Cost-Effectiveness of Negative Pressure Wound Therapy in Patients with Many Comorbidities and Severe Wounds of Various Etiology

Vickie R. Driver, MS DPM FACFAS[1,2,3], Kristen A. Eckert, MPhil[4], Marissa J. Carter, PhD MA[4], Michael A. French, JD[5]

[1]Brown University School of Medicine, Providence, RI; [2]HBO and Wound Healing Center, Rhode Island Hospital, Providence RI; [3]Novartis Institutes for Biomedical Research, New Indications Discovery Unit, Cambridge, MA; [4]Strategic Solutions, Inc, Cody, WY; [5]VA Providence Medical Center, Providence, RI

Correspondence and reprints

Vickie R. Driver, MS, DPM, FACFAS

Mailing address: 830 Chalkstone Ave, Providence, RI 02908

Tel: 253-691-9197

E-mail: drvdriver@aol.com

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Abstract

This study analyzed a cross-section of patients with severe chronic wounds and multiple comorbidities at an outpatient wound clinic, with regard to the cost-effectiveness and cost-benefit of negative pressure wound therapy (intervention) versus no negative pressure wound therapy (control) at 1 and 2 years. Medicare reimbursement charges for wound care were used to calculate costs. Amputation charges were assessed using diagnosis-related groups. Cost-benefit analysis was based on ulcer-free months and cost-effectiveness on quality-adjusted life-years. Undiscounted costs, benefits, quality-adjusted life-years, undiscounted and discounted incremental net health benefits, and incremental cost-effectiveness ratios were calculated for unmatched and matched cohorts. There were 150 subjects in the intervention group and 154 controls before matching and 103 subjects in each of the matched cohorts. Time to heal for the intervention cohort was significantly shorter compared to the controls (270 vs 635 days, $p = 1.0 \times 10^{-7}$, matched cohorts). The intervention cohort had higher benefits and quality-adjusted life-year gains compared to the control cohort at years 1 and 2; by year 2, the gains were 68%-73% higher. In the unmatched cohorts, the incremental net health benefit was $9,933 per ulcer-free month at year 2 for the intervention; the incremental cost-effectiveness ratio was –825,271 per quality-adjusted life-year gained (undiscounted costs and benefits). For the matched cohorts, the incremental net health benefits was only $1,371 per ulcer-free month for the intervention, but the incremental cost-effectiveness ratio was $366,683 per quality-adjusted life-year gained for year 2 (discounted costs and benefits). In a patient population with severe chronic wounds and serious comorbidities, negative pressure wound therapy resulted in faster healing wounds and was more cost-effective with greater cost-benefits than not using negative pressure wound therapy.

Regarding overall cost-effectiveness, the intervention was still expensive, but that is the reality amidst limited treatment options for such serious cases of chronic wounds.

Introduction

There is a dire need for cost-effective treatment strategies for chronic wounds, which have been suggested to cost $25 billion annually.[1] Diabetic wounds and their related amputations and pressure ulcers (PUs) have a combined annual cost of nearly $22 billion.[2,3] Simply put, society cannot afford unhealed chronic wounds.

The use of negative pressure wound therapy (NPWT) in wound care has grown in popularity since it was first reported in the late 1990s.[4,5] The beneficial actions of NPWT include the stimulation of angiogenesis, epithelialization, and granulation tissue formation[6,7] and control of wound exudate and bacterial burden.[8] There is a wide array of NPWT technology available, ranging from commercial devices to homemade devices, but the traditional standard remains V.A.C.® Therapy (Kinetic Concepts Inc, an Acelity Company, San Antonio, TX), which involves an open-cell foam dressing.

After Philbeck et al.[9] first reported in 1999 that the mean cost to heal a PU with NPWT as an adjuvant ($14,546) was 62% less than the mean cost to heal using standard of care alone ($23,465), there have been many cost studies published regarding NPWT as an adjunct treatment for chronic wounds,[10-16] all of which support the cost-effectiveness of NPWT. Studies comparing costs of traditional NPWT with conventional therapy have analyzed the costs of different NPWT technology available[10,13,16] and have calculated the costs and savings of early initiation of NPWT.[15] However, few studies have used patients with multiple comorbidities and severe wounds, and none published have used horizon times longer than 1 year. This is of interest, because there may be limitations to the utility of NPWT when wounds are severe and patients have many comorbidities that can interfere with wound healing.

The goal of this study was to analyze a cross-section of patients with severe chronic wounds and multiple comorbidities likely to interfere with wound healing at an outpatient wound clinic, with regard to the cost-effectiveness and cost-benefit of NPWT.

Methods

Patients were seen at the Boston Medical Center outpatient clinics at least once by a podiatric or vascular surgeon, and patient data were derived from inpatient and outpatient data from Boston Medical Center clinics and hospital. The study was approved by Boston University IRB and Providence VA Medical Center IRB and complied with the Declaration of Helsinki.

Study eligibility

To be eligible for this study, subjects had to have visited a clinic at least once and seen either a podiatric or vascular surgeon. They also had to have had a diagnostic code in their medical record for diabetes or peripheral arterial disease (PAD) and at least one diagnosis code for an ulcer of any etiology in their medical record, or they had the word “ulcer” or “amputation” present in an outpatient note, discharge summary, operations report, or visiting nurse report.

Subjects were excluded based on Current Procedural Terminology (CPT) and International Classification of Diseases, Ninth Revision codes that corresponded to the following conditions: HIV positive status, traumatic injury, burn injury, or liver failure. Additionally, subjects with any of these noted conditions found during chart review were excluded. No exclusion was made based on Wagner grade or wound severity.

Case subjects were selected based on having received NPWT, defined as the presence of at least one of the following words in an outpatient note, discharge summary, operations report, or visiting nurse report: “VAC”, “Vacuum”, or, “Vacuum Assisted Therapy” (and all commonly misspelled derivations). Confirmation of the use of NPWT for a period of at least 7 days was confirmed via chart review for these identified cases.

Controls were subjects that did not receive NPWT and were matched to case subjects based on age (within 5 years) and gender. The lack of NPWT was confirmed via chart review. Control subjects were included in the dataset, provided that a patient was not entered into the electronic medical records system under more than one unique identifier and the patient had at least one follow-up visit. Additionally, subjects were not included in the dataset if it was found during chart review that the patient's ulcer resulted from traumatic or burn injury, or the patient was HIV positive or suffered from liver failure. All patients received standard of care for their wounds regardless of whether they received NPWT.

Database description

Data were contributed to a university based hospital/medical center data warehouse in which data from the hospital and clinic settings are collected and integrated into a single relational data warehouse. These data include registration, outpatient, inpatient, operating room, emergency department, infection, appointment, and anesthesia data. Boston University researchers that comply with the Health Insurance Portability and Accountability Act (HIPAA) and obtain approval from the Boston University Institutional Review Board may request data.

A data request was submitted to the data manager at the Boston Medical Center Data Warehouse after IRB approval was obtained. The data request was made for dates of records from June 1, 2006 through January 1, 2011. Patient level demographic data requested included date of birth, gender, race, and zip code. Problem level data (other patient/wound characteristics) requested included the following relevant medical conditions: ulcer type, infection type, diabetes, PAD, anemia, stroke, hypertension, congestive heart disease, rheumatoid arthritis, osteoarthritis, cancer history, autoimmune disease, deep vein thrombosis, edema, lipodermatosclerosis, varicosities, and dermatitis. Visit level data requested included visit type, date of visit, diagnosis, admission date, discharge date, procedure type, procedure date, laboratory test date, and laboratory test result. Data from the data warehouse were received in Microsoft Excel spreadsheet format.

Data from the review of charts were first collected on paper case report forms and then inputted into a Microsoft Access database. Problem level and visit level data were collected on variables that did not appear in the data available at the data warehouse. These variables included: wound size, wound classification, wound characteristics, amputation level, deformity, and secondary ulcers. Additionally, a review of procedures was conducted to ensure inclusion of secondary procedures and a review of ulcer type was conducted to ensure proper classification of ulcer.

Data analysis was performed on de-identified data translated from Microsoft Excel spreadsheet and Microsoft Access database formats into SPSS format.

Data Analysis

From the dataset, 255,193 records of 325 patients with no valid CPT (current procedural terminology) code were deleted, leaving 265,096 records. A duplicate CPT code existed on the same date of service for 19,830 records; these records were deleted, leaving 245,266 records to be analyzed. (Records in this context mean a patient visit.)

Data were sufficiently complete for 150 NPWT subjects (intervention) and 154 non-NPWT subjects (controls) to calculate total costs and benefits, but exact comparisons between the cohorts for more accurate analysis required matching patients for comorbidities and wound severity. Thus, to obtain 1:1 matched cohorts, adjusting for patient comorbidities and severity of wounds, a propensity score was developed for all subjects based on group membership for having any amputation using PASW 19 (IBM, Chicago, IL). The propensity score for a given wound represents the probability of it being associated with an amputation based on the covariates used in the logistic regression; propensity scores lie in the range of 0 to 1. The initial covariates entered into the logistic regression analysis were: PAD, diabetes, congestive heart failure (CHF), coronary heart disease (CHD), stroke, end-stage renal disease (ESRD), smoking, patient age, initial wound area, and exposure level of wound based on Wagner grade. Wagner grades are usually applied only to diabetic foot ulcers (DFUs), but the level of tissue exposure can be mapped to wounds of other etiology to differentiate whether the wound is full thickness (dermal basis) or deeper.

Only PAD, diabetes, patient age, and exposure level were significant in the final model. Naglekerke R^2 was 0.237, and Hosmer and Lemeshow test was barely significant ($p = 0.034$), indicating the model could be refined further with additional relevant covariates if these were available (Table 1). However, this fit was deemed acceptable given that the excess of controls was not large. Overall classification was 69.7%.

There were 150 NPWT subjects (intervention) and 154 non-NPWT subjects (controls) prior to matching. Propensity scores were then matched from lowest to highest using the nearest neighbor algorithm with a prespecified caliper of 0.002 (difference between matched pair propensity scores) and a window of ± 4 (i.e., for any intervention score, there had to be a control score on a scaled side-by-side score comparison that was within 4 cases of the case propensity score that also met the caliper limits). Final mean propensity scores were: 0.3268 (NPWT) and 0.3256 (no NPWT), n = 103 each.

Costs

Relevant services and procedures for wound care were identified from the CPT book.[17] Older (obsolescent) CPT codes were identified from the dataset and matched to current codes. Costs were equated to Medicare reimbursement charges, which were calculated from components categorized as physician, facility, laboratory, Multiple Procedure Payment Reduction (MPPR) rate, or Durable Medical Equipment, Prosthetics/Orthotics, and Supplies (DMEPOS). Laboratory components represented the Clinical Diagnostic Laboratory Fee Schedule for 2014 for laboratory services, which did not apply to physician or facility fees. MPPR components cover Physical, Occupation, and Speech Therapy Services. Orthotics codes that did not apply to physician or hospital Outpatient Prospective Payment System (OPPS) facility fees were covered by the DMEPOS fees for 2014.

Physician charges for each relevant CPT code were obtained from the Centers for Medicare and Medicaid Services (CMS) web site[18] after accepting the license agreement, by selecting year (2014), the Healthcare Common Procedure Coding System code, national payment amount, the code (enter the code), and, finally, the global modifier. Some physician fees (99241-99245, 99386-99403, and G0108) were sourced by CodeMap® (Wheaton Partners, LLC, Schaumburg, IL).[19] Facility fees are normally reimbursed via OPPS. These charges were obtained from the Payment Rate column of the CMS file, *Addendum.B-Final OPPS Payment for HCPCS Code for CY 2014.*[20] In this OPPS file, there are status indicators (column SI) that indicate whether or not CPT codes for the facility fees were bundled and/or were not reimbursed through OPPS, but rather another CMS system. These status indicators are defined in the CMS file, *Addendum D1 – Patient Status Indicators.*[21] Charges for codes 87070-87899, which were laboratory services covered by the Clinical Diagnostic Fee Schedule for 2014, were also obtained from CMS using the 57 states and states' regions' clinical diagnostic laboratory fees to determine the national average cost.[22] Likewise, charges for the orthotics codes L3002-L4386, which were covered by the DMEPOS fees for 2014, were obtained from CMS using the national average payment calculated from the 53 states, Puerto Rico, and the Virgin Islands.[23] MPPR charges, which substituted for facility fees, were obtained for codes 99760 and 99761 from CMS using national averages based on MPPR fees for 90 localities.[24] A 50% reduction rate was also applied when services are bundled. Finally, charges for codes Q4101 (for Apligraf), Q4102 (for Oasis), and Q4104 (for Integra) were based on the average sales price, which was only applicable to office-based (not facility-based) physician reimbursement. The 2014 CMS reimbursement rates for each of these codes were taken directly from each wound care product's manufacturer web sites.[25-27] Because of the changes that took place in 2015 in regard to reimbursement, some of these 2014 rates are no longer available from manufacturer web sites.

Total costs (except for amputations) with algorithms showing how total costs were calculated are shown in Table 2.

Charges for major and minor amputations were assessed using diagnosis-related groups (DRGs): DRG#616 for minor amputations and 618 for major amputations, with a major amputation defined as below the knee or a higher level. Using the United States (U.S.) HCUP (Healthcare Cost and Utilization) database (2012, all patients, national averages),[28] mean charges were $40,363 for 616 and $109,754 for 618. In case of multiple amputations, charges were summed based on the number and type of amputations incurred for each patient. Costs were not inflated to 2014, as the adjustments would be very minor.

Total costs were first aggregated for each patient based on the relevant CPT codes and then pro-rated for year 1 and year 2 based on the length of time under treatment. For example, if a patient had a total in-service time of 3 years and 12 weeks, then *individual* costs for year 1 (and year 2) would be 365/1179, but total costs by the end of year 2 (used in subsequent cost-effectiveness calculations) would be 730/1179. As another example, if a wound healed within 150 days, then total costs for year 1 and 2 would be identical in any cost-effectiveness calculations, but the incremental costs for year 2 would be 0. Because many patients had very long in-service times of many years, it was decided that the bias induced by the pro-rated cost method would be acceptable as opposed to increases in accuracy gained by time-consuming calculations to calculate exact costs by year. Means and standard deviations (SDs) were then calculated for year 1 and year 2 (year 2 includes any additional costs accumulated for year 1). Costs were discounted at 3% only for year 2, as recommended by the U.S. Preventive Services Task Force.[29]

Calculation of utility weights

A utility weight represents the value placed upon the presence of a medical condition or disease(s) (a health state) by a panel or patient in which 1 represents perfect health and 0 represents death. For example, patients have assigned a utility of 0.84 to the presence of diabetes by itself but in combination with an uninfected ulcer lower utility to 0.75.[30] However, there is a paucity of information regarding utility values in wound care. Therefore, given that the dataset contains wounds of many different etiologies, some reasonable compromises were made. Many wounds in the dataset were of multiple types (e.g., arterio-venous ulcer). Thus, it was decided to assign utilities based on the appropriate primary etiology.[30-34] For example, in a mixed venous leg ulcer (VLU), the primary etiology is venous. The alternative of using multiplication of utility values to arrive at a final utility value in some of these cases might have been misleading, as the multiplicative method often breaks down when there are 3 or more comorbidities present. For surgical and other types of wound, no suitable utility values could be found in the literature; thus, for healed and unhealed wounds, means were taken using the utility values of DFUs, VLUs, PUs, and arterial ulcers (AUs), respectively. The mean for an unhealed surgical/other wound type would thus be: (0.75+0.64+0.785+0.46)/4 = 0.659 (Table 3). For a healed surgical/other wound, it would be: (0.84+0.73+0.9+0.63)/4 = 0.775.

Occasionally, wounds other than DFUs and AUs had an outcome of a minor or major amputation. Because utility values have not been measured for wounds of these etiologies with an outcome of an amputation, it was decided to use the utility weights assigned to DFUs to aid in the calculations. This is because an amputation is generally perceived by individuals as being worse than the unhealed wound. However, patients perceive an amputation (whether the stump is healed or not) as being slightly better than an unhealed AU. Although seemingly contradictory, this might be so because the effects of critical limb ischemia are so bad; nevertheless this might not be an appropriate model for other wound etiologies. The differential utility value between an unhealed (uninfected) DFU and a minor or major amputation is 0.07, and 0.15, respectively. Thus, for wounds other than DFUs or AUs, this differential was subtracted from the utility value of an unhealed wound. For example, if a patient had an unhealed VLU and a subsequent major amputation, whether or not the stump healed, the final utility change would be 0.64–0.15 = 0.49.

The utility gain or loss was calculated as the final health state – the initial health state. For example, if a patient had a PU that healed, the utility gain would be 0.9–0.785 = 0.115. If a patient had an AU that resulted in a healed minor amputation, the utility gain would be 0.54–0.46 = 0.08. If a patient with a DFU had a major amputation, the utility change would be 0.75–0.6 = –0.15, which represents a utility loss.

The quality-adjusted life-year (QALY) equates to a year of life in perfect health and as such can be used as a unit of health state change. QALY gains or losses for the first year were calculated by calculating the time spent in each health state with the assigned utility. For amputations, the date of occurrence was not known in the dataset. It would be unlikely that the amputation would occur immediately or toward the end of the observed time period. Therefore, for the purposes of calculation, it was assumed that the amputation occurred halfway through the observation period. This was applied regardless of how many amputations actually occurred. If a patient had multiple amputations that were different (e.g., a major amputation and minor amputation), it was assumed that the minor preceded the major in a hierarchical fashion. The following are provided as examples:

- Unhealed VLU for 1 year: 0.64–0.64 = 0 QALYs (no change)
- PU that healed after 250 days, calculation for year 1: ((365-250)/365)*(0.9–0.785) = 0.036 QALYs (a gain)
- A DFU that resulted in a minor amputation; the observation period was 445 days, so it was assumed the amputation occurred on day 224.5. For year 1, the calculation would be: ((365–224.5)/365)*(0.68–0.75) = –0.027 QALYs (a loss)
- An "other" wound type that resulted in a minor amputation that was assumed to occur on day 100 of the 200-day observation period. For year 1, the calculation would be: ((365–100)/365)*(0.07) = –0.051 QALYs (a loss)
- A DFU patient had a minor amputation and a major amputation over the observation period of 71 days. It is assumed that the amputations occurred at equal intervals of (71/3) = 23.7 days. The calculation for year 1 is: ((23.7/365)*0.75)+((23.7/365)*0.68)+((23.7/365)*0.6)+(((365-71)/365)*0.6)-(0.75*1) = –0.135 QALYs (a loss).

In complicated cases—more than one amputation—we first created n+1 blocks of time based on the in-service time, in which n is the number of amputations, and multiplied the utility value by the time period measured in years for each block (areas A, B, and C, respectively, Figure 1). Next, the number of theoretical QALYs over the in-service time was calculated assuming no change in health state (area A+B+C+D). Finally, the difference in QALYs was calculated (D), and the proportion of QALYs belonging to year 1 and years 1+2 were proportioned using the in-service time in years as the divisor.

Cost-effectiveness analysis

The units of effectiveness chosen for the cost-effectiveness analysis were ulcer-free QALYs and ulcer-free months for cost-benefit analysis. Horizon times of 1 year and 2 years were selected. Consequently, incremental net health benefits (INHBs) were calculated as [cost of intervention – cost of standard of care]/[ulcer-free months (intervention) – ulcer-free months (controls)] on a patient basis over these time periods, in which the intervention is specified as NPWT and standard of care. Standard of care included wound debridement, infection management, moist wound care, offloading of the wound (DFUs and PUs), high compression bandaging (VLUs) but contraindicated for VLUs with substantial ischemia, and amputation (minor or major) of the lower extremity to avoid loss of life while maximizing tissue preservation. Incremental cost-effectiveness ratios (ICERs) were calculated as [cost of intervention – cost of standard of care]/[QALYs (intervention) – QALYs (controls)] over the same time periods.

Undiscounted costs, benefits, and QALYs were calculated for unmatched and matched cohorts by intervention (NPWT vs no NPWT), as well as several other covariates of interest, including presence/absence of PAD, patient age, wound etiology, and initial wound area.

Undiscounted and discounted INHBs and ICERs were calculated for the unmatched and matched cohorts. Probabilistic sensitivity analysis was conducted on the matched cohorts using TreeAge Pro software (TreeAge Software, Williamstown, MA), based on the assumption that the means and SDs calculated in the discounted INHB analysis were drawn from normal populations.

Other statistical analysis

All cost and cost-effectiveness/cost-benefit calculations were performed using Excel (Microsoft, Redmond, WA). Categorical variables were described using frequencies and percentages; continuous variables were described using mean and SD (standard deviation), with median, interquartile range (IQR), and range (minimum to maximum) added if distribution was non-normal. If statistical testing by group or other factor was conducted, chi-square or Fisher exact tests were employed for nominal variables, gamma and Kendall's tau b for ordinal variables, and t tests or Mann-Whitney U (MWU) tests for normally distributed variables or non-normal/Poisson distributions, respectively. Time to heal analyses utilized the Kaplan-Meier approach with differences tested using the logrank test and right censoring for unhealed wounds or death within the specified timeframe; amputations counted as non-healed wounds.

An alpha of 0.05 was considered statistically significant. All statistical analysis was conducted using PASW 19 (IBM, Chicago, IL).

Results

In the unmatched cohorts, there were very statistically significant differences regarding prevalence of PAD and ESRD, the number of other wound types, and wound area (Table 4). In the matched cohorts, which were also formally tested for significant differences without regard to correction of familywise error, the control cohort had a much lower prevalence of PAD (45.6% vs 71.1% for the intervention cohort), a lower prevalence of ESRD (29.1% vs 46.4%), a continued higher prevalence of other types of wounds (2.9% vs 18.4%), a much lower wound area (2 cm^2 vs 6.6 cm^2), and a higher proportion of wounds that probed to bone (59% vs 48.6%). Overall, however, the differences between unmatched and matched cohorts demonstrated that the matching process had improved (narrowed) the differences between the groups. While the proportion of wounds that healed without regard to time, including amputation stumps, and the number of amputations were similar in both matched and unmatched cohorts, time to heal for the intervention cohort was significantly shorter compared to the control cohort (270.2 vs 635.4 days, $p = 1.0 \times 10^{-7}$, matched cohorts; Table 5). Likewise, time in service was significantly shorter for the intervention cohort with a significantly shorter number of clinic visits (308.6 vs 676.6 days, $p = 1.1 \times 10^{-7)}$. However, the number of days in hospital was more than double for the intervention group compared to the control group (28.0 vs 11.5 days, $p = 2.2 \times 10^{-8}$).

Mean undiscounted costs were more than double for the intervention vs the control cohort (unmatched cohorts) at year 1, although by year 2 the difference had narrowed (Table 6). While mean ulcer-free months were always much higher for the intervention cohort vs the control cohort at both years, total QALY gains were higher at both years for the control cohort compared to the intervention cohort. However, for the matched cohorts, intervention costs were only 53% higher compared to control costs at year 1, and by year 2, the mean difference was only $4,875. Both benefits and QALY gains were consistently higher for the intervention cohort compared to the control cohort at years 1 or 2, but by year 2, the gains were 68%-73% higher.

Looking at both cohorts together by stratification variables, patients with PAD had accumulated about 2.5-fold more costs compared to patients without PAD regardless of year. Benefits were also consistently much lower for patients with PAD. Patient age showed little change with regard to ulcer-free months, although QALY gains were always higher in the elderly compared to patients younger than 80 years. Interestingly, costs were also always substantially lower for the elderly. When DFUs were compared to other kinds of wounds, there were large differences in costs and benefits, with DFUs always incurring higher costs and lower benefits at any year. Finally, wound area had little effect, although larger wounds had much higher QALY gains compared to smaller wounds by year 2 (Table 7).

In the unmatched cohorts, the INHB was \$9,933 per ulcer-free month at year 2 for the intervention, but the ICER was –\$825,271 per QALY gained when costs and benefits were not discounted (Table 7). While this latter figure apparently represents huge cost savings for every QALY gain (a dominated situation), the basis of the calculation showed that per individual there was only a gain of 0.02 QALYs for attendant cost savings of \$16,063. Discounting costs and benefits did not change the dominated situation by NPWT. However, for the matched cohorts, the INHB was \$1,371 per ulcer-free month for the intervention, and the ICER was \$366,683 per QALY gained for year 2 when costs and benefits were discounted (Table 8), which represents a change compared to the unmatched cohorts.

The probabilistic sensitivity analysis is shown as a scatterplot (Figure 2) and the willingness to pay (WTP) curve (Figure 3). The WTP curve shows that the intervention is likely to be successful about 53% of the time for \$2,500, increasing to 60% with \$10,000.

Discussion

In wound care, it is quite common for adjunctive therapies to be applied to wounds that are recalcitrant to healing, which often results in these therapies being used on more severe wounds or sicker patients. This appears to be the case in our study. The demographics show that the cohort treated with NPWT had a higher prevalence of comorbidities likely to interfere with wound healing and the wounds were much larger. The number of amputations also speaks to the severity of the wounds in both cohorts. Consequently, it is likely that the cohorts are not properly balanced, despite the propensity scoring, because an excess pool of control subjects was not available. Nevertheless, despite these differences, the addition of NPWT succeeded in reducing time to heal on average by 57% in the matched cohorts, with a similar reduction in-service time in the wound care clinic (Table 5). Although the number of hospital days was about 2.5 times larger for the intervention cohort compared to the control cohort, it is probable that the difference was related to non-wound problems, given the differences in comorbidities between the groups.

The cost-effectiveness analysis at 2 years showed an INHB of $1,371 per ulcer-free month for the intervention, with an ICER of $366,683 per QALY gained when costs and benefits were discounted in the matched cohorts (Table 8). This represents, therefore, a fairly expensive proposition in terms of cost benefits or cost-effectiveness. For example, in the U.S., ICERs exceeding $100,000 per QALY gained are not considered cost-effective.[35] However, it must be pointed out that these are old benchmarks, which have not been updated for inflation and are quite arbitrary. The World Health Organization has suggested benchmarks for the cost-effectiveness of interventions based on regions.[36] When the cost-effectiveness value is more than 3 times the gross domestic product (GDP), interventions are not considered cost-effective. The GDP for the U.S. in 2013 was $53,042,[37] so the interventions would still not be considered cost-effective by these standards. The results are also reflected in the WTP curve for the IHNB (Figure 3), which shows that at $10,000, the intervention is only likely to be successful about 60% of the time. Nevertheless, for the population of patients represented in our study, there are limited options to heal wounds without severe complications, and cost-effectiveness should only be one of many parameters by which the utility of an adjunct therapy should be judged.

Strengths of the study include the comprehensiveness of wound-related procedures and the length of time over which data were collected. Previous cost studies that evaluated NPWT on chronic wounds involved limited wound etiologies and comorbidities, did not evaluate costs for multiple years of wound care, and did not measure true cost-effectiveness. For example, two often-referenced NPWT cost studies were post hoc retrospective analyses of diabetic-related wounds only from randomized controlled trials that compared standard NPWT with the V.A.C. system to conventional therapy[11] and advanced moist wound therapy.[12] Apelqvist et al.[11] used data from 162 patients with postamputation diabetic foot wounds to calculate the direct per-patient costs, based on resource usage, for 8 to 16 weeks of care. They found the mean direct per-patient cost of care for NPWT to be $27,270, which was approximately 75% of the mean direct per-patient cost of advanced moist wound therapy. These savings were a result of the NPWT patients requiring less debridement procedures, dressing changes per patients, and outpatient visits than the group treated with advanced moist wound therapy. Driver and Blume[12] performed a similar analysis using data from 364 patients with Grade 2 or 3 DFUs, who were treated with either NPWT or advanced moist wound therapy over 12 weeks. They had a much smaller cost margin with the mean per-patient cost for NPWT being $11,984 (vs $13,557 for advanced moist wound therapy).

A recent cost analysis by Law et al.[10] used a large pool of retrospective data from a national claims database of patients with chronic wounds of various etiologies and with comorbidities over a period of 12 months, which is the maximum time frame used in previous cost studies. However, the authors compared V.A.C. Therapy to other NPWT devices. Other NPWT technology has been reported to be less costly than the V.A.C. system.[16,38,39] At 12 months, there were 7,860 patients treated with V.A.C. Therapy and 378 patients in the cohort of other NPWT devices.[12] Although V.A.C. Therapy is more expensive than other devices ($p = 0.04$), the mean total costs were significantly lower for VAC-treated patients at $80,768 per patient vs $112,212 ($p = 0.03$). These lower costs for the VAC system were attributed to significantly lower inpatient ($p = 0.01$), emergency room ($p < 0.01$), and home ($p = 0.05$) costs. These findings would suggest that V.A.C. Therapy is still the better value for NPWT.

As a retrospective analysis, the current study does have a number of limitations. First, cohorts could not be matched properly due to the lack of excess controls. Given the disparity in such patient factors as PAD and ESRD, differences in the types of wound mix, and initial wound areas, it is possible that we could have overestimated costs for the intervention group while underestimating costs for the control group. Using group membership for amputation in the propensity scoring as an attempt to control for amputation, which represents the largest cost element, rather than group membership based on NPWT, may also have resulted in bias. Likewise, benefits or QALY gains could have been over- or underestimated. Second, the sample sizes are fairly small—a sample size 10 times the one used in the study would be likely to provide more accurate results. Third, some wound-related hospital costs might not have been captured although the most expensive—amputations—were. Fourth, at the end of 2014, there were some large changes in the way that CMS reimbursed charges for cellular- and tissue-based products, and although these products were not used extensively in our study patients, the generalizability of our results could be affected for study populations in which this is not the case.

In a patient population with multiple and severe chronic wounds, serious comorbidities, and a high number of amputations, patients who received NPWT had faster healing wounds than patients who were not treated with NPWT. Treating a wound with NPWT was demonstrated to be more cost-effective with greater cost-benefits than not treating a wound with NPWT. However, in terms of overall cost-effectiveness, NPWT was still found to be expensive, and direct costs were high, but that is the unfortunate reality of treating such serious cases of chronic wounds with limited treatment options in the wound care setting.

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List of Abbreviations

AU: arterial ulcer

CHD: coronary heart disease

CHF: congestive heart failure

CMS: Centers for Medicare and Medicaid Services

CPT: Current Procedural Terminology

DFU: diabetic foot ulcer

DMEPOS: Durable Medical Equipment, Prosthetics/Orthotics and Supplies

ESRD: end-stage renal disease

GDP: gross domestic product

HCPCS: Healthcare Common Procedure Coding System

ICER: incremental cost-effectiveness ratio

INHB: incremental net health benefits

MPPR: Multiple Procedural Payment Reduction rate

NPWT: negative pressure wound therapy

OPPS, (hospital): Outpatient Prospective Payment System

PAD: peripheral arterial disease

PU: pressure ulcer

QALY: quality-adjusted life-year

SD: standard deviation

U.S.: United States

VLU: venous leg ulcer

WTP: willingness to pay.

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Figure Legends

Figure 1: Plot of in-service time vs health state for a hypothetical diabetic foot ulcer in which a minor amputation occurs followed by a major amputation over equal periods of time. Area D represents the loss in quality-adjusted life-years over the period of in-service time.

Figure 2: Scatterplot of probabilistic sensitivity analysis of net health benefit using discounted costs and benefits at 2 years. NPWT, negative pressure wound therapy; SOC, standard of care.

Figure 3: Willingness to pay curve for the intervention vs no intervention calculated using discounted costs and net health benefits. NPWT, negative pressure wound therapy; SOC, standard of care.

Table 1. Logistic regression model used for propensity scoring in which the dependent variable is the subject having one or more (subsequent) amputations.

Covariate	P	OR	95% CI (OR)	
			Lower	Upper
PAD	< 0.0005	4.12	2.32	7.52
Diabetes	0.023	2.53	1.13	5.63
Patient age (years)	0.033	0.98	0.96	0.998
Exposure Level[a]				
2	0.203	2.79	0.58	13.51
3	0.016	6.87	1.43	32.94
4	0.003	12.25	2.35	63.85

CI, confidence interval; OR, odds ratio; PAD, peripheral arterial disease

[a] Exposure level 1.

Table 2 (online only). Original Current Procedural Codes (CPT) codes, replacement CPT codes, total charges, algorithms used to calculate total charge, and applicable comments for CPT codes.

Original CPT Code[a]	Replacement CPT Code(s)[a]	Charge ($)	Total Charge Algorithm[b]	Comments
10021		220.11	Physician + Facility	
10022		478.59	Physician + Facility	
10060		257.1	Physician + Facility	
10061		341.28	Physician + Facility	
10120		379.77	Physician + Facility	
10140		964.91	Physician + Facility	
11000		304.18	Physician + Facility	
11040	97597	172.11	Physician + Facility	
11041	97598	11.82	Physician	For OPPS payment, this code is bundled with 97597. There is no separate facility fee for 97598.
11042		337.86	Physician + Facility	
11043		436.01	Physician + Facility	

11044		881.28	Physician + Facility	
11055		100.21	Physician + Facility	
11056		107.01	Physician + Facility	
11057		177.84	Physician + Facility	
11100		170.67	Physician + Facility	
11101		49.79	Physician	For OPPS payment, this code is bundled with 11100. There is no separate facility fee for 11101.
11200		157.88	Physician + Facility	
12001		129.94	Physician + Facility	
12002		144.63	Physician + Facility	
12021		343.04	Physician + Facility	
12032		396.41	Physician + Facility	
12034		409.67	Physician + Facility	
13121		682.02	Physician + Facility	
15000	15002	642.62	Physician + Facility	
A15340	15271 and	1139.11	2/3 (15271) + 1/3 C5271, based	OPPS payment is for when Q4101 is applied. C5271

	C5271		on practice patterns during study period	is used for OPPS payment, instead of 15271, when Q4102 and Q4104 are applied. SI = T, indicating it is paid as a separate APC via OPPS. Physician fee does not change.
15341	15272 and C5272	17.55	Physician	For OPPS payment, this code is bundled with 15271, when Q4101 is applied. There is no separate facility fee. C5272 is used for OPPS payment, instead of 15272, when Q4102 and Q4104 are applied. T fee is bundled with C5271. Physician fee does not change.
15342	15271	1139.11	2/3 (15271) + 1/3 C5271, based on practice patterns during study period	OPPS payment is for when Q4101 is applied.
15360	15271	1139.11	2/3 (15271) + 1/3 C5271, based on practice patterns during study period	OPPS payment is for when Q4101 is applied.

15365	15275 and C5275	1153.44	2/3 (15275) + 1/3 C5275, based on practice patterns during study period	OPPS payment is for when Q4101 is applied. C5275 is used for OPPS payment, instead of 15275, when Q4102 and Q4104 are applied. SI = T, indicating it is covered as a separate APC under OPPS. Physician fee does not change.
15430	15271, 15276 and C5276	1139.11	2/3 (15271) + 1/3 C5271, based on practice patterns during study period	OPPS payment is for when Q4101 is applied. For OPPS payment, this code is bundled with 15275 for when Q4101 is applied. There is no separate facility fee. C5276 is used for OPPS payment instead of 15276 for when Q4102 and Q4104 are applied. The fee is bundled with C5275. Physician fee does not change.
15740		2242.04	Physician + Facility	
28120		2196.37	Physician + Facility	
28124		2022.28	Physician + Facility	
28190		778.47	Physician + Facility	

28232		1934.15	Physician + Facility	
28272		1944.54	Physician + Facility	
29405		199.57	Physician + Facility	
29425		196.34	Physician + Facility	
37224		4621.87	Physician + Facility	
37226		9652.74	Physician + Facility	
37228		4997.55	Physician + Facility	
73700		319.55	Physician + Facility	
73701		487.94	Physician + Facility	
73706		668.46	Physician + Facility	
73718		665.9	Physician + Facility	
73719		849.92	Physician + Facility	
73720		1013.43	Physician + Facility	
73725	C8912, C8913, and C8914	830.44	Physician + ((C8912+C8913+C8914)/3)	73725 for OPPS payments: the code is either not paid under OPPS or there is an alternate code that is recognized by OPPS. 73725 is for providers only.

			Hospitals subject to OPPS should report C8912, C8913, or C8914, depending on the definition.
75710	2753.05	Physician + Facility	
75716	2787.79	Physician + Facility	
87070	11.59	Clinical Diagnostic Fee	
87075	12.55	Clinical Diagnostic Fee	
87076	10.56	Clinical Diagnostic Fee	
87077	10.56	Clinical Diagnostic Fee	
87081	8.57	Clinical Diagnostic Fee	
87101	10.11	Clinical Diagnostic Fee	
87102	11.06	Clinical Diagnostic Fee	
87106	13.37	Clinical Diagnostic Fee	
87107	13.37	Clinical Diagnostic Fee	
87116	13.93	Clinical Diagnostic Fee	
87118	14.46	Clinical Diagnostic Fee	
87140	7.4	Clinical Diagnostic Fee	

87149	26.65	Clinical Diagnostic Fee
87181	5.08	Clinical Diagnostic Fee
87184	9.29	Clinical Diagnostic Fee
87185	5.08	Clinical Diagnostic Fee
87186	11.44	Clinical Diagnostic Fee
87188	8.61	Clinical Diagnostic Fee
87205	5.68	Clinical Diagnostic Fee
87206	7.13	Clinical Diagnostic Fee
87207	7.9	Clinical Diagnostic Fee
87210	5.75	Clinical Diagnostic Fee
87230	24.95	Clinical Diagnostic Fee
87252	33.69	Clinical Diagnostic Fee
87253	25.12	Clinical Diagnostic Fee
87324	15.78	Clinical Diagnostic Fee
87327	15.78	Clinical Diagnostic Fee
87430	15.78	Clinical Diagnostic Fee

87449	15.78	Clinical Diagnostic Fee
87641	45.29	Clinical Diagnostic Fee
87653	45.29	Clinical Diagnostic Fee
87798	45.29	Clinical Diagnostic Fee
87799	57.09	Clinical Diagnostic Fee
87899	15.78	Clinical Diagnostic Fee
88104	93.99	Physician + Facility
88108	98.65	Physician + Facility
88112	99.58	Physician + Facility
88160	84.32	Physician + Facility
88161	78.59	Physician + Facility
88172	74.29	Physician + Facility
88173	183.4	Physician + Facility
88300	34.53	Physician + Facility
88302	49.93	Physician + Facility
88304	79.88	Physician + Facility

88305	107.1	Physician + Facility	
88307	349.84	Physician + Facility	
93922	159.38	Physician + Facility	
93923	271.13	Physician + Facility	
93924	306.95	Physician + Facility	
93925	438.73	Physician + Facility	
93926	276.79	Physician + Facility	
97597	172.11	Physician + Facility	
97605	111.31	Physician + Facility	
97606	177.84	Physician + Facility	
97760	77.97	Physician + MPPR	Not paid under OPPS. National average taken from MPPR fees for 90 localities. 50% reduction equivalent to $28.34.
97761	67.84	Physician + MPPR	Not paid under OPPS. National average taken from MPPR fees for 90 localities. 50% reduction equivalent to $25.79

99201	G0463 for OPPS	119.04	Physician + Facility based on G0463	For OPPS payment an alternate code is recognized by OPPS. In 2014, 99201-9205 and 99211-99215 were collapsed into a new code G0463, hospital outpatient clinic visit for assessment and management of a patient for OPPS fees.
99202	G0463 for OPPS	143.04	Physician + Facility based on G0463	
99203	G0463 for OPPS	169.55	Physician + Facility based on G0463	
99204	G0463 for OPPS	224.36	Physician + Facility based on G0463	
99205	G0463 for OPPS	262.69	Physician + Facility based on G0463	
99211	G0463 for OPPS	101.84	Physician + Facility based on G0463	
99212	G0463 for	117.96	Physician + Facility based on	

	OPPS		G0463	
99213	G0463 for OPPS	144.11	Physician + Facility based on G0463	
99214	G0463 for OPPS	171.7	Physician + Facility based on G0463	
99215	G0463 for OPPS	203.94	Physician + Facility based on G0463	
99218	For OPPS: G0378/G0379, G0378, G0308/G0379, and G0378/G0379	99.59	Physician	99218 is for physician fee only. For OPPS, there is an alternative code. In 2014, OPPS observation payments were recognized as "Extended Assessment and Management." For G0378, it is bundled. When observation is < 8 hrs, then no fee is applied. When observation is < 8 hrs, then G0318 is payable under APC 8009, $1198.91. For both G0378/G0379, OPPS fee is $327.85 when initial nursing assessment of patient directly referred to

			observation and does not otherwise meet criteria for observation. Both G0378/G0379 is payable under APC 8009, $1198.91, when observation period is minimum of 8 hrs after nursing assessment of patient directly referred patient to observation.
99241	34.03	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99242	70.93	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99243	98.87	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99244	156.55	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap

			(19)
99245	194.52	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99354	93.50	Physician	OPPS payment is now bundled with G0463.
99355	91.35	Physician	OPPS payment is now bundled with G0463.
99386	120.72	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99387	129.68	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99395	90.27	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99396	98.15	Physician	Not covered by Medicare (not paid under OPPS or

			other Medicare system). Charge from CodeMap (19)
99397	103.53	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99401	24.72	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99402	51.23	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99403	75.94	Physician	Not covered by Medicare (not paid under OPPS or other Medicare system). Charge from CodeMap (19)
99406	36.1	Physician	
G0108	53.38	Physician	Not paid under OPPS. Hospitals subject to OPPS

			will be paid under the Physician Fee Schedule when billing G0108. Charge from CodeMap (19)
L3002	151.54	Physician	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); not paid under OPPS.
L3020	186.16	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); not paid under OPPS.
L3030	71.61	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); not paid under OPPS.
L3260	25.00	Commercial cost	Surgical boot/shoe not covered by Medicare (not paid under OPPS or other Medicare system); price is commercial estimate
L3440	71.61	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin

			Islands); not paid under OPPS.
L3510	27.44	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); not paid under OPPS.
L4350	89.49	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); not paid under OPPS.
L4360	271.09	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); SI = A, not paid under OPPS.
L4386	148.77	DMEPOS	Covered by DMEPOS (national average payment calculated from 53 states, Puerto Rico, and Virgin Islands); not paid under OPPS.
Q4101	1478.88	DMEPOS	Q4101 is based on Average Sales Price, which changes on a quarterly basis. This price is only applicable to office-based (not facility-based)

			physician reimbursement and is equivalent to $33.61/sq cm. The physician office payment is up to $1,478.88. The facility fee is bundled. Q4101 is bundled with the procedure codes 15271, 15272, and 15275.
Q4102	186.29	DMEPOS	Q4102 is based on Average Sales Price, which changes on a quarterly basis. This price is only applicable to office-based (not facility-based) physician reimbursement and is equivalent to $8.871/sq cm. The physician fee is then calculated by: 8.871*3*3.5sq cm = $93.15, or 8.871*3*7 = $186.29 for total Medicare allowable office-based reimbursement. The facility fee is bundled. Q4102 is bundled with the procedure codes C5271, C5272, and C5275 due to being a low skin substitute category with a cost of < $32 per sq cm.

Q4104	22.11	DMEPOS	Q4104 is based on the Average Sales Price, which changes on a quarterly basis. This price is applicable only to office-based (not facility-based) physician reimbursement and is equivalent to $22.11/sq cm. No cap is provided, as done for Q4101 and Q4104. The facility fee is bundled. Q4104 is bundled with the procedure codes C5271, C5272, and C5275 due to being a low skin substitute category with a cost of < $32 per sq cm.

APC, Ambulatory Payment Classification; CPT, Current Procedural Code; DMEPOS, Durable Medical Equipment Prosthetics/Orthotics and Supplies; MPPR, Multiple Procedure Payment Reduction rate; OPPS, Outpatient Prospective Payment System; SI: Status Indicator.

[a]Wound care CPT codes were from the CPT book;[17] [b]most physician charges were taken from the Centers for Medicare and Medicaid Services web site,[18] although some were sourced by CodeMap[19] and are indicated in the "Comments" column. Most facility charges were obtained from OPPS,[20] and SIs indicate if the charge is bundled and/or are not reimbursed via OPPS;[21] charges for laboratory services were from the Clinical Diagnostic Fee Schedule for 2014;[22] orthotics fees were from the DMEPOS;[23] MPPR fees substituted

facility charges for codes 99760 and 99761.[24] For codes Q4101, Q4102, and Q4104, the manufacturer web sites were the source of average sales price.[25-27]

Table 3. Health states and utility weights used from the literature[30-34] to calculate quality-adjusted life-year (QALY), by ulcer type.

Ulcer Type	**Health State**	**Utility Weight (Reference(s))**
Diabetic	Diabetes + DFU, not infected	0.75[30]
	Healed diabetes + DFU, not infected	0.84[30]
	Minor amputation, diabetes	0.68[30]
	Major amputation, diabetes	0.6[30a]
Venous	Unhealed VLU	0.64[31,32]
	Healed VLU	0.73[31,32]
Pressure	Unhealed PU	0.785[33b]
	Healed PU	0.9[33]
Arterial	Unhealed AU	0.46[34c]
	Healed AU	0.63[34d]
	Unhealed amputation, arterial disease	0.48[34]
	Healed amputation, arterial disease	0.54[34]

AU, arterial ulcer; DFU, diabetic foot ulcer; PU, pressure ulcer; VLU, venous leg ulcer

[a]Based on mean major amputation utility weights of 0.57 and 0.63; [b]based on a mean of the utility weights for Stage 3 and Stage 4 pressure ulcers (0.84 and 0.73, respectively); [c]based on a mean arterial wound utility weight of 0.42 and 0.50; [d]based on a mean of 0.64 and 0.62 for healed arterial wounds.

Table 4. Demographics of the unmatched and matched cohorts.

Variable	Unmatched Cohorts		Matched Cohorts		P[a]
	NPWT	Control	NPWT	Control	
Gender, n (%)					
Male	60.0 (90)	59.1 (91)	61.1 (64)	60.2 (62)	NSS[b]
Female	40.0 (60)	39.9 (63)	38.9 (39)	39.8 (41)	NSS
Race, n (%)					
Caucasian	43.3 (65)	36.4 (56)	39.8 (41)	38.8 (40)	
African American	42.7 (64)	40.9 (63)	45.6 (47)	35.9 (37)	NSS
Hispanic	11.3 (17)	18.2 (28)	12.6 (13)	22.3 (23)	NSS
Other	2.7 (4)	4.5 (7)	2.0 (2)	3.0 (3)	
Age (years), mean (SD, n)	60.3 (14.35, 150)	63.5 (14.63, 154)	62.1 (14.34, 103)	62.6 (14.06, 103)	NSS
					NSS
Comorbidity, % (n)					
Diabetes	85.4 (144)	78.6% (154)	83.5 (81)	83.5 (86)	NSS
PAD	70.8 (102)	36.4 (56)	71.1 (69)	45.6 (47)	$^{-9}$
					0.00026
CHD	49.3 (71)	40.9 (63)	52.6 (51)	46.6 (48)	NSS
					NSS
CHF	31.3 (45)	37.7 (58)	34.0 (33)	39.8 (41)	NSS
					NSS
ESRD	49.3 (71)	27.3 (42)	46.4 (45)	29.1 (30)	9.0×10^{-5}
					0.012
Stroke	4.0 (6)	11.7 (18)	6.2 (6)	11.7 (12)	0.013
					NSS
Current smoker, % (n)	42.4 (61)	36.4 (56)	38.1 (37)	40.8 (42)	NSS
					NSS

Variable	Unmatched Cohorts		Matched Cohorts		P[a]
	NPWT	Control	NPWT	Control	
Wound etiology, % (n)					
DFU	54.0 (81)	63.6 (98)	54.4 (56)	65.0 (67)	
PU	13.3 (20)	10.4 (16)	12.6 (13)	7.8 (8)	
VLU	6.0 (9)	9.7 (15)	6.8 (7)	8.7 (9)	1.6 x 10^{-5}
AU	7.3 (11)	9.1 (14)	7.8 (8)	10.7 (11)	0.002
Surgical	0 (0)	4.6 (7)	0 (0)	4.9 (5)	
Other	19.3 (29)	2.6 (4)	18.4 (19)	2.9 (3)	
Initial wound area (cm^2), mean (SD, n)	5.6 (9.11, 149)	2.1 (2.20, 154)	6.6 (10.65, 103)	2.0 (1.48, 103)	1.0 x 10^{-5} 2.4 x 10^{-5}
Exposure level, % (n)					
Full-thickness (skin)	10 (6.7)	7 (4.6)	8.7 (9)	1.9 (2)	
Tendon	65 (43.3)	56 (36.8)	42.7 (44)	29.1 (30)	NSS
Bone	75 (50.0)	89 (41.4)	48.6 (50)	59.0 (69)	0.002

AU, arterial ulcer; CHD, coronary heart disease; CHF, congestive heart failure; diabetic foot ulcer; ESRD, end-stage renal disease; DFU, diabetic foot ulcer; NPWT, negative pressure wound therapy; NSS, not statistically significant; PAD, peripheral arterial disease; PU, pressure ulcer; VLU, venous leg ulcer.

[a]The first result represents statistically testing unmatched cohort variables and the second result testing the same variables in the matched cohort; [b]not statistically significant

Table 5. Patient and wound outcomes.

Variable	**Unmatched Cohorts**		**Matched Cohorts**		**P[d]**
	NPWT	**Control**	**NPWT**	**Control**	
Healed, % (n)[a]	78.7 (118)	74.0 (114)	75.7 (78)	73.8 (76)	NSS
Time to heal (days), mean (SD, n)[b,c]	289.5 (377.8, 118)	571.2 (447.6, 114)	270.2 (310.0, 103)	635.4 (483.6, 103)	1 x10^{-7}
In-service time (days), mean (SD, n)	314.1 (423.0, 150)	605.6 (501.9, 154)	308.6 (409.8, 103)	676.6 (539.9, 103)	1.1 x 10^{-7}
Amputations (minor), % (n)					
1	19.3 (29)	16.9 (26)	15.5 (16)	21.4 (22)	NSS
2	6.7 (10)	5.2 (8)	5.8 (6)	5.8 (6)	
≥3	0 (0)	0.6 (1)			
Amputations (major), % (n)					
1	12.7 (19)	5.8 (9)	8.7 (9)	7.8 (8)	NSS
2	1.3 (2)	(0.6) 1	1.0 (1)	1.0 (1)	
Number of clinic visits, mean	14.5 (16.74, 138)	22.4 (16.74, 146)	14.3 (18.10, 92)	24 (18.05, 98)	0.00027

(SD, n)					
Days in hospital, mean (SD, n)	28.9 (26.46, 150)	10.0 (14.60, 153)	28.0 (24.13, 103)	11.5 (15.22, 102)	2.2×10^{-8}

NPWT, negative pressure wound therapy; NSS: not statistically significant.

[a]Healed defined as healed wound or amputation stump; [b]mean derived from standard not survival analysis using only healed wounds; [c]range: 5-2,411 (NPWT), 59-2,145 (control); [d]testing matched cohort variables by statistical tests.

Table 6. Mean undiscounted benefits and costs by intervention (unmatched and matched cohorts) or stratification variable (non-matched cohorts). Year 2 costs, effectiveness, and benefits include year 1 costs.

	NPWT[a]		**NPWT[b]**		**History of PAD[a]**		**Age[a]**		**Wound Etiology[a]**		**Wound Area[a]**	
	Yes n=150	**No n=154**	**Yes n=103**	**No n=103**	**Yes n=158**	**No n=140**	**< 80 y n=267**	**≥ 80 y n=37**	**Diabetic n=179**	**Other n=125**	**<5 cm^2 n=258**	**≥5 cm^2 n=45**
Ulcer-free Months												
Year 1	2.60	1.46	2.81	1.19	1.76	2.15	2.03	1.99	1.29	3.08	2.02	2.08
Year 2	7.27	5.65	7.91	4.57	5.42	7.22	6.48	6.20	4.76	8.87	6.31	7.41
QALY Gain												
Year 1	0.002	0.007	0.009	0.005	-0.002	0.010	0.004	0.010	-0.008	0.023	0.004	0.006
Year 2	0.014	0.034	0.032	0.019	0.005	0.040	0.022	0.037	-0.013	0.077	0.020	0.045
Costs												
Year 1 ($)	39,073	18,397	32,036	20,945	40,585	16,020	29,986	18,587	32,389	23,171	28,882	27,517
Year 2 ($)	41,667	25,604	34,080	29,235	47,107	19,366	35,143	21,887	37,601	27,700	33,446	34,563

NPWT, negative pressure wound therapy; PAD, peripheral arterial disease; QALY, quality-adjusted life-year

[a] Unmatched cohorts; [b] Matched cohorts.

Table 7. Incremental net health benefits and incremental cost-effectiveness ratios of NPWT vs no NPWT at 1 and 2 years without and with discounting (3% costs and benefits) for unmatched cohorts.

Undiscounted				Discounted	
Cost ($) per UFM at 1 Year	**Cost ($) per UFM at 2 Years**	**Cost ($) per QALY at 1 Year**	**Cost ($) per QALY at 2 Years**	**Cost ($) per UFM at 2 Years**	**Cost ($) per QALY at 2 Years**
18,162	9,933	–3,672,231[a]	–825,271[a]	9,762	–801,179[a]

NPWT, negative pressure wound therapy; QALY, quality-adjusted life-year; UFM, ulcer-free month.

[a] dominated for no NPWT.

Table 8. Incremental net health benefits and incremental cost-effectiveness ratios of NPWT vs no NPWT at 1 and 2 years without and with discounting (3% costs and benefits) for matched cohorts.

Undiscounted				Discounted	
Cost ($) per UFM at 1 Year	**Cost ($) per UFM at 2 Years**	**Cost ($) per QALY at 1 Year**	**Cost ($) per QALY at 2 Years**	**Cost ($) per UFM at 2 Years**	**Cost ($) per QALY at 2 Years**
6,858	1,451	2,839,270	389,284	1,371	366,683

NPWT, negative pressure wound therapy; QALY, quality-adjusted life-year; UFM, ulcer-free month.

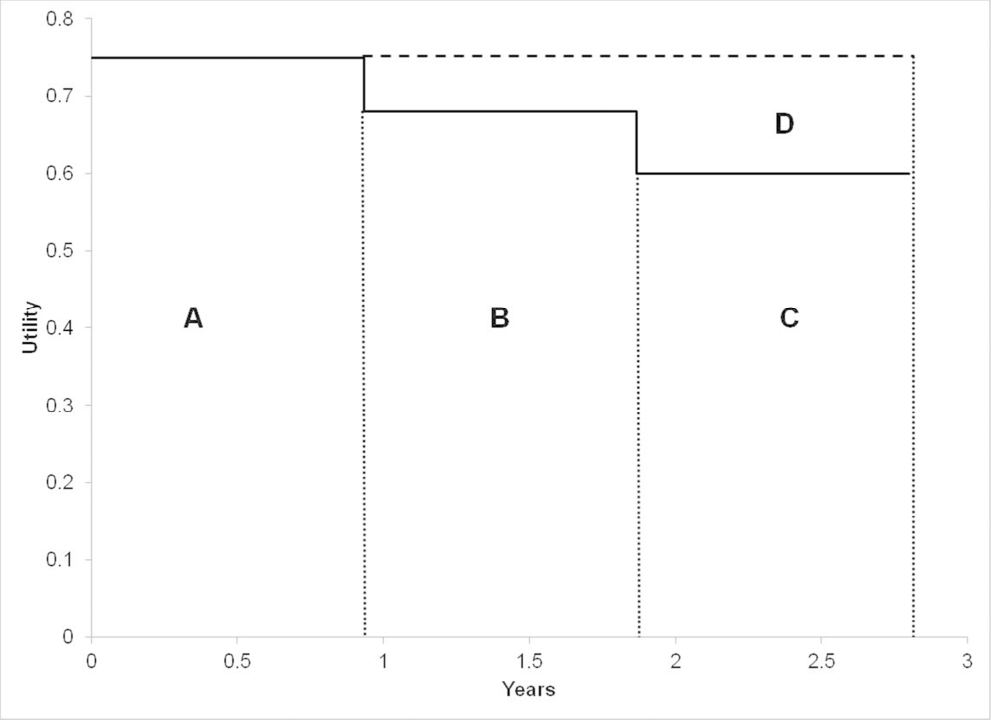

Figure 1. Plot of in-service time vs health state for a hypothetical diabetic foot ulcer in which a minor amputation occurs followed by a major amputation over equal periods of time. Area D represents the loss in quality-adjusted life-years over the period of in-service time.
Figure 1
64x46mm (600 x 600 DPI)

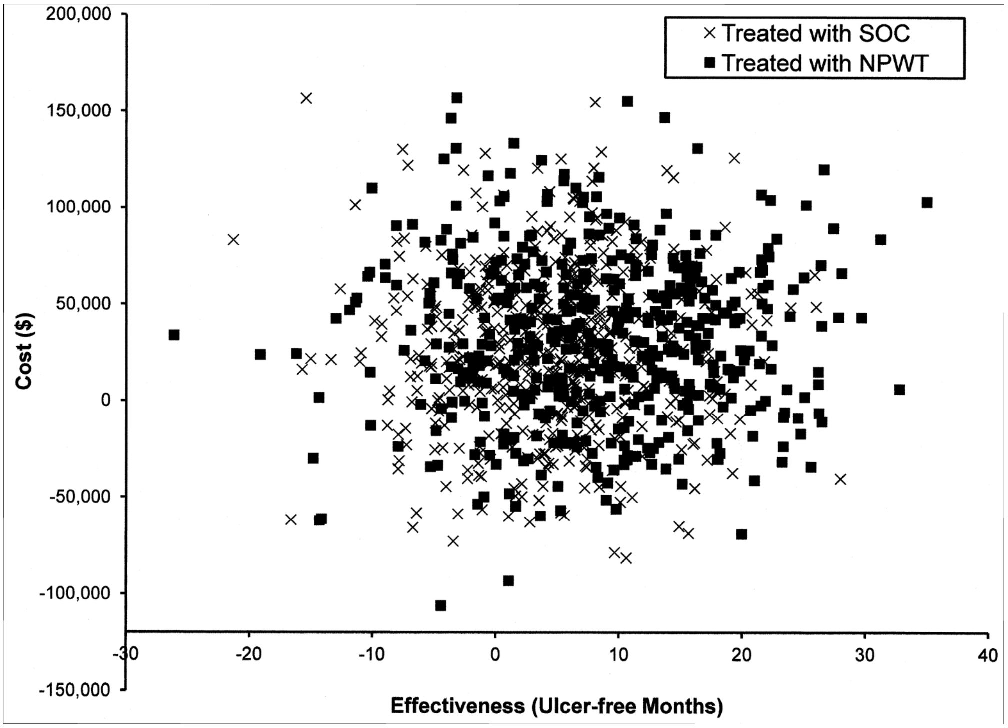

Figure 2. Scatterplot of probabilistic sensitivity analysis of net health benefit using discounted costs and benefits at 2 years. NPWT, negative pressure wound therapy; SOC, standard of care.
Figure 2
100x72mm (600 x 600 DPI)

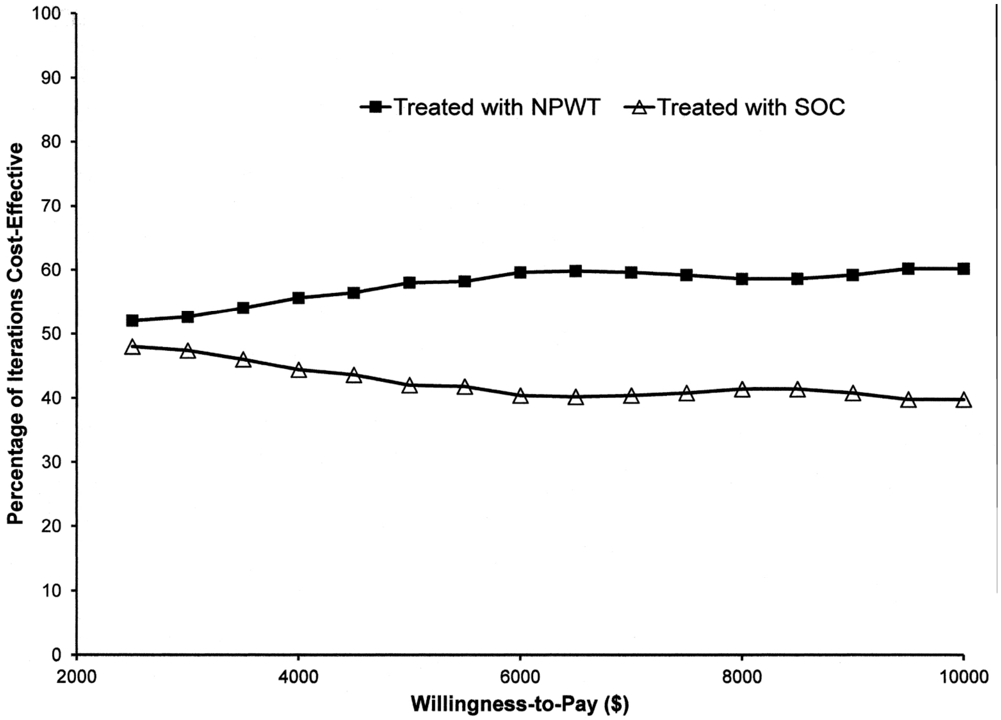

Figure 3. Willingness to pay curve for the intervention vs no intervention calculated using discounted costs and net health benefits. NPWT, negative pressure wound therapy; SOC, standard of care.
Figure 3
100x71mm (600 x 600 DPI)