cm²): NR Infection status (%): NR Wound prep prior to study txs: NA; NR</p> | <p>(weeks) – NR</p> <p>Comparator tx: Unspecified wound care tx either prior to the start of NPWT or among pts who never received NPWT; brand – NA; dressing type – NA; recommended changing interval – NA; suction and pressure (mmHg) – NA; reusable – NA; instillation system – NA; duration of use – NA</p> <p><i>Outcome measures:</i> Adverse events</p> | <p>Infection (antibiotics): V.A.C. pts had fewer antibiotic prescriptions (numbers NR), <i>P</i><0.05 Infection (culture): V.A.C. pts had fewer cultures taken (numbers NR), <i>P</i><0.05 Pain (measured by provision of pain medication): <i>P</i>=NS</p> | <p><i>Conflicts of interest:</i> Project funded by KCI. Three of the authors report financial interests associated with Intellicure.</p> |
| <p>Lerman et al. (2010) O'Connor Wound Care Clinic; O'Connor Hospital; Stanford University School of Medicine; Spiracur Inc.</p> <p>Prospective cohort and retrospective matched-control comparisons</p> <p><i>F/u:</i> 4 mos</p> <p><i>Time frame:</i> 2008-2009</p> <p><i>Funding source:</i> Industry</p> | <p>n=78 pts</p> <p>SNaP: n=36 Control: n=42</p> <p><i>Inclusion criteria:</i> DFUs; venous ulcers</p> <p><i>Exclusion criteria:</i> Aged <18 yrs; ulcer size <1.5 cm in narrowest diameter; ulcer size >10 cm in greatest diameter; wound surrounded by 2 cm or less of intact epithelium around the wound edge; wounds that healed following >14 days of traditional tx</p> <p><i>Clinical hx/pt characteristics (SNaP grp; control grp):</i> Mean age (yrs): 64.0; 66.8</p> | <p>Tx setting: Outpatient</p> <p>NPWT tx: SNaP (Smart Negative Pressure) Wound Care System; brand – NR (portable); dressing type – gauze; antimicrobial/hydrocolloid dressing layer; recommended changing interval – twice wkly; suction and pressure setting (mmHg) – multiple setting 75-125; reusable – single use; instillation system – NR; duration of use (wks) – 7.44</p> <p>Comparator tx: Modern wound care protocols that included the use of Apligraf, Regranex, and skin grafting;</p> | <p><i>Clinical outcomes (NPWT grp; Control grp):</i> Complete wound healing: 1 mo (all population): 0%; 0% 2 mos (all population): 20%; 7.1% 3 mos (all population): 66.2%; 21.4%, 4 mos (all population): 83.1%; 35.7%</p> <p>Time to complete wound healing (mean ± SD) (days): 74.25±20.1; 148.73±63.1; <i>P</i><0.0001</p> <p><i>Complications (NPWT grp; Control grp) (# pts):</i> Unspecified: 7 pts; NR Infection requiring discontinuation of NPWT: 1; NA</p> | <p><i>Limitations:</i> Potential for differential concomitant txs between intervention and control grps; high overall attrition.</p> <p><i>Study quality:</i> Poor</p> <p><i>Conflicts of interest:</i> Work supported by a research grant from Spiracur Inc. Two authors report professional relationships with Spiracur, Inc.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|--|---|---|--|---|
| | % men: 42.9%; 45.2% % smoker: 42.9%; 20.0% Wound etiology: DM: 47.6%; 50% Venous: 52.4%; 50% Wound location: NR Mean wound age (wks): 36.4; 31.2 Mean wound size (cm ²): NR Infection status (%): NR Wound prep prior to study txs: Debridement in NPWT grp | brand – NA; dressing type – NA; recommended changing interval – NA; suction and pressure (mmHg) – NA; reusable – NA; instillation system – NA; duration of use – NA <i>Outcome measures:</i> Complete wound healing by secondary intention; time to complete wound healing; adverse events | | |
| <p>Armstrong et al. (2011) Southern Arizona Limb Salvage Alliance (SALSA), University of Arizona College of Medicine, Tucson, AZ</p> <p>RCT (interim analysis of study presented in Armstrong et al., 2012)</p> <p><i>F/u:</i> 16 wks</p> <p><i>Time frame:</i> NR</p> <p><i>Funding source:</i> Industry (Spiracur Inc., manufacturer of the SNaP device)</p> | <p>n=65 pts</p> <p>SNaP: n=32 VAC: n=33</p> <p><i>Inclusion criteria:</i> DFUs; venous ulcers</p> <p><i>Exclusion criteria:</i> Aged <18 yrs; ulcer size <1 cm²; ulcer size >100 cm²; clinical infection; ankle/brachial index <0.7 or >1.2; ulcer size >10 cm in widest diameter; wounds present for <30 days</p> <p><i>Clinical hx/pt characteristics (SNaP grp; VAC grp):</i> Mean age (yrs): 65.8; 65.1 % men: 48%; 50% % smoker: 20%; 12.5% Wound etiology: NR Wound location: NR Mean wound age (wks): NR</p> | <p>Tx setting: 12 outpatient clinics</p> <p>NPWT tx: SNaP (Smart Negative Pressure) Wound Care System; brand – Spiracur (portable); mechanically powered; dressing type – gauze; recommended changing interval – every 3 days; suction and pressure setting (mmHg) – NR; reusable – no; instillation system – NR; duration of use (wks) – NR</p> <p>Comparator tx: VAC tx system; electrically powered; brand – KCI, ActiV.A.C. and V.A.C. models (portable); dressing type – foam; recommended changing interval – every 2 days; suction and pressure (mmHg) – NR; reusable – pump device is reusable; instillation system – NR;</p> | <p><i>Clinical outcomes (SNaP grp; VAC grp) (% pts):</i> Complete wound healing: 4 wks: 0%; 0% 8 wks: 11.8%; 13.6% 12 wks: 38.2%; 36.7% 16 wks: 59.7%; 64.8%</p> <p>There was no significant difference (P=0.99) in the proportion of pts healed over time, indicating that the effect of the SNaP System was not significantly different than that of the VAC System in promoting complete wound closure in the population studied.</p> <p><i>Patient-centered outcomes:</i> <u>Pain – exit interview responses (n=25):</u> The study investigators reported that there were no differences in reported pain, perceived effectiveness, and pt satisfaction between the devices used to apply negative pressure. However, the SNaP System interfered less with overall activity, sleep, and social interactions than the VAC System. <u>Change in overall activity after NPWT – exit interview response (n=25, VAC grp vs SNaP</u></p> | <p><i>Limitations:</i> See Armstrong et al. (2012)</p> <p><i>Study quality:</i> See Armstrong et al. (2012)</p> <p><i>Conflicts of interest:</i> Study was sponsored by a grant from Spiracur Inc., manufacturer of the SNaP device. Two authors have received research funding from both Spiracur and K.C.I.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|---|--|---|--|
| | <p>Mean wound size (cm²): NR Infection status (%): NR Wound prep prior to study txs: Debridement in both grps</p> | <p>duration of use – NR</p> <p><i>Outcome measures:</i> Complete wound healing by secondary intention</p> | <p><u>grp</u>): Chi-square $P=0.0210$ Fisher’s exact test $P=0.0179$</p> <p><i>Complications (SNaP grp; VAC grp) (# pts) (% pts):</i> Infection: 2(6.3%); 1(3%)</p> | |
| <p>Hutton et al. (2011) University of Michigan, Ann Arbor, MI</p> <p><i>Type of EE:</i> Cost comparison of SNaP device compared with standard care and electrically powered NPWT devices</p> <p><i>Design:</i> Decision analytic modelling</p> <p><i>Perspective:</i> Medicare; private payers</p> <p><i>Time horizon:</i> 16 wks</p> <p><i>Funding source:</i> Spiracur Inc.</p> | <p>Decision analytic modelling approach using an economic model with peer-reviewed data to simulate outcomes for treatment with different therapies</p> | <p>Tx setting: Home</p> <p>NPWT device: SNaP Wound Care System</p> <p>Powered device: Not specified</p> <p>Assumptions: Authors assumed equal efficacy between SNaP and powered NPWT devices based on preliminary studies and ongoing clinical trials (83.1% healed). Modern dressings are assumed to be 35.7% effective in healing.</p> <p>Base case analysis was based on a single study directly comparing the SNaP system with modern dressing protocols.</p> <p>Costs: Costs of tx include direct costs and other healthcare costs for individuals with diabetic lower extremity wounds. Costs are based on the</p> | <p>Base case results: The SNaP Wound Care System saved \$9699 (42%) over modern dressings, \$2774 (17%) over powered NPWT for a private payer, and \$2296 (15%) over powered NPWT for Medicare.</p> <p>Cost by category: SNaP costs \$4445 more for the equipment and supplies than modern dressings but saves \$1853 in dressing changes, \$1846 in additional healthcare costs, \$3425 in costs of complications, and \$7020 in long-term costs for pts who do not heal.</p> <p>NOTE: Costs are 2010 USD.</p> | <p><i>Conflicts of interest:</i> 1 author was paid consultant of Spiracur Inc.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
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| | | literature comparing NPWT to modern dressings and Medicare reimbursement rates. | | |
| <p>Armstrong et al. (2012) Southern Arizona Limb Salvage Alliance (SALSA), University of Arizona College of Medicine, Tucson, AZ</p> <p>RCT</p> <p>F/u: 16 wks</p> <p>Time frame: NR</p> <p>Funding source: Industry</p> | <p>n=132 pts</p> <p>SNaP: n=64 VAC: n=68</p> <p><i>Inclusion criteria:</i> DFUs; venous ulcers</p> <p><i>Exclusion criteria:</i> Aged <18 yrs; ulcer size <1 cm²; ulcer size >100 cm²; clinical infection; ankle/brachial index <0.7 or >1.2; ulcer size >10 cm in widest diameter. Wounds not present for >30 days despite appropriate wound care prior to entry</p> <p><i>Clinical hx/pt characteristics (SNaP grp; VAC grp):</i> Mean age (yrs): 65.8; 65.1 % men: 48.4%; 63.2% % smoker: 17.2%; 7.4% Wound etiology: NR Wound location: NR Mean wound age (wks): 68.8 Mean wound size (cm²): 9.95 Infection status (%): NR Wound prep prior to study txs: Debridement in both grps</p> | <p>Tx setting: 17 outpatient clinics</p> <p>NPWT tx: SNaP (Smart Negative Pressure) Wound Care System; brand – Spiracur (portable); dressing type – NR; recommended changing interval – NR; suction and pressure setting (mmHg) – continuous; reusable – no; instillation system – NR; duration of use (wks) – NR</p> <p>Comparator tx: VAC tx system; brand – KCI, ActiV.A.C. and V.A.C. models (portable); dressing type – NR; recommended changing interval – NR; suction and pressure (mmHg) – NR; reusable – NR; instillation system – NR; duration of use – NR</p> <p><i>Outcome measures:</i> Complete wound healing by secondary intention</p> | <p><i>Clinical outcomes (SNaP grp; VAC grp) (% pts):</i> Complete wound healing: 4 wks: 9.2%; 5.3%</p> <p><i>Patient-centered outcomes:</i> <u>Pain – exit interview responses (n=53):</u> The authors report no significant difference between the grps for perceived pain associated with tx. Pain was measured against an expected sum; the authors do not explain how the expected sum was determined. <u>Able to work and do normal activities while being treated with NPWT device:</u> VAC grp % agree + strongly agree: 48.1% + 9.6% = 57.7% SNaP grp % agree + strongly agree: 43.4% + 35.9 = 79.3%</p> <p><u>Return to prior level of functional activity – exit interview response (n=53; VAC grp vs SNaP grp) (% pts):</u> Less active: 17.0% vs 51.9% More active: 11.3% vs 3.9% Stayed the same: 71.7% vs 44.2% Fisher’s exact test P<0.05</p> <p><u>Able to work – exit interview response (n=53; VAC grp vs SNaP grp):</u> Agree: 43.4% vs 48.1% Disagree: 5.7% vs 21.2% Neutral: 13.2% vs 13.5%</p> | <p><i>Limitations:</i> Potentially meaningful differences in wound size between grps at baseline; the utilization of 2 different V.A.C. (KCI) systems in the comparison grp without presenting separate analyses for each device; differential tx between grps with respect to personnel who changed wound dressings, and pt outcome data were obtained from an exit interview and subject to recall and attrition bias, as well as the potential for bias because of the lack of blinding to which device was used.</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> Sponsored through a grant from Spiracur Inc. In addition, 2 investigators have reported receiving research funding from both Spiracur Inc. and K.C.I.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|---|---|--|---|
| | | | <p>Strongly agree: 35.9% vs 9.6% Strongly disagree: 1.9% vs 7.7%</p> <p><i>Complications (SNaP grp; VAC grp) (# pts) (% pts):</i> Infection: 5 (7.4%); 2 (3.1%) Pain: 4 (5.9%); 1 (1.6%)</p> | |
| <p>Yao et al. (2012) Center for Restorative Medicine, Boston Medical Center; Boston University School of Medicine; Boston, MA Cohort study F/u: 8 yrs Time frame: 2002-2010 Funding source: NR</p> | <p>n=342 pts NPWT: n=171 Control: n=171 <i>Inclusion criteria:</i> Arterial ulcers; DFUs; PUs or pressure sores; venous ulcers <i>Exclusion criteria:</i> Aged <18 years; HIV positive; sickle cell disease; traumatic and burns ulcers; active malignancy with chemotherapy <i>Clinical hx/pt characteristics (NPWT grp; Control grp):</i> Mean age (yrs): 60.8; 61.3 % men: 57.9%; 57.9% % smoker: 40.6%; 34.5% Wound etiology (% pts): DM: 81.8%; 69.4% Pressure: 13.45%; 10.1% Venous: 8.8%; 10.6% Arterial: 66.7%; 34.9% Wound location (% pts): Leg: 15.7%; 29.2% Foot: 84.21%; 70.76% Mean wound age (wks): NR Mean wound size (cm²): NR</p> | <p>Tx setting: continuum of care settings (real world) NPWT tx: Model – NR; brand – KCl; dressing type – NR; recommended changing interval – NR; suction and pressure setting (mmHg) – NR; reusable – no; instillation system – NR; duration of use (wks) – ≥1 Comparator tx: NR; brand – NA; dressing type – NR; recommended changing interval – NA; suction and pressure (mmHg) – NA; reusable – NA; instillation system – NA; duration of use – NA <i>Outcome measures:</i> Complete wound healing by secondary intention (arterial, diabetic, pressure, venous stasis)</p> | <p><i>Clinical outcomes (NPWT grp; Control grp):</i> Complete wound healing: Arterial ulcers (person yrs): 99.54; 102.89 Arterial ulcers (event rate/100 person yrs): 78.36 (95% CI, 62.56-97.83); 35.96 (95% CI, 26.05-49.63) Arterial ulcers (unadjusted HR): 2.33 (95% CI 1.57-3.48) Arterial ulcers (adjusted HR): 2.27 (95% CI, 1.56-3.78) Diabetic ulcers (person yrs): 112.01; 205.65 Diabetic ulcers (event rate/100 person yrs): 83.92 (95% CI, 68.56-102.72); 38.9 (95% CI, 31.25-48.43) Diabetic ulcers (unadjusted HR): 2.38 (95% CI, 1.75-3.23) Diabetic ulcers (adjusted HR): 3.26 (95% CI, 2.21-4.83) PUs (person yrs): 11.96; 16.77 PUs (event rate/100 person yrs): 142.14 (95% CI, 88.36-228.65); 77.52 (95% CI, 45.01-133.51) PUs (unadjusted HR): 2.19 (95% CI, 1.03-4.66) PUs (adjusted HR): 1.72 (95% CI, 0.43-6.95) Venous stasis ulcers (person yrs): 7.79; 30.69 Venous stasis ulcers (event rate/100 person yrs): 154.04 (95% CI, 87.48-271.24); 46.62 (95%</p> | <p><i>Limitations:</i> Poor reporting of outcomes, potentially meaningful differences between grps at baseline. <i>Study quality:</i> Fair <i>Conflicts of interest:</i> NR</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|---|---|---|---|
| | Infection status (%): 79.5%; 91.9% Wound prep prior to study txs: NR; NA | | CI, 27.02-77.03) Venous stasis ulcers (unadjusted HR): 4.90 (95% CI, 1.72-13.59) Venous stasis ulcers (adjusted HR): 6.31 (95% CI, 1.49-26.6) All ulcers (person yrs): 131.47; 274.36 All ulcers (event rate/100 person yrs): 90.51 (95% CI, 75.63-108.32); 43.01 (95% CI, 35.91-51.51) All ulcers (unadjusted HR): 2.25 (95% CI, 1.73-3.96) All ulcers (adjusted HR): 2.63 (95% CI, 1.87-3.70) Grade I ulcers (person yrs): 56.61; 77.41 Grade I ulcers (event rate/100 person yrs): 107.95 (95% CI, 83.99-138.74); 65.88 (95% CI, 50.07-86.69) Grade I ulcers (unadjusted HR): NR Grade I ulcers (adjusted HR): NR Grade II ulcers (person yrs): 74.96; 194.41 Grade II ulcers (event rate/100 person yrs): 77.96 (95% CI, 59.81-100.08); 33.43 (95% CI, 26.22-42.63) Grade II ulcers (unadjusted HR): NR Grade II ulcers (adjusted HR): NR | |
| Driver and Blume (2014) Veterans Affairs New England Health Care Division, Providence, RI Post-hoc retrospective medical records review of | n=324 pts NPWT: n=162 AMWT: n=162 <i>Inclusion criteria:</i> See Blume et al. (2008) | Tx setting: See Blume et al. (2008); proportion of inpatient/outpatient days were not reported for the cost analysis population NPWT: See Blume et al. | <i>Results:</i> Avg cost per pt regardless of wound closure: \$11,984 for NPWT and \$13,557 for AMWT Pts who achieved wound closure, avg cost: \$10,172 for NPWT and \$9505 for AMWT | <i>Limitations:</i> Post-hoc retrospective analysis; also see Blume et al. (2008) for assessment of original RCT. |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
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| <p>pts enrolled in an RCT for cost analysis (pts were enrolled in the Blume et al. [2008] article cited above)</p> <p>F/u: 112 days</p> <p>Timeframe: NR</p> <p>Funding source: NR</p> | <p><i>Exclusion criteria:</i> See Blume et al. (2008); also pts with missing data for hospitalizations during which a split- or full-thickness skin graft or flap was performed were excluded from the cost analysis (n=7 NPWT; n=4 AMWT)</p> <p><i>Clinical hx/pt characteristics (NPWT grp, AMWT grp):</i> Mean ± SD age (yrs): 58±12; 59±12 % men: 84%; 74% % smoker: 20.4%; 19.8% Wound etiology: DM Wound location: Foot Mean wound age (days): NR Mean wound size (cm²): NR Infection status (%): NR Wound prep prior to study txs: All debridement within 2 days to random allocation per study protocol</p> | <p>(2008) AMWT: See Blume et al. (2008)</p> <p><i>Economic analysis:</i> Wound tx costs: Dressings or the NPWT system, and labor during dressing changes</p> <p>Nonwound tx costs: Concomitant antibiotic tx, acute inpatient services (including acute care hospitalizations and wound-related surgical procedures performed in an acute care facility), extended care hospitalizations (i.e., stays in skilled nursing facilities, rehabilitation clinics, or hospice), and outpatient surgical procedures</p> <p>Costs were calculated from pts' healthcare utilization, including hospital costs (Healthcare Cost and Utilization Project Nationwide Inpatient Sample), physical services for surgical procedures (Medicare Resource-Based Relative Value Scale 2007), and extended-care facility cost per day (Medicare reimbursement rate).</p> | <p>Pts who did not achieve wound closure, avg cost: \$13,262 for NPWT and \$15,068 for AMWT</p> <p>Non-wound tx costs were higher for pts undergoing AMWT than NPWT.</p> <p>Pts who achieved wound closure, avg non-wound tx cost: \$10,716 for NPWT and \$13,525 for AMWT</p> <p>Pts who did not achieve wound closure, avg non-wound tx cost: \$13,694 for NPWT and \$17,927 for AMWT</p> | |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
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| <p>Law et al. (2015) Claims data assessed by KCI and Optum Life Sciences Retrospective claims database analysis F/u: NR Time frame: Claim submitted between January 2009 and June 2012 Funding source: Study sponsored by KCI</p> | <p>n=13,556 pts with chronic (81%) or acute wounds NPWT-V: n=12,843 NPWT-O: n=713 <i>Inclusion criteria:</i> ≥1 NPWT claims during time frame in outpatient setting in U.S. from an insurance company; had continuous medical and pharmacy benefits at least 12 mos before index tx and 3 mos post-tx <i>Exclusion criteria:</i> NR <i>Clinical hx/pt characteristics (NPWT-V grp; NPWT-O grp):</i> Mean age (yrs): 59; 64 % men: 48%; 48% % smoker: NR Wound etiology: NR Wound location: NR Mean wound age (wks): NR Mean wound size (cm²): NR Infection status (%): NR Wound prep prior to study txs: NR</p> | <p>Tx setting: Outpatient NPWT-V: NPWT with VAC (KCI). No information about administration available. NPWT-O: NPWT with all other models from other manufacturers. No other information available. <i>Outcome measures:</i> Readmission; inpatient stays; ER visits</p> | <p><i>Economic analysis</i> NPWT with V.A.C. (KCI) (n=12,843 at 3 mos, n=7860 at 12 mos) was compared with non-KCI model NPWT devices (n=713 at 3 mos, n=378 at 12 mos) At 3 mos: Per-pt cost for NPWT with V.A.C.: \$35,498 [\$4224 (11%) lower than NPWT with other devices, (P=0.08)] Per-pt cost for non-KCI models: \$39,722. At 12 months: Per-pt cost for NPWT with V.A.C.: \$80,768 (\$30,444 [27%] lower than NPWT with other devices, [P=0.03]) Per-pt costs for non-KCI models: \$111,212 <i>Complications (NPWT-V grp, NPWT-O grp) (# pts) (% pts):</i> Readmission, any, 3 mos: 2954 (23%), 221 (31%) Readmission, wound-related, 3 mos: 642 (5%), 57 (8%) Readmission, any, 6 mos: 3433 (31%); 258 (43%) Readmission, wound-related, 6 mos: 664 (6%); 66 (11%) Inpatient stay, 3 mos: All, wound-related: 64 (0.5%), 8 (1.1%); P<0.0001 Nonhealing surgical: 51 (0.4%), 4 (0.6%); P=0.14 Open: 51 (0.4%), 9 (1.2%); P=0.03 PU: 128 (1.0%), 15 (2.1%); P=0.002</p> | <p><i>Limitations:</i> Retrospective analysis; heterogeneous pt population and separate analyses were provided for only some of the included wound types; potentially meaningful baseline differences in 3-mo analysis grp and patient demographic results were not presented for 6- and 12-mo populations; methods state that data were analyzed at 12 mos, but results were not provided; different grp sizes; methods do not indicate that analyses were adjusted to control for confounding variables. <i>Study quality:</i> Poor (for adverse events) <i>Conflicts of interest:</i> Lead author employee of KCI; other 2 authors paid consultants of KCI.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
|---|--|---|---|---|
| | | | <p>Inpatient stay, 6 mos: All, wound-related: 89 (0.8%), 102 (1.7%); $P<0.0001$ Nonhealing surgical: 55 (0.5%), 5 (0.8%); $P=0.13$ Open: 66 (0.6%), 9 (1.5%); $P=0.04$ PU: 188 (1.7%), 20 (3.3%); $P=0.01$</p> <p>ER visit, 3 mos: All, wound-related: 13 (0.1%), 4 (0.6%); $P<0.0001$ Nonhealing surgical: 13 (0.1%), 4 (0.5%); $P=0.0007$ Open: 13 (0.1%), 8 (1.2%); $P=0.0005$ PU: 51 (0.4%), 5 (0.7%); $P=0.11$</p> <p>ER visit, 6 mos: All, wound-related: 22 (0.2%), 5 (0.9%); $P<0.0001$ Nonhealing surgical: 11 (0.1%), 4 (0.7%); $P=0.002$ Open: 11 (0.1%), 10 (1.6%); $P=0.0001$ PU: 66 (0.6%), 7 (1.1%); $P=0.16$</p> | |
| <p>Marston et al. (2015) University of North Carolina, Chapel Hill, NC</p> <p>Multicenter RCT; subanalysis of Armstrong et al. (2012), assessing VLU pts who had 16 wks of tx or healing recruited from 13 sites in the U.S.</p> <p>F/u: 16 wks</p> | <p>n=40 pts</p> <p>SNaP: n=19 VAC: n=21</p> <p><i>Inclusion criteria (for full study population):</i> DFUs; lower extremity venous ulcers; in location amenable to creation of airtight seal using study dressings; adequate blood perfusion</p> <p><i>Exclusion criteria:</i> Aged <18 yrs;</p> | <p>Tx setting: Outpatient</p> <p>SNaP: Mechanically powered SNaP (Smart Negative Pressure) Wound Care System; brand – Spiracur (portable); mechanically powered; dressing type – gauze; recommended changing interval – every 3 days; suction and pressure setting (mmHg) – NR; reusable – no; instillation</p> | <p><i>Clinical outcomes (SNaP grp; VAC grp):</i> Complete wound healing: Data NR, but authors reported no significant difference in healing rates among study completers between grps whether or not adjusted for baseline wound size. (Data on this outcome for a larger population appear to have been reported in Armstrong et al. [2012].)</p> <p><i>Complications (SNaP grp; VAC grp) (# pts) (% pts):</i> Infection: 1 (5%); 2 (10%) (infection also</p> | <p><i>Limitations:</i> In addition to the limitations of the main study, this subanalysis is limited by having conducted a completers analysis; it is unclear whether this was a pre-planned analysis or post-hoc analysis.</p> <p><i>Study quality:</i> See Armstrong (2012)</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
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| <p><i>Time frame:</i> July 2009 – March 2011 (according to ClinicalTrials.gov database)</p> <p><i>Funding source:</i> Industry (Spiracur Inc., manufacturer of the SNaP device)</p> | <p>ulcer size <1 cm²; ulcer size >100 cm²; clinical infection; ankle/brachial index <0.7 or >1.2; ulcer size >10 cm in widest diameter; wounds not present for >30 days despite appropriate wound care prior to entry; active infection; untreated osteomyelitis; pregnancy; allergies to study materials; cause of wound included cancer, burn, collagen vascular disease, sickle cell, vasculopathy or pyoderma gangrenosum; active Charcot arthropathy; on renal dialysis; active chemotherapy; previous tx with NPWT, growth factors, hyperbaric oxygen, or bioengineered tissue product within 30 days of enrollment; >30% reduction in wound surface area during wk prior to enrollment</p> <p><i>Clinical hx/pt characteristics (SNaP grp; VAC grp):</i> Mean age (yrs): 67.5; 66.8 % men: 42%; 52% % smoker: 21%; 10% Wound etiology: Diabetic venous ulcers, per inclusion criteria Wound location: Foot, per inclusion criteria Mean wound age (days): <30, per inclusion criteria Mean (SD) wound size (cm²): 4.85</p> | <p>system – NR; duration of use (weeks) – NR</p> <p>VAC: Electrically powered VAC tx system; brand – KCI, ActiV.A.C. and V.A.C. models (portable); dressing type – foam; recommended changing interval – every 2 days; suction and pressure (mmHg) – NR; reusable – pump device is reusable; instillation system – NR; duration of use - NR</p> <p><i>Outcome measures (SNaP grp; VAC grp):</i> Complete wound healing by secondary intention</p> | <p>reported in Armstrong et al. [2011] among more pts) Maceration: 3 (16%); 3 (14%) Allergic reaction to dressing: 1 (5%); 3 (14%) Pain: 1 (5%); 3 (14%) Blisters: 3 (16%); 2 (10%) Other: 2 (11%); 2 (10%) The authors wrote that these were not significantly different between grps and were similar to the total pt pool in Armstrong et al. (2012).</p> | <p><i>Conflicts of interest:</i> This study was sponsored by a grant from Spiracur Inc., manufacturer of the SNaP device. Two authors have received research funding from both Spiracur and K.C.I.</p> |

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
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| | (± 4.49); 11.60 (± 12.12) Infection status (%): NR Wound prep prior to study txs: Debridement in both grps | | | |

APPENDIX Vb

STUDIES OF SURGICAL WOUNDS

Key: BPI, Brief Pain Inventory; EQ-5D, European Quality of Life-5 Dimensions; f/u, follow-up; grp(s), group(s); HbA1c, hemoglobin A1c; hx, history; IQR, interquartile range; mmHg, milliliter of Mercury; NPWT, negative pressure wound therapy; NR, not reported; prep, preparation; pt(s), patient(s); RCT, randomized controlled trial; RR, risk ratio; tx, treatment (or therapy); VAS, visual analog scale

| Authors/Study Design | Study Population | Treatment | Results | Quality/Comments |
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| <p>Armstrong et al. (2005) Apelqvist et al. (2008) Scholl’s Center for Lower Extremity Ambulatory Research (CLEAR), Rosalind Franklin University of Medicine and Science; Chicago, IL RCT (multicenter, n=18) F/u: 16 wks (112 days) Time frame: NR Funding source: Kinetic Concepts Inc.</p> | <p>n=162 NPWT: n=77 Standard tx: n=85 <i>Inclusion criteria:</i> Aged ≥18 years; wound from diabetic foot amputation to the transmetatarsal level; adequate perfusion; all wound correspond to University of Texas grade 2 or 3 depth <i>Exclusion criteria:</i> Active Charcot arthropathy of the foot; wounds resulting from burns; venous insufficiency; untreated cellulitis or osteomyelitis (after amputation); collagen vascular disease; malignant</p> | <p>Tx setting: Inpatient and home care; 89.1% of days were home care, 10.9% were inpatient (Apelqvist et al., 2008); % for each grp NR NPWT: VAC system (KCI); electrically powered; dressing type NR; recommended changing interval – changes of VAC dressings were performed every 48 hrs; suction and pressure setting (mmHg) – NR; reusable – NR; instillation system – NR; duration of use (wks) – NR Standard tx: Dressing type – moist wound tx with alginates, hydrocolloids, foams, or hydrogels; recommended changing interval – changed every day unless otherwise recommended by treating clinician; duration of use (wks) – NR All pts received off-loading tx as indicated</p> | <p><i>Clinical outcomes (NPWT grp, Standard tx grp):</i> Proportion of wounds healed: 43 (56%), 33 (39%); P=0.04; difference in proportions = 0.1702 (95% asymptotic CI, 0.0184-0.322) Healed by secondary intention: 31 (40%), 25 (30%); P=NR Healed wounds after surgical closure: 12 (16%), 8 (9%); P=0.244 Time to complete wound healing (median [IQR]): 56 days (26-92), 77 (40-112) P=0.005 <i>Patient-centered outcomes:</i> NR <i>Complications (NPWT; Standard tx):</i> Second amputation: 2 (3%), 9 (11%); P=0.060; RR 0.225 (95% CI, 0.05-1.1); 5 (6%) of standard tx grp received high-level (above foot) amputation—2 above knee, 3 below knee; no high-level amputations were done in the NPWT grp Infections and infestations: 25 (32%), 27 (32%); P=1.000 Wound infection: 13 (17%), 5 (6%)</p> | <p><i>Limitations:</i> Use of different wound dressings in the comparison grp based on provider discretion and potential for bias in tx/assessment decisions due to lack of blinding of providers and outcome assessors to tx. <i>Study quality:</i> Fair <i>Conflicts of interest:</i> Authors received research funding and are members of the speaker’s bureau for KCI, the manufacturer of the device used in the study.</p> |

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| | <p>disease in the wound or uncontrolled hyperglycemia (HbA1c >12%)</p> <p><i>Clinical hx/pt characteristics (NPWT grp, standard tx grp):</i> Mean (SD) age (yrs): 57.2 (13.4), 60.1 (12.3), 59 (12.8) overall</p> <p>% men: 86%, 78%</p> <p>% currently use tobacco: 5%, 13%</p> <p>Wound etiology: Diabetic foot amputation</p> <p>Wound location: Foot</p> <p>Mean (SD) wound age (mos): 1.2 (3.9), 1.8 (5.9)</p> <p>Mean (SD) wound size (cm²): 22.3 (23.4), 19.2 (17.6)</p> <p>Infection status (%):</p> | <p><i>Outcome measures:</i> <u>Primary outcome:</u> Proportion of wounds with complete closure (100% epithelialization without drainage assessed based on data from wound assessments and photographs taken by treating clinician)</p> <p><u>Secondary outcomes:</u> Rates of wound healing or facilitation of surgical wound closure; foot salvage; tx related complications</p> <p><u>Economic analysis:</u> The analysis included inpatient stays for acute care, extended care, and other inpatient hospital care initiated or caused by foot lesion during the study. Costs estimates for surgical procedures are based on the minimum commercial fee according to Medicare and include only those costs accumulated during the 112-day study period. Costs for oral and systemic antibiotics were calculated using duration of treatment and number of courses. Outpatient treatment visits included clinic visits and visits to patients' homes. The cost per visit included estimated cost for personnel time and estimated cost of a clinic visit. Topical wound dressing costs were based on average use of primary topical treatments. Calculations for these</p> | <p>In the NPWT grp, 3 infections were classified as mild, 6 as moderate, 4 as severe; none were deemed related to tx. In the Standard tx group, 2 were classified as mild, 1 as moderate, and 2 as severe; 2 of the 5 events were deemed to be related to the tx, 1 of which was serious.</p> <p>Tx-related adverse events: 9 (12%), 11 (13%). One event in the NPWT was classified as serious; 5 events in the Standard tx grp were classified as serious.</p> <p><i>Cost analysis results (NPWT grp, Standard tx grp):</i> Avg direct cost per pt treated for 8 wks or longer (regardless of clinical outcome): \$27,270, \$36,096 Avg total cost to achieve healing: \$25,954 (n=43); \$38,806 (n=33)</p> | |

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| | <p>NR</p> <p>Wound prep prior to study txs: Amputation to transmetatarsal level foot</p> | <p>costs included actual number of dressing changes, estimated material costs based on primary dressing material, estimated time for each dressing change, and cost per hour of personnel performing the dressing change. Dressing changes done by patients or family members were treated separately.</p> | | |
| <p>Biter (2014) Sint Franciscus Gasthuis, Rotterdam, The Netherlands</p> <p>RCT</p> <p>F/u: 6 mos</p> <p>Time frame: Surgery occurred between October 2009 and May 2012</p> <p>Funding source: NR, but authors noted no financial disclosures</p> | <p>n=49</p> <p>NPWT: n=24 Dressing: n=25</p> <p>Does not include 4 early terminations (see <i>Complications</i>) or 2 losses to f/u after completion of 2-wk examination</p> <p><i>Inclusion criteria:</i> Symptomatic pilonidal sinus with or without a previous abscess of the sinus</p> <p><i>Exclusion criteria:</i> Aged <16 yrs; previous attempt at surgical excision of pilonidal disease; inability to undergo frequent f/u; pilonidal sinus</p> | <p>Tx setting: Outpatient</p> <p>NPWT: Brand NR; NR if powered; dressing type – open-pore foam covered by adhesive semipermeable dressing; recommended changing interval – sponge replaced at 3, 7, 10 days postsurgery; suction and pressure setting (mmHg) – 125; reusable – NR; instillation system – NR; duration of use – 14 days</p> <p>Silicone dressing: Dressing type – silicone wound dressing applied to wound and topped with absorbent bandage; recommended changing interval – pts advised to rinse wound 3x daily for 2 wks after excision; duration of use (wks) – NR. Special dressings applied only if the wound appeared sloughy and/or retained pus.</p> <p>All: Same pre-wound care surgical technique. For pain, paracetamol or if necessary nonsteroidal anti-</p> | <p><i>Clinical outcomes (NPWT grp; Silicone dressing grp):</i> Time to complete wound healing (median) (range) (days): 84 (34-349), 93 (43-264); $P=0.44$</p> <p>Wound volume (cm³): Day of surgery: 60, 56 ($P=0.61$) 14 days later: 24, 40 ($P=0.10$)</p> <p>Wound size reduction (ratio): 0.30; 0.57 ($P=0.02$)</p> <p>Recurrence <6 mos after wound closure (# pts) (% pts): 3 (13%); 1 (4%) ($P=0.30$)</p> <p><i>Patient-centered outcomes (NPWT grp n=24; Silicone dressing grp n=25):</i> <u>Pain (median):</u> Day of surgery: 1.5; 1.7 ($P=0.24$) 14 days after surgery: 2.2; 2.5 ($P=0.29$) <u>Walk without pain (14 days):</u> 16 (67%); 21 (84%) ($P=0.13$) <u>Sit without pain (14 days):</u> 12 (50%); 14 (56%) ($P=0.67$) <u>Time to return to work or school (days) (median) (range):</u> 27 (7-126); 29 (6-63) ($P=0.92$) None of the pt-oriented outcomes was</p> | <p><i>Limitations:</i> No power calculations reported and unclear data analysis methods for primary outcome.</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> The authors reported no conflicts of interest.</p> |

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| | <p>situated <3 cm from anus</p> <p><i>Clinical hx/pt characteristics (NPWT grp; Silicone dressing grp):</i> Median age (range) (yrs): 23 (16-44); 29 (16-65)</p> <p>% men: 75%; 92%</p> <p>% smoker: 25%; 24%</p> <p>Wound etiology: Pilonidal sinus disease</p> <p>Wound location: Pilonidal sinus (cleft at top of buttocks)</p> <p>Mean wound age (wks): NR</p> <p>Mean wound size (cm²): NR. cm³: 60; 56 (P=0.61)</p> <p>Infection status (%): NR</p> <p>Wound prep prior to study txs: Surgical excision</p> | <p>inflammatory drugs recommended.</p> <p><i>Outcome measures:</i> Time to achieve wound healing (days until full skin closure); wound infection (pain and redness of the wound); pain (mean score on VAS); time to return to daily activities such as work or school</p> | <p>statistically significantly different between grps.</p> <p><i>Complications (NPWT grp; Silicone dressing grp):</i> Wound infection/abscess (# pts) (% pts): 2 (8%), 2 (8%) (P=1.00)</p> <p>Early termination of NPWT: 4 (17% of 24 randomly allocated): Due to pain (n=2), bad odor (n=1), or unspecified "practical considerations" (n=1)</p> <p>Any "concerns": 16 (67%), 19 (76%)</p> | |

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| <p>Monsen et al. (2014) Monsen et al. (2015) Acosta et al. (2013) Vascular Center, Malmo-Lund, Skane University Hospital; Malmo and Lund, Sweden RCT F/u: Median 14 mos Time frame: February 13, 2007 – November 24, 2011 Funding source: NR</p> | <p>n=20 NPWT: n=10 Dressing: n=10 Does not include 4 additional randomized pts who were excluded from time to wound healing outcome due to skin transplantation (n=1 from NPWT grp), secondary skin closure (n=1 from Dressing grp) or death prior to healed wound (n=2 from Dressing grp)</p> <p><i>Inclusion criteria:</i> Deep perivascular groin infections (Szilagyi grade III) that occurred after arterial surgery</p> <p><i>Clinical hx/pt characteristics (NPWT grp, Dressing grp):</i> Mean Age (yrs): 71; 73</p> | <p>Tx setting: Hospital as long as graft material or native artery was visible, then outpatient</p> <p>NPWT: VAC system (KCI); electrically powered; dressing type – silicone-based (Mepitel; Mölnycke Health Care AB); recommended changing interval – changes of VAC dressings were performed 3x/wk; suction and pressure setting (mmHg) – 125; reusable – pump is reusable; instillation system – NR; duration of use (wks) – NR</p> <p>Dressing: Dressing type –Alginate dressing (Sorbalgon [Hartmann ScandiCare AB], Anderstorp or Melgisorb [Mölnycke Health Care AB]); recommended changing interval – as often as indicated clinically; duration of use (wks) – NR</p> <p>All pts received the same debridement prior to wound tx of either type</p> <p><i>Outcome measure:</i> Time to complete wound healing; EQ-5D; BPI; quality of life; adverse events</p> | <p><i>Clinical outcomes (NPWT grp; Dressing grp):</i> Time to complete wound healing (median (range) (days): 57 (25-115) (for n=9); 104 (57-175) (for n=7); P=0.026</p> <p>Tx failure (visible graft material or femoral artery after 1 mo of tx or amputation or death due to groin infection) (# pts) (% pts): 1 (10%), 5 (50%)</p> <p><i>Patient-centered outcomes:</i> <u>Quality of Life, EQ-5D (NPWT grp n=6 with healed wound; Dressing grp n=6 with healed wound) (Monsen et al., 2015):</u> EQ-D – Index: 0.69 (0.30-0.80), 0.66 (0.52-0.86); P=NS EQ-5D – VAS (median [q1-q3]): 70 (63.75-750), 55 (35-85.5) Neither scale was statistically significantly different between grps either before or after tx. <u>Pain, BPI (NPWT grp n=9 after 4 weeks; Dressing grp n=8 after 4 weeks) (Monsen 2015):</u> No statistically significant differences between groups before or after tx. Overall summary scores NR.</p> <p><i>Complications (NPWT grp; Dressing grp):</i> Amputation: 3 (30%), 2 (20%) In NPWT grp, 3 transfemoral amputations due to groin infection (n=2) or worsening of critical limb ischemia (n=1). In Dressing grp, 1 underwent transfemoral amputation due to groin infection and 1 underwent metatarsal amputation because of</p> | <p><i>Limitations:</i> Possible selection bias during recruitment; lack of adequate randomization technique; unclear method for calculating time to wound healing; use of different types of alginate dressings in comparison grp; unclear mean length of f/u in each grp.</p> <p><i>Study quality:</i> Fair</p> <p><i>Conflicts of interest:</i> The authors report no conflicts of interest.</p> |

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| | <p>% men: 80%, 50%</p> <p>% smoker: NR</p> <p>Wound etiology: Arterial surgery, per inclusion criteria</p> <p>Wound location: Groin, per inclusion criteria</p> <p>Wound age (wks): Time of index procedure to randomization, median 16 days each grp</p> <p>Wound size (median) (range) (cm²): 13 (7.6-37.6); 20.5 (4.6-44.5)</p> <p>Infection status: All, per inclusion criteria</p> <p>Wound prep prior to study txs: All had debridement, per inclusion criteria</p> | | <p>worsening of critical limb ischemia.</p> <p>Mortality, in-hospital: 0, 1 (10%) 1 pt in Dressing grp died during hospital stay. Mortality, total: 2 (20%), 5 (50%) by end of f/u (P=0.35)</p> <p>In an “early interim analysis” (Acosta et al., 2013), adverse events were reported at median 29.5 mos (range 4-51) for the first 5 pts enrolled in each grp (NPWT grp n=5 with healed wound; Dressing grp n=5 with healed wound). Tx failures: 1 (due to re-bleeding); 3 (2 failures to heal within 2 mos, 1 visible interposition bypass graft in the groin after 1-mo tx requiring wound closure with sutures) Erysipelas of groin, late: 1, 0</p> | |

APPENDIX VI

SUMMARY OF PRACTICE GUIDELINES

Key: FDA, Food and Drug Administration; NPWT, negative pressure wound therapy; PU, pressure ulcer

| Sponsor, Title | Relevant Recommendations | Quality*/Main Limitations |
|---|--|---|
| <p>International Expert Panel on Negative Pressure Wound Therapy (NPWT-EP) (Vig et al., 2011)</p> <p><i>Evidence-based recommendations for the use of NPWT in chronic wounds: steps towards an international consensus</i></p> | <ul style="list-style-type: none"> ● Pressure ulcers <ul style="list-style-type: none"> ○ NPWT may be used until surgical closure is possible/desirable. ○ Alternatively, NPWT should be considered to achieve closure by secondary intention. ○ NPWT should be used to reduce wound dimensions. ○ NPWT should be used to improve the quality of the wound bed. ● Diabetic foot ulcers <ul style="list-style-type: none"> ○ NPWT must be considered as an advanced wound care therapy for postoperative Texas grade 2 and 3 diabetic feet without ischemia. ○ NPWT must be considered to achieve healing by secondary intention. ○ Alternatively, NPWT should be stopped when wound has progressed suitably to be closed by surgical means. ○ NPWT should be considered in an attempt to prevent amputation or re-amputation. ● Ischemic lower limb wounds <ul style="list-style-type: none"> ○ The cautious use of NPWT in chronic limb ischemia when all other modalities have failed may be considered in specialist hands but never as an alternative for revascularization. ○ NPWT may be considered as an advanced wound care therapy for lower limb ulceration after revascularization. ○ The use of NPWT is NOT indicated in acute limb ischemia. ● VLUs <ul style="list-style-type: none"> ○ If first-line therapy (compression) is not efficacious, NPWT should be considered to prepare the wound for surgical closure as part of a clinical pathway. ○ Use of gauze may be considered to reduce pain during dressing changes in susceptible patients. | <p>5.3 – Fair (more discussion of the strengths and limitations of body of evidence needed; the expert panel, literature review, and guideline development and writing was funded and lead by Smith and Nephew, membership in the Expert Panel is not described; authors state that the manuscript was not unfairly influenced by the funder and that the recommendations reflect the independent and unbiased views of the expert panel)</p> |

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| <p>Association for the Advancement of Wound Care (AAWC, 2010)</p> <p><i>Association for the Advancement of Wound Care (AAWC) Guideline of Pressure Ulcer Guidelines</i></p> | <p>D. ADVANCED OR ADJUNCTIVE INTERVENTIONS IF PU IS UNRESPONSIVE TO A-LEVEL MANAGEMENT</p> <p>3. Negative Pressure Wound Therapy—No consistent effect on PU healing. Increased granulation, less fibrin compared to Redon drain, earlier use may shorten home care stays. Lower cost than gauze. The FDA has advised caution in selecting patients for this therapy due to serious, occasionally fatal, complications. Please read the FDA notice at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm190658.htm</p> | <p>4.0—Fair (criteria for selecting evidence not described, methods for formulating recommendations not described, guideline review and update process not described)</p> |
| <p>National Pressure Ulcer Advisory Panel (NPUAP, 2014)</p> <p><i>Treatment of pressure ulcers. In: Prevention and treatment of pressure ulcers: clinical practice guideline</i></p> | <p>Negative Pressure Wound Therapy</p> <ol style="list-style-type: none"> 1. Consider negative pressure wound therapy (NPWT) as an early adjuvant for the treatment of deep, Category/Stage III and IV pressure ulcers. (Strength of Evidence = B; Strength of Recommendation = Weak positive recommendation) <p><i>Caution: NPWT is not recommended in inadequately debrided, necrotic or malignant wounds; where vital organs are exposed; in wounds with no exudate; or in individuals with untreated coagulopathy, osteomyelitis or local or systemic clinical infection. Cautious use by an experienced health professional is recommended for individuals on anticoagulant therapy; in actively bleeding wounds; or where the wound is in close proximity to major blood vessels.</i></p> <ol style="list-style-type: none"> 2. Debride the pressure ulcer of necrotic tissue prior to the use of NPWT. (Strength of Evidence = C; Strength of Recommendation = Strong positive recommendation) 3. Follow a safe regimen in applying and removing the NPWT system. (Strength of Evidence = C; Strength of Recommendation = Strong positive recommendation) 4. Evaluate the pressure ulcer with each dressing change. (Strength of Evidence = C; Strength of Recommendation = Weak positive recommendation) 5. If pain is anticipated or reported consider: <ol style="list-style-type: none"> 1. Placing a nonadherent interface dressing on the wound bed, underneath the foam 2. Lowering the level of pressure, and/or changing type of pressure (continuous or intermittent) 3. Using a moist gauze filler instead of foam (Strength of Evidence = C; Strength of Recommendation = Weak positive recommendation) 6. Educate the individual and his/her significant others about negative pressure wound therapy when used in the community setting. (Strength of Evidence = C; | <p>6.4 – Good (procedure for updating not identified)</p> |

| Sponsor, Title | Relevant Recommendations | Quality*/Main Limitations |
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| | Strength of Recommendation = Strong positive recommendation) | |
| <p>International Working Group on the Diabetic Foot (Game et al., 2016)</p> <p><i>IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes</i></p> | <p>6. Topical negative pressure wound therapy may be considered in postoperative wounds even though the effectiveness and cost-effectiveness of the approach remain to be established. (weak; moderate)</p> <p>It is not possible to make a recommendation on the use of NPWT in nonsurgical wounds because of the lack of available evidence.</p> | <p>6 – Good (unclear if guidelines were reviewed externally by experts, a procedure for updating was not identified)</p> |
| <p>Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) (O'Donnell et al., 2014)</p> <p><i>Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum</i></p> | <p>Guideline 4.24: Negative Pressure Therapy We suggest against routine primary use of negative pressure wound therapy for venous leg ulcers. [GRADE - 2; LEVEL OF EVIDENCE - C]</p> <p>There is currently not enough information to support the primary use of negative pressure wound therapy for VLUs. Evidence supports positive effects with the use of negative pressure therapy for wound healing in general. Tissue granulation, area and volume reduction, and reductions in bioburden have all been reported. There have been few studies specifically studying negative pressure therapy for VLUs, with most studies reporting on mixed wound causes. There has been an increase in the use of negative pressure wound therapy for wound bed preparation to augment skin graft healing.</p> | <p>6.2 – Good (criteria for selecting evidence is not clearly described; need to update I mentioned, but the method for updating was not identified)</p> |

*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on a scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).