



Draft

Negative Pressure

Wound Therapy

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

In 2007 the Oregon Health Resources Commission (HRC) appointed a technology subcommittee to perform evidence-based reviews of medical technologies. Members of the subcommittee for this review consisted of five physicians, and an attorney who serves as the consumer representative. All meetings were held in public with appropriate notice provided. The technologies chosen for review are chosen by the HRC which takes into account stakeholder input when deciding on topics to consider. The HRC utilizes source documents from sources previously approved by the Commission. In conducting the review process and working with our source providers the HRC defines the patient populations of interest, technologies to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence is specifically sought for subgroups

of patients based on race, ethnicity and age, demographics. Using standardized methods, the subcontractors review systematic databases, and the medical literature. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The HRC utilized materials from The National Institute for Clinical Excellence (NICE) The Cochrane Collaboration and AHRQ materials to complete the report, “Negative Pressure Wound Therapy”, May, 2010”. This report was circulated to subcommittee member. The subcommittee met to review the document and this report is the consensus result of those meetings and input from the HRC. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the source documents, the subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. This report may be updated if indicated at the discretion of the Health Resources Commission

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

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There will be a charge for copying and handling in providing hard copy documents from the Office of Oregon Health Policy & Research.

Source Documents

1. *Negative Pressure Wound Therapy*. Technology Assessment. November 2009.

Rockville, MD: Agency for Healthcare Research and Quality.

<http://www.ahrq.gov/clinic/ta/negpresswtd/>

2. *Interventional procedure overview of negative pressure wound therapy for the open abdomen*. NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE INTERVENTIONAL PROCEDURES PROGRAMME, March 2009.

<http://www.nice.org.uk/nicemedia/live/12102/44739/44739.pdf>

3. Wasiaak J, Cleland H. *Topical negative pressure (TNP) for partial thickness burns*. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD006215. DOI: 10.1002/14651858.CD006215.pub2.
4. Ubbink DT, Westerbos SJ, Evans D, Land L, Vermeulen H. *Topical negative pressure for treating chronic wounds*. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD001898. DOI: 10.1002/14651858.CD001898.pub2.
5. *Negative Pressure Wound Therapy for Wound Healing*. Hayes Directory, Hayes Inc. November 9, 2009 (Rescanned without update 2008, 2009, 2010).

Critical Policy

Health Resources Commission

- “Clinical outcomes are the most important indicators of comparative effectiveness”
- “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

Negative pressure wound therapy (NPWT) applies a localized vacuum to draw the edges of the wound together while providing a moist environment conducive to rapid wound healing. The development of negative pressure techniques for wound healing is based on two theories:

- (1) the removal of excess interstitial fluid decreases edema and concentrations of inhibitory factors, and increases local blood flow; and
- (2) stretching and deformation of the tissue by the negative pressure is believed to disturb the extracellular matrix and introduce biochemical responses that promote wound healing.

NPWT systems include a vacuum pump, drainage tubing, and a dressing set. The pump may be stationary or portable, may rely on AC or battery power, allows for regulation of the suction strength, has alarms to indicate loss of suction, and has a replaceable collection canister. The dressing sets may contain either foam or gauze dressing to be placed in the wound and an adhesive film drape for sealing the wound. The drainage tubes come in a variety of configurations depending on the dressings used or wound being treated. NPWT Systems currently available in the U.S. at the time of the review are listed in Table 1.

This report specifically examined the use of NPWT for the treatment of the following wound types: diabetic foot ulcers, pressure ulcers, vascular ulcers (includes venous ulcers and arterial ulcers), burn wounds, surgical wounds (especially infected sternal wounds and open abdominal wounds) and trauma-induced wounds. More than 2.8 million patients in the United States suffer from chronic wounds.⁵ The prevalence of chronic ulcers has been estimated to be 120 per 100,000 patients between the ages of 45 and 64 years; prevalence increases to more than 800 per 100,000 patients over age 75.⁵ Chronic wounds have not completed the process of healing in the expected time frame, usually within 30 days, or have proceeded through the healing phase without establishing the expected functional result.⁶ These wounds usually do not close without interventions, and are sometimes resistant to healing interventions. Diabetic foot ulcers, pressure ulcers or “bed sores,” vascular ulcers, and complications of surgically created sternal wounds

commonly become chronic wounds because their etiologies impede healing and they persist without proper medical care. For the purposes of this review, we consider chronic wounds to be those wounds present for more than 30 days and acute wounds to be those present for less than 30 days. Diabetic foot ulcers, pressure ulcers, venous leg ulcers, and infected sternal wounds are the chronic wounds most often treated with NPWT. Surgical wounds, burn wounds and trauma wounds are the most common acute wounds treated with NPWT.

The studies evaluated NPWT for the following types of wounds:

Classifications:

- Acute: Acute donor sites, abdominal wound closure, excised wounds, degloving injuries, deep abrasions, avulsions, gunshot wounds, eviscerations, nonosseous traumatic injury, amputation, burns.
- Subacute: Dehiscence, infected and uninfected open wounds with exposed orthopedic hardware, post femoral-popliteal bypass inguinal wounds, skin graft failures, and sternotomy infection following coronary artery bypass grafting.
- Chronic: Pressure ulcers, venous stasis ulcers, cystic hidradenitis, and trauma-related and radiation related wounds.

Studies also investigated NPWT in the treatment of high-risk fractures, poststernotomy mediastinitis, and deep sternal wound infection.

Principles of NPWT

In his book on vacuum therapy, published in 2006, Willy¹⁰ lists five mechanisms by which the application of negative pressure to a wound may aid in the healing process:

- 1) Wound retraction
- 2) Stimulation of granulation tissue formation
- 3) Continuous wound cleansing after adequate primary surgical debridement
- 4) Continuous removal of exudate, and
- 5) Reduction of interstitial edema.

Wound retraction under negative pressure brings the edges of the wound closer together while also putting mechanical stress on the tissue. The externally applied stress is thought to create microdeformations in individual cells that induces the production of cellular messengers responsible for increasing matrix synthesis and cell proliferation within the wound.

Increased rates of granulation tissue formation have been noted in studies using NPWT.^{7,8,9} Continuous wound cleansing may reduce the bacterial burden present in a wound⁷ as well as remove substances that inhibit wound healing. However, some studies have noted no change or an increase in the bacterial burden during the use of NPWT that did not affect the healing process.^{11,12} Interstitial fluid (exudate) that accumulates in a wound may mechanically compress local capillaries and restrict blood flow into the wound. Removal of exudate from a wound may reduce tissue edema and promote blood flow back into the wound area.^{7,13,14}

Manufacturers of NPWT devices use different wound dressings. The two most commonly used dressings are foam and moistened cotton gauze.

Table 1. Negative Pressure Wound Therapy Devices Marketed in the U.S.¹

Manufacturer	Trade or Brand Names of Negative Pressure Wound Therapy Devices
Blue Sky Medical Group 6965 El Camino Real, Suite 105-602 La Costa, CA 92009 (Blue Sky Medical Group is now owned by Smith & Nephew, Inc.)	V1STA Negative Wound Therapy (portable unit) EZCARE Negative Wound Therapy (stationary unit)
Boehringer Wound Systems, LLC P.O. Box 910 Norristown, PA 19404	Engenex® Advanced NPWT System (Boehringer Laboratory Suction Pump System) ConvaTec (Skillman, NJ) markets and distributes the Engenex® NPWT system
Innovative Therapies Inc. 10948 Beaver Dam Rd, Suite C Hunt Valley, MD 21030	SVEDMAN™ and SVED™ Wound Treatment Systems
Kalypto Medical 6393 Oakgreen Ave. Hastings, MN 55033 (Iasis Medical, Inc.)	NPD 1000 Negative Pressure Wound Therapy System (no manufacturer information currently available from a Web site)
KCI, USA Inc. (Kinetic Concepts, Inc.) 8023 Vantage Dr. San Antonio, TX 78230	InfoV.A.C.® Therapy Unit (stationary unit) ActiV.A.C.® Therapy Unit (portable unit) V.A.C.® Freedom™ V.A.C.® ATSTM V.A.C.® Instill System (delivery of topical solutions)
Medela AG Medical Equipment Laettichstrasse 4b 6341 Baar Switzerland; Medela Healthcare Medela, Inc. 1101 Corporate Drive McHenry, IL. 60050	Invia Liberty Wound Therapy (portable) Invia Vario 18 c/i Wound Therapy (stationary, mobile with battery)
MediTop BV Vlasakker 22 3417 XT Montfoort The Netherlands; The Medical Company P.O. Box 2116 3800 CC Amersfoort The Netherlands	Exusdex® wound drainage pump
Premco Medical Systems, Inc. 699 Main Street New Rochelle, NY 10801 USA	Prodigy™ NPWT System (PMS-800 and PMS-800V)
Prospera 2831 Bledsoe Street Fort Worth, TX 76107 (Prospera Technologies LLC owns the Prospera NPWT systems and brand)	PRO-I™ (stationary and portable) PRO-II™ (portable) PRO-III™ (stationary and portable)
Smith & Nephew, Inc. 970 Lake Carillon Drive, Suite 110 St. Petersburg, FL 33716	V1STA Negative Pressure Wound Therapy (portable unit) EZCARE Negative Pressure Wound Therapy (stationary unit) RENASYS™ EZ Negative Pressure Wound Therapy
Talley Group Ltd. Premier Way Abbey Park Romsey, Hants SO 51 9 DQ England; U.S. Talley Medical 4740 Ladestone Dr. Williamston, MI 48895	Venturi™ Negative Pressure Wound Therapy (portable or stationary)

Key Questions

The following questions were used to guide this review.

Key Question 1: Is there evidence to support a difference in the efficacy/effectiveness of negative pressure wound therapy compared to standard treatment?

Key Question 2: Is there evidence to support a difference in adverse events/harms for negative pressure wound therapy compared to standard treatment?

Key Question 3. Are there subgroups in which there is a difference in wound healing for patients treated with negative pressure wound therapy compared with standard treatment?

Conclusions

Limitations of the Evidence:

1. No studies were identified that were rated high quality.
2. Many of the included studies are of poor quality, have small sample sizes and short duration of follow up. Small and heterogeneous patient populations, lack of blinding and insufficiently defined patient selection criteria and outcome measures compromised the overall quality of the evidence.
3. Study populations were not similar enough to allow for pooling of evidence for meta-analysis. There was significant variation in wound classification, outcome measures and control group design.
4. Many studies look at intermediate outcomes such as decrease in wound size rather than health outcomes such as time to complete healing.
5. Lack of access to unpublished study results data raises doubts about the completeness of the evidence base on Negative Pressure Wound Therapy (NPWT).

Contraindications to Negative Pressure Wound Therapy (NPWT)

1. NPWT is contraindicated in patients with any of the following conditions: active bleeding, anticoagulant use, difficult wound hemostasis, exposed vital organs, inadequately debrided wounds, untreated osteomyelitis, necrotic tissue with eschar, malignancy in the wound, or fistulas to organs or body cavities.

Conclusions:

Key Question 1: Is there evidence to support a difference in the efficacy/effectiveness of negative pressure wound therapy compared to standard treatment?

1. There is moderate evidence from randomized controlled trials that NPWT improves wound healing in carefully selected patients who have wounds that are refractory to or have failed standard therapies, who are not suitable candidates for surgical wound closure or are at high risk for delayed or non-healing wounds.
2. Limited fair evidence indicates NPWT achieved results similar to standard therapy for wound healing times, wound recurrence rates, quality of life, infection rates, and bacterial loads.
3. Limited fair evidence supports the use of NPWT, as an adjunct to standard wound care, in patients with acute or subacute wounds or wounds that have received skin grafts, when delayed healing or non-healing is likely due to factors such as compromised blood flow, diabetic complications and similar situations.

4. Due to the paucity of clinical trials that focus on specific types of wounds, the patient selection criteria for NPWT have not been well defined.
5. There is insufficient evidence to determine a comparative difference in efficacy/effectiveness for the comparison of NPWT vs. other treatments in the care of open abdominal wounds or partial thickness burns.

Key Question 2: Is there evidence to support a difference in adverse events/harms for negative pressure wound therapy compared to standard treatment?

1. Evidence from short-term randomized controlled trials and medium to long-term case series and retrospective controlled studies indicates that, in general, NPWT is a safe technology with only minor, reversible side effects comparable with those experienced with standard wound dressings.

Key Question 3. Are there subgroups in which there is a difference in wound healing for patients treated with negative pressure wound therapy compared with standard treatment?

1. No evidence for subgroups was identified that met inclusion criteria.

Supporting Evidence

In their systematic review of clinical studies of NPWT, Peinemann et al.¹⁸ sought to identify unpublished completed or discontinued RCTs to gain a broader knowledge of the NPWT evidence. The authors were concerned that previous systematic review conclusions on efficacy and safety based on published data alone may no longer hold after consideration of unpublished data. The authors invited two NPWT device manufacturers KCI. (V.A.C.®) and BlueSky Medical Group Inc. (Versatile 1 Wound Vacuum System) and authors of conference abstracts to provide information on study status and publication status of sponsored trials. Responses were received from 10 of 17 (59%) authors and both manufacturers. BlueSky Medical Group Inc., however, had not sponsored relevant RCTs and only provided case reports. The authors determined that of 28 RCTs, 13 had been completed, six had been discontinued, six were ongoing, and the status of three could not be determined. Nine trials were unpublished, and no results were provided by the investigators. Peinemann et al. concluded that the “lack of access to unpublished study results data raises doubts about the completeness of the evidence base on NPWT.”¹⁸

Key Question 1: Is there evidence to support a difference in the efficacy/effectiveness of negative pressure wound therapy compared to standard treatment?

Of 40 studies comparing a NPWT system to another wound care therapy in the AHRQ review, all were studies of the Kinetics Concepts Inc. (KCI) V.A.C.® system and only nine were RCTs. The overall quality of the evidence base of 40 studies was considered low (significant potential for bias). None of the studies received a high-quality rating; seven (18%) were rated moderate, and 33 (82%) were rated low. Typical study limitations included lack of concealment of treatment allocation, lack of blinding patients and assessors, lack of reporting patient characteristics, and small study populations.

The seven moderate quality studies evaluated the use of the V.A.C.® system in the treatment of diabetic foot ulcers,(108,109) pressure ulcers,(110) chronic leg ulcers,(111) and wounds with mixed etiologies.(112-114) Two studies evaluated the use of the V.A.C.® system to secure split thickness skin grafts.(112,115) Comparators included bolster dressings,(112) standard of care,(113) the Healthpoint System of topical gel products,(110) and advanced moist wound therapy (i.e., hydrogels, hydrocolloids, or alginates).(108,109,111,114) Primary endpoints included measures of wound reduction or time to complete wound healing. Four studies concluded that the V.A.C.® system provided additional benefit when compared to other interventional treatments. (108,110,113,115) Vuerstaek et al.(115) evaluated 60 patients with chronic leg ulcers (venous, atherosclerotic, or mixed etiologies) randomized to treatment by V.A.C.® or alginate/hydrocolloids. Time to complete healing was significantly reduced in the V.A.C.® group: 29 days (95% CI: 25.5 to 32.5) versus 45 days (95% CI: 36.2 to 53.8). Results for secondary outcomes included a greater relapse at one-year follow up (52% of all healed V.A.C.® ulcers relapsed compared with 42% in the control group). Both groups reported significant increases in quality of life and similar decreases in pain. One moderate-quality study of 342 diabetic foot wounds,(108) reported a mean change in wound size in favor of the V.A.C.® system (-4.32 cm² versus -2.53 cm², p = 0.021), as well as a higher proportion of V.A.C.®-treated wounds achieving complete closure (43% vs. 28.9%). Data, however, were only reported for day 28 during the “active treatment phase,” whereas both three and nine month follow-up assessments were completed for patients achieving ulcer closure. This study reported the highest attrition rate (over 30%) of any controlled study; 40 patients (13% V.A.C.® due to adverse events). Ford et al. reported increased rates of pressure ulcer wound healing, superiority in decreasing inflammation at the wound site, and increased number of capillaries (suggesting the promotion of formation of granulation tissue) for the V.A.C.® system compared to the Healthpoint System (HP).(110) The HP system includes three gel products: Accuzyme (papain-urea debridement ointment), Iodosorb (0.9% cadexomer iodine) and Panafil (papain-urea, chlorophyllin, and copper ointment). However, in this interim report of the six-week study, complete wound healing was reported for only four wounds: two (10%) with V.A.C.® and two (13%) with the HP products. In a similar length study, Joseph et al.(113) studied 24 patients with 36 chronic non healing wounds (79% pressure ulcers). Average initial wound volume was larger for V.A.C.® wounds (38 cubic centimeters (cc) vs 24 cc), however, a significant reduction in wound volume was still demonstrated (78% vs 30% control). A significantly greater reduction in wound depth (66% vs. 20% control; p = 0.00001) and width was reported; however, improvement in width, depth, and volume did not extrapolate to wound length (p = 0.38). Three studies concluded a comparable benefit in comparisons of the V.A.C.® to control treatments.(109,112,114) Moisisid et al.(112) enrolled 22 patients (used as their own controls) with wounds clinically ready for skin graft. At two weeks, a quantitative assessment by a clinician blinded to treatment reported no significant difference in degree of epithelialization. A greater degree of epithelialization was reported in six cases (30%), the same degree in nine cases (45%), and less epithelialization in five cases (25%) of V.A.C.® versus control-treated wounds.

Armstrong et al.(109) reported results of a post hoc analysis of their 16-week study of 164 diabetic foot amputation wounds. Results for this evaluation of the impact of wound chronicity indicated no significant difference for proportion of acute (<30 days, 75% of study patients) and chronic (>30 days, 25% of the study population) wounds achieving complete wound closure (acute $p = 0.072$, chronic $p = 0.320$) between NPWT and control groups. However, the authors found improved time to complete healing with NPWT compared to control treatments for both acute and chronic wounds.

Braakenburg et al.(114) evaluated 65 patients with chronic and acute wounds. Similar results were reported for overall change in wound area (0.1 cm²/day), time to satisfactory healing (median 16 days (V.A.C.® vs. 20 days [control]) and overall change in the amount of granulation.

The NICE overview² considered a randomized controlled trial of 51 patients who had exploratory laparotomy requiring temporary abdominal closure after damage-control laparotomy, massive visceral edema or planned re-exploration reported that there was no statistically significant difference in the rate of delayed fascial closure achieved in patients treated with NPWT (31%) and those treated with mesh closure (26%) (absolute figures and length of follow-up not reported)¹⁵. Negative pressure wound therapy (NPWT) failed in two patients in whom evisceration occurred around the device and whose wounds were converted to mesh treatment.

In the Cochrane review by Ubbink et al.⁴ seven RCT's were found that compared NPWT to other conventional therapeutic interventions in chronic wound management. Four trials (total n=110) compared NPWT with saline-moistened gauze dressing, one trial compared NPWT with a gauze/hydrocolloid regimen (n=10), one trial compared NPWT with modern wound dressings: wound gel products (n=28), and one compared NPWT compared with modern dressings (hydrocolloid and alginate) (n=60)

Only one of the four studies comparing NPWT with saline-moistened gauze dressing, Joseph 2000¹⁶, reported a significant reduction in wound volume of 78% in the NPWT group compared with 30% in the gauze group within 6 weeks ($p=0.038$), but no standard deviations (SD) were reported and this analysis could not be verified⁴.

In another study (Vuerstaek 2006; n=60) reported a reduction in the median time to complete healing for the NPWT group (29 days [95% CI 25.5 to 32.5]) vs. the control group treated with modern hydrocolloid and alginate dressings (45 days [95% CI 36.2 to 53.8] $p=0.001$; Kaplan-Meier)¹⁷. However no statistical analysis of this difference was given or possible to calculate⁴. Vuerstaek also reported an increased survival rate of split-thickness skin grafts for NPWT treated patients. This was defined as the percentage of successfully adhered skin grafts after 4 days of complete bed rest and local therapy. Median survival rates were reported as 83% (with a SD of 14%) for NPWT compared with 70% (SD: 31%) in the control group ($p=0.011$). No means are given so these analyses could not be verified⁴. Median wound bed preparation time was reported as 7 days (95% CI 5.7 to 8.3) in the NPWT group and 17 days (95% CI 10 to 24) in the control group¹⁷.

Ubbink's review cited several methodological flaws including lack of allocation concealment and intention to treat analyses as well as short follow up periods. They also cited lack of comparable groups and outcomes which prevented meta-analysis. They concluded that any statistically significant findings should be "considered with caution"⁴.

Wasiak³ searched the literature for evidence related to NPWT for treatment of partial thickness burns. Only one RCT met inclusion criteria and it was rated poor quality and will not be considered in this review.

In the Hayes Directory report studies evaluating the safety and efficacy of NPWT that met criteria for detailed review included: 11 RCTs; 1 nonrandomized controlled trial; 2 prospective uncontrolled studies; 3 case series, one of which included a control population; 2 retrospective analyses, and 7 retrospective controlled analyses.

They noted in their analysis of the literature that “small and heterogeneous patient populations, lack of blinding, and insufficiently defined patient selection criteria and outcome measures compromised the overall quality of the evidence.” Results for different areas of interest are discussed below:

Wound Healing

In a study by Armstrong and Lavery (2005)¹⁹ an RCT comparing wound healing in diabetic foot amputations showed wound closure rates during the 3 month follow up period of 56% vs 39% in the control group.

Two controlled studies evaluated changes in wound size, and, the results of these studies do not permit definitive conclusions regarding this outcome measure. In a randomized trial of NPWT for patients with full thickness wounds, a greater mean wound size reduction of 3.8% per day occurred in patients who received NPWT compared with 1.7% per day for those who received standard moist gauze dressing¹² (Mouës et al., 2004). This difference was statistically significant. All NPWT-treated wounds decreased in size, whereas only 77% of wounds in the control group decreased.

In a randomized trial of NPWT for pressure ulcers, the overall reduction in wound size was similar for NPWT (51.8%) compared with the control group (42.1%)²⁰ (Ford et al., 2002).

In a randomized controlled trial of NPWT for chronic wounds, NPWT was compared with noncontact normothermic wound therapy¹⁶ (Joseph et al., 2000) NPWT demonstrated greater reductions in wound depth, wound width, wound volume, and wound length than the comparator group.

Time to wound closure:

Wound healing times for NPWT were similar or superior to those achieved with standard wound care^{17,21}.

The randomized controlled trials reported the following median wound healing times:

Various wound types: NPWT 16 days versus 20 days for the control group (Braakenburg et al., 2006)²¹.

Chronic foot ulcers: NPWT 29 days versus 45 days for the control group (Vuerstaek et al., 2006).¹⁷

Partial diabetic foot amputation: NPWT 56 days versus 77 days for the control group.

Wound healing times were significantly shorter for chronic and acute wounds in the NPWT group than for the control group^{19,22} (Armstrong and Lavery, 2005; Armstrong et al., 2007).

Pressure sores following spinal injury: Mean time to 50% wound closure was similar for both groups (27 days for NPWT versus 28 days for the control group)²³ (Wanner et al., 2003).

Poststernotomy mediastinitis: NPWT 21 days versus 26 days for irrigation with providone-iodine solution (not statistically significant)²⁴ (Fuchs et al., 2005).

Granulation tissue formation:

In a randomized controlled trial, median time to achieve granulation in diabetic foot amputation was significantly shorter for NPWT-treated wounds (42 days) versus moist wound dressing (84 days) for acute wounds^{19,22} (Armstrong and Lavery, 2005; Armstrong et al., 2007).

Wound recurrence rates:

Ulcer recurrence rates were evaluated in one randomized controlled trial of NPWT for chronic leg ulcers¹⁷ (Vuerstaek et al., 2006) and one prospective uncontrolled study of NPWT for acute, subacute, and chronic wounds²⁵ (Argenta and Morykwas, 1997). At 12 months follow-up, ulcers recurred in 53% of 30 patients who received NPWT and 42% of 30 patients who underwent standard wound care. This difference was not statistically significant¹⁷. Of 141 patients with pressure ulcers, none of the NPWT-treated ulcers recurred in the uncontrolled study; however, new ulcers appeared at other sites.²⁵

Skin Graft Take Rate and Graft Quality:

Across studies, graft take rates ranged from 83% to 100% for NPWT and from 70% to 89% for standard treatment, and, overall, the results were similar for NPWT and standard treatment (Scherer et al., 2002²⁶; Llanos et al., 2006²⁷; Moisisidis et al., 2006; Vidrine et al., 2006²⁹; Vuerstaek et al., 2006¹⁷; Kim et al., 2007³⁰). The differences in graft take or graft loss rate between NPWT and standard treatment were not statistically significant in four studies^{17,26,28,29} and were statistically significant in two studies^{27,30}. In addition to graft take and graft loss rates, some studies also evaluated the quality of graft take and the extent of graft take or graft loss. In one study, the quality of the graft was equal to standard bolster dressings in 35% of cases and was superior to standard bolster dressing in 50% of cases. However, in 15% of cases, standard bolster dressing had a qualitatively better graft than NPWT-treated wounds²⁸. In the second study, mean graft size was larger for NPWT-treated wounds (387 cm²) versus standard bolster dressing (984 cm²). At 4 weeks follow-up, major graft loss, characterized by a graft loss >20% of the graft occurred in 10% of NPWT and 28% of control patients; minor graft loss (< 20%) occurred in 30% and 20% of patients, respectively²⁹. The observed differences in the treatment effect did not reach statistical significance. Possible lack of adequate sample size may have led to inability to either prove equivalence/noninferiority or superiority of NPWT compared with standard care. Other factors limiting the quality of the evidence were short follow-up and insufficiently defined patient selection criteria.

Quality of Life (QOL):

QOL was evaluated in one randomized controlled trial of NPWT for chronic leg ulcers¹⁷ and one retrospective, controlled study (Immer et al., 2005)³¹. The randomized controlled trial compared NPWT in 30 patients with standard wound care (hydrogels, alginates with compression treatment) for the treatment of chronic leg ulcers. The EuroQOL and EQ-DSI instruments were used to measure QOL. QOL improved for NPWT and for the control group but there was no overall difference between the two groups. In the retrospective study, NPWT was used to treat deep sternal wound infection in 19 patients with sternal wound closure, 19 patients without sternal wound closure, and a historical control group consisting of 17 patients previously treated with sternal excision and primary musculocutaneous flap. QOL was assessed using the SF-36® Health Survey (Medical Outcomes Trust). Patients in the first group rated better in the aspects of

physical functioning, general health, and vitality. The study result is limited by the use of historical controls, small sample size, and the differences in the clinical presentation among these groups. This study design is not suited for a valid comparison of NPWT versus standard treatment and precludes conclusions regarding NPWT's efficacy and safety compared with standard care.

Pain:

In one randomized controlled trial, NPWT decreased pain intensity compared with standard treatment¹⁷

Bacterial Load of Infected Wounds and Infection Rates:

In three randomized controlled trials, bacterial load and/or the incidence of bacterial infection were evaluated^{12,21,32} (Mouës et al., 2004; Braakenburg et al., 2006; Stannard et al., 2006³²). In all three studies, no statistical difference in these outcome measures was noted between NPWT and the standard dressing.

Mortality and Survival Rates in Poststernotomy Mediastinitis:

Overall, NPWT achieved similar or better survival and/or mortality rates compared with standard treatment. In a prospective study, 46 patients with poststernotomy mediastinitis underwent NPWT. The control group consisted of 4781 patients who had not developed poststernotomy mediastinitis³³ (Sjögren et al., 2005). The 30-day mortality rate was similar for NPWT (0%) and the control group (2.4%). The incidence of late deaths was also similar between the two groups; 8.7% for NPWT and 8.2% for the control group. There was no difference in actuarial 1-, 3-, and 5-year survival rates between groups. Similar results were obtained in a retrospective, controlled study, which compared NPWT to irrigation with a providone-iodine solution²⁴ (Fuchs et al., 2005). However, while cumulative survival rates were not statistically different, NPWT had higher survival rates (97.1%) than the control group (74.7%).

In prospective uncontrolled case series study of 102 patients who received NPWT to treat poststernotomy mediastinitis, the mortality rate was 3.7%³⁴ (Domkowski et al., 2003).

Need for Additional Procedures:

The need for foot amputation was 3% for NPWT, 11% for the control group ($P=0.06$)¹⁹. In a prospective case series of 96 patients who underwent NPWT, 43 patients underwent additional procedures (e.g., vascular flap reconstruction)³⁴. In a randomized controlled trial of NPWT for split-thickness grafts, fewer patients were in need of re-grafting in the NPWT (6.7%) compared with the control group (40%)²⁷. However, in this latter study, the control was not standard wound dressing but the NPWT set-up without pressure being applied. While this is a true control, the NPWT dressing, itself, without negative pressure applied, may not constitute an effective wound care. Had the wounds received standard care, the treatment effect may have been much smaller. In another randomized controlled study of NPWT for skin grafting, NPWT was compared with conventional tie-over dressing over paraffin. In this group, neither the NPWT nor control group required additional procedures²⁸.

Duration of NPWT:

The length of treatment was noted in two studies. In the first study, which included different types of wounds, reported median treatment duration of 57.5 days³⁵ (Philbeck et al., 1999). In the second study, a retrospective controlled study on NPWT for the treatment of skin graft wounds, NPWT was applied for a mean of 4.8 days versus 5.2 days for the control group, a standard bolster dressing and splinting.²⁹

Hospital Length of Stay (LOS):

LOS ranged from 25 to 89 days, varied depending on the type and size of the wound, and was similar or shorter for NPWT versus standard treatment. For the treatment of skin grafting, LOS was similar for NPWT (27 days) and bolster dressing (32 days) in one study²⁶ but was shorter than in the control group (same set-up as NPWT but negative pressure was not applied) at 13.5 versus 17.0 days. In this latter study, one may question whether the dressing without negative pressure is an appropriate control. While it may be a true control, this type of dressing may not be suitable to treat these wounds and may actually produce worse wound healing. A standard dressing would be a more appropriate control for this type of technology and indication.

In one retrospective, controlled study of NPWT for the treatment of post-sternotomy mediastinitis (n=68 patients), NPWT had shorter LOS (median 25 days) versus the control group that received irrigation with a providone-iodine solution (34 days)²⁴.

Key Question 2: Is there evidence to support a difference in adverse events/harms for negative pressure wound therapy compared to standard treatment?

Adverse events were reported in 37 of 40 (92%) studies evaluated in the AHRQ review comparing NPWT to other treatments. Of the 37 studies reporting events, seven (19%) studies described NPWT as a safe treatment. Fewer complications were reported in the NPWT-treated patients than in those receiving other wound therapies in 19 (51%) studies (1,23,71,72,106,108,110,113, 114,117-126) and similar complications were reported in 8 (22%) studies.(109,127-133) Most commonly reported adverse events included pain (k = 8), bleeding (k = 6), infection (k = 13), mortality (k = 10), and other complications (k = 17). Reports were similar for bleeding, infection, amputation, and other complications (i.e, fistulae). However, fewer secondary amputations (7 versus 17) were reported in NPWT groups (all studies reported using V.A.C.® system).

A randomized controlled trial of 51 patients¹⁵ reported no statistically significant difference in the rate of enterocutaneous fistula development between the NPWT group (21%) and the mesh treatment group (5%) (p = 0.14) (absolute figures not reported). One patient in the mesh group developed a pancreatic fistula¹⁵. In the same study there was no statistically significant difference in the occurrence of abdominal abscess between the NPWT group (44%) and the mesh group (47%) (measure of significance and absolute numbers not reported).

Vuerstaek 2006^{4,17} reported no difference in mean score for present pain intensity (PPI) in the eighth week of treatment (0.2 (SD 0.7) for NPWT and 0.4 (SD 0.6) for the control group; (WMD -0.20; 95% CI -0.53 to 0.13), or Quality of Life at 8 weeks which was measured by the EuroQol (EQ-5D) and the Short form McGill Pain Questionnaire (SF-MPQ). There was also no difference in complications between groups (40% in the NPWT group compared with 23% in the wound gel group; (RD 0.17; 95% CI -0.06 to 0.40).

Hayes reported rates and types of complications. Complications related to NPWT included the following: mild pain; pain requiring narcotic analgesia; excessive in-growth of granulation tissue into foam dressing; possible infection, bleeding, or odor if dressing

is not changed every 48 hours; tissue desiccation and tissue necrosis if an inadequate seal is obtained; bleeding; late infection; fistula formation; toxic shock syndrome secondary to *Staphylococcus aureus* infection; periwound maceration; and periwound cellulitis.

In one study of NPWT in the treatment of post sternotomy mediastinitis²⁴, the death of 1 patient's (2.9%) was felt to be related to NPWT vs. 12.1% of patients died in the control group, in which a providone-iodine solution was used to irrigate the wounds.

In a prospective uncontrolled study (n=300)²⁵ noted complications in the study included pain, ingrowth of granulation tissue, and bleeding (# NR); late infection (0.7%); enteric fistula (0.3%); 0% deaths or re-hospitalization due to NPWT; 7 (2.3%) pts died of unrelated causes during treatment.

In a small (n=24 pts., 36 wounds), partially industry funded, single-blind, randomized, controlled trial¹⁶ (Joseph et al. 2000) found complications more frequent in the control group which utilized noncontact normothermic wound management compared w/ NPWT group (44% vs 17%; $P=0.0028$); osteomyelitis (n=1) and calcaneal fractures (n=2) were the only complications occurring in NPWT group.

In a randomized, controlled, multicenter, open clinical study (n=68) to evaluate NPWT following partial diabetic foot amputation²⁴ found the following with respect to complications for NPWT vs. control group: Overall complications (52%, 54%); treatment-related complications (12%, 6%); serious events (1 pt, 2 pts).

Key Question 3: Are there subgroups in which there is a difference in wound healing for patients treated with negative pressure wound therapy compared with standard treatment?

No evidence was found that met inclusion criteria that evaluated subgroups.

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Addendum:

Considerations from a single wound care (nurse) specialist:

1. Patient selection is important. Patient must be assessed. Wound care requires a case by case individualized approach.
2. Large abdominal wounds, post amputation wounds may be good candidates for negative pressure wound therapy.
3. Diabetics need to have a vascular assessment such as toe pressure and ABI.
4. If there is more than a 20-30% slough in the wound bed then negative pressure wound therapy may not be the right choice.
5. Wounds need to be re-evaluated, if no improvement in 2 weeks needs further evaluation to determine appropriate therapy.
6. Our one expert opinion suggests that patients on anticoagulation therapy are not absolutely contraindicated, but INR and PT as well as the patient must be watched closely.
7. Contraindications to NPWT include; unexplained fistulas, malignant wounds, and untreated osteomyelitis.
8. When considering costs, must include cost of nursing time to do dressing changes for non-NPWT patients. These costs can be significant especially in highly exudative wounds.
9. NPWT can be used in places where standard wound therapy is either impractical or routinely unsuccessful (e.g. Peri-anal wounds).