Received: 5 June 2020 | Revised: 2 July 2020 | Accepted: 7 July 2020

DOI: 10.1111/iwj.13468

ORIGINAL ARTICLE

IWJ WILEY

An economic evaluation examining the cost-effectiveness of continuous diffusion of oxygen therapy for individuals with diabetic foot ulcers

Brian C.-F. Chan[1,2] | **Karen E. Campbell**[3]

[1]KITE – Toronto Rehabilitation Institute, University Health Network, Toronto, Canada

[2]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

[3]School of Physical Therapy, Faculty of Health Science, Western University, London, Canada

Correspondence
Brian C.-F. Chan, PhD, KITE – Toronto Rehabilitation Institute, University Health Network, 520 Sutherland Drive Room 206, Toronto, Ontario, M4G 3V9, Canada.
Email: brian.chan@uhn.ca

Funding information
EO2 Concepts Incorporated

Abstract

Continuous delivery of oxygen therapy has been observed to improve healing for individuals with an advanced diabetic foot ulcer (DFU). However, this intervention requires the purchasing of an oxygen delivery device and moist dressings. It is unknown whether this upfront financial investment represents good value for money. Thus the aim of this project is to evaluate the cost-effectiveness of treating advanced DFU using continuous delivery of oxygen compared with negative pressure wound therapy from the perspective of the public health care payer in Ontario, Canada. A microsimulation model was constructed with inputs from peer-reviewed journal publications and publicly available reports. The 5-year costs and quality-adjusted life-years were compared between treatment and comparator. Sensitivity analyses were conducted to evaluate the robustness of results. The model predicted that continuous delivery of oxygen would cost $4800 less compared with negative pressure wound therapy and increased quality-adjusted life years by 0.025. Lower cost and improved outcomes were observed in most scenario analyses. The results of this economic evaluation suggest that CDO therapy may reduce health care economic burden with a modest increase in quality of life outcomes. Health care decision-makers should consider the inclusion of CDO for the treatment of DFU.

KEYWORDS

cost-benefit analysis, diabetic foot

1 | INTRODUCTION

Diabetic foot ulcers (DFU) are a significant health burden for individuals with diabetes and the health care system. This condition is found in approximately 8% of all individuals with diabetes and increases to 19% for individuals with concurrent peripheral artery disease.[1] Globally, DFU impacts approximately 18.6 million (95% CI, 15.0-22.9) individuals, translating to a prevalence of approximately 270 per 100 000 individuals.[2] Individuals with diabetes experiencing a foot ulcer are also at a higher risk for mortality compared with individuals without ulcer.[3] More than half of foot ulcers will be infected,[4] placing the individual at risk for ischaemic tissue

necrosis.[5,6] In a long-term follow-up of individuals treated at a German hospital for DFU approximately 22% of the cohort required a major amputation within 10 years after hospital discharge.[7] The experience of a lower limb amputation places an individual in further risk for a re-amputation and greater risk for mortality.[8,9] The 5-year mortality of DFU is estimated to be 30.5%, increasing to 46.2% for those requiring minor amputations and 56.6% for major amputations.[10] In total, DFU is estimated to result in 2.5 million years lived with disability worldwide.[2] The substantial health care burden translates to a substantial economic burden to treat foot ulcers. This condition results in an excess of $5300 (2012 US dollars) in health expenditures for Medicare, $9600 for private insurance, in the first year after diagnosis.[11] The lifetime excess cost of DFU requiring hospitalisation costs the public health care payer in Ontario, Canada an estimated $619 300 (Canadian dollar) per person.[12] The total estimated economic burden of DFU in the US including individuals with diabetes and peripheral arterial disease may be greater than the five costliest cancers (breast, colorectal, lung, prostate, and leukaemia),[13] costing a total of $79 billion in 2017.[10] Overall, the evidence of health care burden demonstrates the need for effective interventions that can facilitate the healing of DFU in a timely fashion.

Current recommendations for the treatment of DFU include: Standard modalities of care include offloading of the foot using different types of casts[14] and various advanced dressings that may contain substances imbedded within that promote healing (files, hydrogels, foams, etc.)[14,15] debridements and surgery. Other advanced therapies for DFU include electrical stimulation, negative pressure wound therapy, bioengineered skin, and growth factors. However, the evidence for these therapies has been mixed.[14] More recently, oxygen therapy has been used for chronic ulcers. The chronic wound is hypoxic and remains this way until blood circulation is restored.[16] As well, many of the steps in the pathway to wound healing, such as angiogenesis/revascularisation, cell metabolism, connective tissue synthesis, and prevention of infection require the presence of oxygen.[16] Thus, the delivery of sustained oxygen to the chronic wound area facilitates the healing of DFU.[17,18] Several modalities for oxygen therapy has been in use for chronic ulcers. One method for the administration of oxygen therapy is through hyperbaric oxygen chambers. As is similar to the clinical evidence of all chronic ulcer treatments, the clinical evidence for hyperbaric oxygen therapy (HBOT) is uncertain given the limited studies and small sample sizes. Systematic reviews suggest that there may be no long-term clinical benefit with HBOT for DFU.[19,20] There has also been scepticism of the effectiveness of the systemic delivery of oxygen to the wound area given that the vascular system is often impaired in the wound area.[21] The use of this treatment modality has also been limited based on availability, cost, and time commitment for a course of treatment.[14] Topical oxygen therapy is another modality that provides sustained oxygen to the wound promoting healing without the need for expensive hyperbaric oxygen chambers and avoid side effects associated with whole-body exposure to pressurised oxygen.[21] This can be provided as topical pressurised oxygen therapy using portable pressure chambers or bags surrounding the wound. Alternatively, continuous delivery of oxygen (CDO) therapy can also be administered through compact, wearable oxygen units that continuously provide oxygen to the wound, eliminating the need for bulky pressure chambers.

CDO is positioned as an advanced treatment option for individuals where standard treatment options have been unsuccessful. A recent prospective double-blinded randomised controlled trial enrolling a total of 146 individuals with hard to heal DFU compared CDO therapy to advanced moist wound therapy.[22] This study observed improved healing rates for CDO at 12 weeks, shorter time to closure, increasing relative healing rate performance with increasing wound size, and sustained healing at an additional 12 weeks follow-up.[22] The improvement in healing resulting from the use of CDO requires an investment in the CDO device that is worn by all individuals receiving treatment. However, this additional upfront investment may be offset by

Key Messages

- Continuous delivery of oxygen (CDO) therapy has been observed to improve outcomes for the healing of advanced diabetic foot ulcers. However, there may be additional treatment expenditures associated with this treatment
- The aim of this study is to examine the cost-effectiveness of CDO therapy compared with negative pressure wound therapy from the perspective of the Ontario, Canada public health care payer. Clinical evidence was used to compare the outcomes of different treatment options and modelled over a 5-year timeframe
- CDO resulted in reductions in health care costs and modest improvements in quality of life
- These results remained consistent even with changes to the model assumptions

decreases in health care utilisation downstream as a result of improvements in wound healing. With various oxygen therapy modalities for DFU and limited resources in clinics and health care facilities in terms of constrained budgets and staffing, it is important to evaluate whether CDO can provide greater value for money than current treatment options.

Thus, the aim of this study was to examine the cost-effectiveness of CDO compared with negative pressure wound therapy (NPWT) for the treatment of individuals with hard to heal DFUs over a 5-year timeframe from the perspective of the Ontario Ministry of Health. Ontario is primarily a publicly funded health care system with 70% of all health care expenditures paid through the Ontario Ministry of Health and Ministry of Long-Term Care.[23] Taking the public health care payer perspective covers most health care expenditures associated with the treatment of DFU in Ontario.

2 | METHODS

A cost-utility analysis was conducted to estimate the incremental cost per quality-adjusted life-year of treatment with CDO compared with negative pressure wound therapy and standard wound cleansing, moist wound therapy, and off-loading. Long-term calculations of outcomes beyond the clinical trial observation periods were estimated using a microsimulation model. In this model, simulated individuals can move between six mutually exclusive states: healed from an ulcer, DFU, minor lower leg amputation, major lower leg amputation, infected ulcer, and death. The cycle length was 1 year, and at the end of the cycle, the individual could transition between health states. In the healed from ulcer state, individuals would have complete re-epithelialisation of the treated DFU with no drainage. Individuals in this health state do not require any more wound care. An individual in the DFU state has a foot ulcer that is not completely re-epithelialised. Minor lower leg amputation includes individuals who receive an amputation at the level of the ankle or below. Individuals in the major lower leg amputation state received an amputation above the ankle. In this model individuals healed of a DFU can experience another foot ulcer in future years and return to the DFU state. At the same time, individuals in the DFU state can be completely healed and move to the healed state in future years with standard wound care. The infectious wound state included individuals who had an infection related to the DFU that required hospitalisation. Individuals in this health state were assumed to have the infection completely healed and progress back to the DFU health state. Individuals with a minor amputation can receive a further minor amputation or a major amputation. If an individual receives a major amputation they no longer have a probability of receiving further amputations. At all health states, there is a probability of death. A pictorial representation of this model is presented in Figure 1. This type of model was selected so that outcomes that an individual may experience as they "travel" through the model can be tracked. This allows for transition probabilities conditional on health outcomes to be incorporated into the calculation.

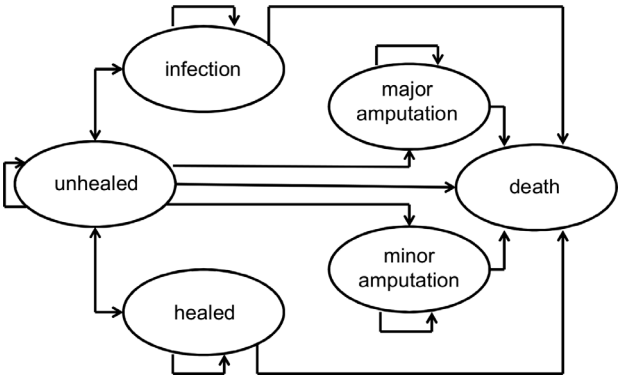


FIGURE 1 Pictorial representation of the cost-effectiveness model

The most appropriate comparator for CDO would be NPWT as this treatment is also non-invasive and portable to allow individuals the option to receive treatment at home without surgery. NPWT requires the application of a sealed wound dressing that provides a low-pressure moist environment that facilitates wound healing. Other non-surgical advanced wound care alternatives such as HBOT require resources that are available in a hospital or clinic, and so treatment is administered on-site and has limited availability. Some studies have considered HBOT to be a separate type of therapy from topical oxygen therapies given the physiological and biochemical differences in effect.[21,24]

The model simulated a cohort of 10 000 individuals with a DFU. The cohort entering the model represents individuals having experienced a DFU and received a 12-week treatment of CDO, NPWT, or standard wound care. At the initiation of treatment, individuals were diagnosed with a DFU that is classified as a Grade IA according to the University of Texas staging system for DFU.[25] In other words, individuals are experiencing an ulcer that does not involve the tendon capsule or bone and is not infected or have ischemia. This cohort is similar to the study cohort participating in the pivotal CDO trial.[22] In this study, a strict two-week run-in period was established prior to randomisation to ensure that ulcers were chronic.[22] Individuals with a decrease in the ulcer

area of 30% or more during the first week or second-week run-in or a greater than 50% reduction in ulcer area during the 2-week run-in period were excluded.[22] The foot ulcer would have been present for greater than 1 month but not more than 1 year. The health state that an individual receiving CDO or standard care will enter the model was informed by the clinical and adverse outcomes reported on the pivotal clinical trial by Niederauer and colleagues.[22] Treatment efficacy for NPWT was based on the percentage ulcer healing at 16 weeks for the intent-to-treat cohort relative to standard care reported in by Blume and colleagues[26] excluding individuals healed surgically ([57/120]/[34/120] = 1.68 relative healing with NPWT compared with standard care). The calculated relative difference in ulcer healed was then multiplied by the number of individuals healed in the standard care arm of the CDO clinical trial to get an estimate of the number of individuals healed with NPWT (1.68 x 12 = 20 individuals healed). It was assumed that the 16-week ulcer healing results were similar at 12 weeks. Inclusion criteria for the NPWT clinical trial by Blume and colleagues were individuals greater than 18 years of age with diabetes and Wagner's scale stage 2 or 3 ft ulcer greater than 2 cm^2 post-debridement.[26] For the model, it was assumed that the participant cohorts in the Niederauer study were similar to the Blume study. Transition probabilities between health states, costs, and utility inputs into the model were based on published literature from various sources. Model input sources include published peer-review papers, reports, government statistics, and data sources. The list of model inputs included in the calculation of transition probabilities is presented in Table 1. The individual-level simulation allowed the use of time-dependent probabilities of transitioning between health states. This was applicable to the probability of ulcer recurrence, minor and major amputation, infection, and the probability of a second amputation. The age and sex of each simulated individual was determined based on the demographic characteristics of the clinical trial by Niederauer and colleagues.[22] The average age in the simulated cohort was 56.3 years of age (12.4 standard deviation), with 22.6% of the cohort being female.[22]

The duration of the model is 5 years. This duration was selected because the important clinical impact of CDO and comparator interventions was assumed to occur only during the 12-week therapy. Longer-term clinical outcomes with the use of CDO has not been investigated yet. Therefore, the assumption in this model is that there are no additional benefits of the CDO treatment for wound healing after the 12-week treatment period and that individuals who do not heal after this period switch to standard wound care. Thus a 5-year duration should capture all-important clinical outcomes related to the treatment options. Two-year and ten-year durations were also included as sensitivity analyses. A lifetime time horizon was not analysed given the lack of long-term outcomes data on foot ulcers in the diabetic population. All costs and outcomes were discounted at 1.5% per annum as per recommendations by the Canadian Agency for Drugs and Technologies in Health (CADTH).[27] Probability of death was sex and age-adjusted based on data from Statistics Canada.[28]

The cost of CDO was based on the manufacturer's reported estimate of $60 per day for the rental of the CDO equipment and dressings multiplied by the mean-time to the closure of 49 days.[22] Treatment costs include weekly physician visits for debridement. NPWT intervention cost was extracted from results published by CADTH.[29] The unit cost per day included the pump equipment rental ($65), dressings ($38 per 2 days), and canisters ($36 per canister changed weekly) along with nursing time for dressing changes ($36.06 for 1 hour with three changes a week). This unit cost was also multiplied by 49 days, assuming a similar time to closure. The long-term age and sex-adjusted cost of health care was based on data from an Ontario diabetes population cohort.[30]

The additional cost of health care, associated with the presence of a foot ulcer for an individual with diabetes was extracted from the observations of the mean expenditure ratio of individuals with DFU compared with individuals without a foot ulcer.[31] The researchers observed an increase in expenditures in the first year and a smaller increase in the second year.[31] It was assumed that there were no additional costs associated with DFU after the second year.

The measure of benefit used in this analysis was the Quality adjusted life years (QALYs), estimated through health state utility values. Utility values associated with each health state in the model were collected from the results of a study by Redekop and colleagues.[32] In this study, the health state utility values were elucidated by presenting a description of the different health states to study participants and collecting preference through time trade-off valuation techniques.[32] The study participants were members of the general public, and thus the utility values represent the public's perspective. A total of 96 individuals participated in the study.[32] It was assumed that the amputation of the foot reported by Redekop and colleagues was representative of a minor amputation. The amputation of one leg reported by the utility study was assumed to be representative of major amputation. For this model it was also assumed that there were no additional foot ulcers are present after amputation. QALYs per person was calculated by multiplying the utility values at each health state with the time spent in each health state. The primary cost and outcome model inputs

TABLE 1 Transition probability model inputs

Variable	Value	Distribution Shape for Sensitivity Analysis	Source
Initial proportions in Markov health states			
Base-case			
Ulcer healed with CDO	32.4% (24/74)	Beta	Niederauer 2018[22]
Ulcer healed with NPWT	27.8% (20/72)	Beta	Blume 2008[26] (1.67 increased risk of healing with NPWT compared to standard care excluding amputation cases)
Major amputation CDO	0% (0/74)	Beta	Niederauer 2018[22]
Major amputation standard wound care	0% (0/72)	Beta	Niederauer 2018[22]
Major amputation NPWT	0% (0/72)	Beta	Assume same as CDO
Minor amputation CDO	0% (0/74)	Beta	Niederauer 2018[22]
Minor amputation standard wound care	0% (0/72)	Beta	Niederauer 2018[22]
Minor amputation NPWT	0% (0/72)	Beta	Assume same as CDO
Long-term outcomes			
Mortality (male)	0.3% to 34.4% depending on age	Normal	Statistics Canada life tables[28]
Mortality (female)	0.2% to 29.7% depending on age	Normal	Statistics Canada life tables[28]
Increase in mortality due to diabetes	1.51 (1.48-1.54, 95% CI)	Normal	Lind 2013[46]
Increase in mortality for individuals with diabetes resulting from presence of foot ulcer	1.89 (1.60-2.23, 95% CI)	Normal	Brownrigg 2012[3]
Increase in mortality for individuals with minor lower leg amputation	1		Assume no additional risk
Increase in mortality for individuals with major lower leg amputation	7.21 (5.70-8.72, 95% CI)	Normal	Al-Rubeaan 2017[47]
Annual probability of long-term ulcer healing after 12-week initial treatment	16.7% (12/72)	Beta	Assume the same as the 12-week standard care results of in clinical trial (Niederauer 2018).[22] Same for both CDO and comparator arms

are presented in Table 2. Additional model inputs are presented in Appendix Table 1.

The total cost and QALYs were calculated by modelling the 10 000 individuals receiving CDO therapy and the same cohort receiving NPWT. The incremental cost and incremental QALYs were calculated by subtracting the total costs and QALYs having received CDO therapy by the total cost and QALYs having received NPWT. Cost inputs were converted and inflated to 2019 Canadian dollars using Organisation for Economic Co-operation and Development purchasing power parity exchange rates[33] and Bank of Canada inflation estimates using consumer price index values.[34] Final results are converted and presented in 2019 US dollars.

Alternative model inputs and the impact of these inputs to the analysis results were evaluated through scenario sensitivity analyses. Different inputs that were not incorporated into the base-case analysis were analysed in separate analyses and incremental cost and QALYs were reported. Scenario analyses included a comparison of CDO to standard moist wound therapy. In this analysis, it was assumed that individuals required a weekly visit to the physician and three weekly visits from a home care nurse for wound changes. Two separate

TABLE 2 Cost and utility model inputs (2019 Canadian dollars)

Variable	Value	Distribution Shape for Sensitivity Analysis	Source
CDO			
Device rental and dressing	$59.63 per day	Not applicable	Manufacturer
Physician visits	$97.35 surgeon + $90.06 anesthesiologist per week	Not applicable	Ontario Physician schedule of benefits (Z228)[48]
Nursing time for dressing changes (assuming 1 h per change, 3 changes a week, 1% of cohort requires nurse for change)	$104.60 per h × 3 h per week × 1% of cohort = $3.14	Not applicable	Wodchis 2012,[22,49] (costs inflated to 2019 Canadian dollars) Niederauer 2018
Moist wound therapy			
Physician visits	$97.35 surgeon + $90.06 anesthesiologist per week	Not applicable	Ontario Physician schedule of benefits (Z228)[48]
Negative pressure wound therapy			
Pump rental	$65 per day	Not applicable	Canadian Coordinating Office for Health Technology Assessment report (2003)[29]
Dressings	$38 every 2 days	Not applicable	Canadian Coordinating Office for Health Technology Assessment report (2003)[29]
Canisters	$36 per week	Not applicable	Canadian Coordinating Office for Health Technology Assessment report (2003)[29]
Nursing time for dressing changes (assume 1 h per change, 3 changes a week)	$104.60 per h × 3 h per week = $313.80	Not applicable	Wodchis 2012[22,49] (costs inflated to 2019 Canadian dollars)
Physician visits	$97.35 surgeon + $90.06 anesthesiologist per week	Not applicable	Ontario Physician schedule of benefits (Z228)[48]
Utility values			
Healed diabetic foot ulcer state	0.84 (95% CI, 0.81-0.87)	Beta	Redekop 2004[32]
Unhealed diabetic foot ulcer state	0.75 (95% CI, 0.71-0.79)	Beta	Redekop 2004[32]
Infected diabetic foot ulcer state	0.70 (95% CI, 0.66-0.75)	Beta	Redekop 2004[32]
Minor foot amputation state	0.69 (95% CI, 0.64-0.73)	Beta	Redekop 2004[32]
Major foot amputation state	0.62 (95% CI, 0.57-0.67)	Beta	Redekop 2004[32]

scenario analyses compared CDO to HBOT. The cost of HBOT was based on the per-session treatment costs reported in the Health Quality Ontario report.[35] It was assumed that individuals receive a total of 42 90 minute sessions (3.5 sessions a week). Each session is supervised by a physician and includes a pre-and post-session assessment. Other scenarios examined included changes in cost inputs, utility values, ulcer chronicity, model timeframe, and discount rates (Table 3). To evaluate the impact of parameter uncertainty on the base-case model inputs, a probability sensitivity analysis was conducted. In this analysis, model inputs selected based on a random selection from the distribution of these inputs. Simulated cohort sizes of 10 000 were calculated, and this was repeated 5000 times to examine the variation in incremental cost and QALYs.

3 | RESULTS

In the simulate cohort of 10 000 individuals, it was estimated that 3278 (32%) would experience wound closure

TABLE 3 Description of scenarios for sensitivity analysis

Scenario	Description	References
Timeframe		
1 year	The base-case model timeframe of 5 years changed to 1 year	
2 years	The base-case model timeframe of 5 years changed to 2 years	
10 years	The base-case model timeframe of 5 years changed to 10 years	
Comparator		
Standard wound care (MWT)	Base-case model comparator NPWT replaced with standard wound care (physician and nursing costs but no device costs). 16.7% (12/72)	Niederauer 2018[22]
HBOT	Base-case model comparator NPWT replaced with HBOT (using data reported at 6 months) (assuming 42 total 90-min sessions). 27.8% (20/72)	Kranke 2015[19]
Costs		
NPWT device cost 1	Theoretical cost of NPWT as calculated by Kim and colleagues ($624 changed to $888 per week)	Kim 2017[50]
NPWT device cost 2	The observed cost of NPWT calculated from a retrospective chart review ($624 changed to $1050 per week)	Kim 2017[50]
Nursing cost	Hourly wage of home care shift nurse reported in Ontario health care administrative data ($316 changed to $189 per week)	Wodchis 2012[48]
Outcome variables		
Wound care outcomes based on sites that provided debridement at almost all follow-up visits	Model inputs for wound care outcomes based on a sub-analysis of study sites that provided debridement more than 92% of follow-up visits based on the number of participants who completed the clinical trial (22 healed of 43 in the intervention arm, 17 of 47 in comparator arm)	Lavery 2019[51]
Wound care outcomes based on individuals who completed the trial	Model inputs for wound care outcomes based on results from participants who completed the clinical trial instead of the intent to treat population (74 changed to 52 in the intervention arm, 72 changed to 53 in comparator arm)	Niederauer 2018[22]
Alternative NPWT healing outcomes 1	The proportion of individuals completely healed in the intent to treat population in the NPWT arm of the clinical trial (57 participants out of 169 study cohort)	Blume 2008[26]
Alternative NPWT healing outcomes 2	Model inputs for NPWT wound care outcomes based on results from Armstrong and colleagues (calculated to be 16 healed out of 72)	Armstrong 2005[52]
Alternative NPWT healing outcomes 3	Model inputs from NPWT wound care outcomes based on results from Liu and colleagues (calculated to be 17 healed out of 72)	Liu 2018[53]
Alternative increase in mortality for individuals with DFU	Model inputs for the increase in mortality for individuals with DFU based on results from Al-Rubeaan and colleagues (1.89 changed to 4.39 increase risk for death with the presence of DFU)	Al-Rubeaan 2017[47]
Including observed amputation rates in NPWT clinical trial	Model inputs include the major and minor amputations observed in the clinical trial for the NPWT arm (2 major amputations, 1 minor amputation)	Blume 2008[26]
Healing outcomes for the subgroup with baseline ulcer size (1.5-2.15 cm^2)	Healing outcomes for individuals with wound sizes in the lowest quartile at baseline (58.33% healing [n = 12] in CDO arm vs 35.71% [n = 14] in MWT arm at 12 weeks)	Niederauer 2018[22]

(Continues)

TABLE 3 (Continued)

Scenario	Description	References
Healing outcomes for the subgroup with baseline ulcer size (2.15-3.0 cm^2)	Healing outcomes for individuals with wound sizes in the second quartile at baseline (46.67% healing [n = 15] in CDO arm vs 25.00% [n = 12] in MWT arm at 12 weeks)	Niederauer 2018[22]
Healing outcomes for the subgroup with baseline ulcer size (3.0-4.9 cm^2)	Healing outcomes for individuals with wound sizes in the third quartile at baseline (42.86% healing [n = 14] in CDO arm vs 16.67% [n = 12] in MWT arm at 12 weeks)	Niederauer 2018[22]
Healing outcomes for the subgroup with baseline ulcer size (>4.9 cm^2)	Healing outcomes for individuals with wound sizes in the highest quartile at baseline (36.36% healing [n = 11] in CDO arm vs 13.33% [n = 15] in MWT arm at 12 weeks)	Niederauer 2018[22]
Healing outcomes for the subgroup with higher ulcer chronicity 1	Healing outcomes for individuals with less than 25% healing per week or total of 40% healing for 2 weeks during the screening period (43.8% healing in CDO arm vs 18.6% in MWT arm at 12 weeks)	Niederauer 2018[22]
Healing outcomes for the subgroup with higher ulcer chronicity 2	Healing outcomes for individuals with less than 20% healing per week or total of 30% healing for 2 weeks during the screening period (43.9% healing in CDO arm vs 13.2% in MWT arm at 12 weeks)	Niederauer 2018[22]
Discount rate		
Three percent	Recommended sensitivity analysis discount rate	CADTH report 2013[27]
Five percent	Recommended sensitivity analysis discount rate	CADTH report 2013[27]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CDO, continuous delivery of oxygen; HBOT, hyperbaric oxygen therapy; MWT, moist wound therapy; NPWT, negative pressure wound therapy.

after initial treatment with CDO therapy compared with 2696 (27%) for NPWT. The base-case mean 5-year cost per person for the cohort receiving CDO is estimated to be $78 500 (95% CI, $77 700-$79 300) compared with $83 300 (95% CI, $82 500-$84 100) for the NPWT cohort. This resulted in an incremental 5-year cost of −$4800 (CDO costs were lower than NPWT). The mean 5-year QALYs per person for the CDO cohort is estimated to be 3.650 (95% CI, 3.639-3.661), and for NPWT it is 3.625 (95% CI, 3.6137-3.637) resulting in an incremental QALY of 0.025. All scenario analyses resulted in a lower cost for CDO therapy. In most scenarios, CDO therapy also resulted in an increase in QALYs. The incremental cost and QALYs for the various scenario sensitivity analyses are presented in Table 4. The distribution of base-case results as a result of parameter uncertainty is presented in the probabilistic sensitivity analysis results for 5000 repetitions of the model simulation in Figure 2. A total of 4367 of 5000 simulations (87%) resulted in a negative mean incremental cost for CDO and 4530 of 5000 simulations (90%) had a positive incremental QALY. Approximately 3947 of 5000 simulations (79%) of cohorts resulted in dominance for CDO (had both a negative mean incremental cost and positive incremental QALY). The probabilistic sensitivity analysis for the results of the 10-year model time horizon is presented in the Appendix Figure 1.

4 | DISCUSSION

Treatment with CDO for advanced DFU results in an overall reduction in health care costs as early as 1-year post-treatment and remains cost-saving at 10 years when compared with NPWT. The reduction in costs with the use of CDO is also observed when compared with HBOT. The outcomes in terms of QALY also show improvement with CDO when compared with NPWT. However, the differences between CDO and NPWT are small, and there is uncertainty due to the lack of a direct comparison between the two treatment options in a clinical trial. Results from the scenario sensitivity analyses suggest that there may be greater reductions in costs when debridement is provided at all follow-up visits when treating larger wound sizes, when treating ulcers that are healing very slowly, and when compared with HBOT. The results observed in the base-case remain relatively robust, even when using different assumptions.

This is the first study to evaluate the cost-effectiveness of CDO for the treatment of DFU. In a review of cost-effectiveness studies for chronic ulcers, Tricco and colleagues identified a total of 16 studies published between 1996 and 2007.[36] Various treatments showed improved outcomes as well as reduced costs. Several studies have examined the cost-effectiveness of HBOT for the treatment of DFU. In a study connected to a randomized

TABLE 4 Scenario sensitivity analysis results (2019 US dollars, costs rounded to nearest tens)

Scenario	Incremental cost	Incremental QALY	Incremental cost per QALY
Timeframe			
1 year	−$3680	0.005	CDO dominates NPWT
2 years	−$4050	0.011	CDO dominates NPWT
10 years	−$5400	0.052	CDO dominates NPWT
Comparator			
Standard wound care (MWT)	−$1860	0.054	CDO dominates MWT
HBOT	−$14 060	0.025	CDO dominates HBOT
Cost			
NPWT device cost 1	−$3960	0.025	CDO dominates NPWT
NPWT device cost 2	−$6680	0.025	CDO dominates NPWT
Nursing cost	−$2600	0.025	CDO dominates NPWT
Outcome variables			
Wound care outcomes based on sites that provided debridement at almost all follow-up visits	−$6100	0.050	CDO dominates NPWT
Wound care outcomes based on individuals who completed trial	−$4940	0.029	CDO dominates NPWT
Alternative NPWT healing outcomes 1	−$3640	−0.004	CDO has decreased costs but worse outcomes compared with NPWT
Alternative NPWT healing outcomes 2	−$4480	0.042	CDO dominates NPWT
Alternative NPWT healing outcomes 3	−$4910	0.032	CDO dominates NPWT
Alternative increase in mortality for individuals with DFU	−$4480	0.025	CDO dominates NPWT
Including observed amputation rates in NPWT clinical trial	−$5780	0.050	CDO dominates NPWT
Healing outcomes for subgroup with baseline ulcer size (1.5-2.15 cm^2)	−$4000	0.004	CDO has decreased costs but worse outcomes compared with NPWT
Healing outcomes for subgroup with baseline ulcer size (2.15-3.0 cm^2)	−$4300	0.019	CDO dominates NPWT
Healing outcomes for subgroup with baseline ulcer size (3.0-4.9 cm^2)	−$5900	0.062	CDO dominates NPWT
Healing outcomes for subgroup with baseline ulcer size (>4.9 cm^2)	−$5450	0.055	CDO dominates NPWT
Healing outcomes for subgroup with higher ulcer chronicity 1	−$5258	0.039	CDO dominates NPWT
Healing outcomes for subgroup with higher ulcer chronicity 2	−$6455	0.085	CDO dominates NPWT
Discount rate			
Three percent	−$4790	0.024	CDO dominates NPWT
Five percent	−$4740	0.023	CDO dominates NPWT

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CDO, continuous delivery of oxygen; HBOT, hyperbaric oxygen therapy; MWT, moist wound therapy; NPWT, negative pressure wound therapy.

controlled trial (RCT) by Abidia and colleagues, HBOT had higher healing rates at a 6-week follow-up compared with control and no statistically significant improvement in the quality of life.[37] This study also observed cost savings as a result of a substantial reduction in visits for dressing changes. In a separate analysis, Guo and

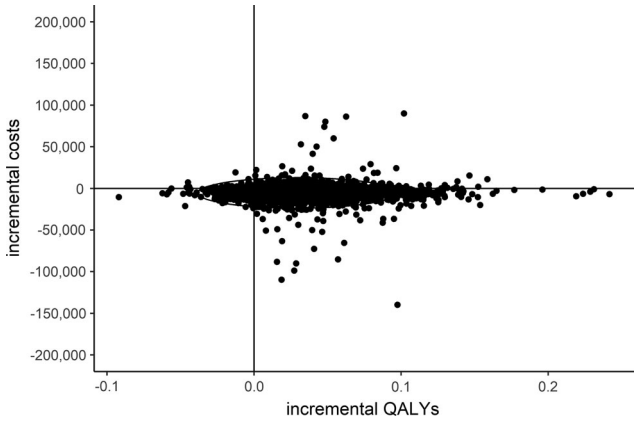


FIGURE 2 Probabilistic sensitivity analysis on the cost-effectiveness plane (base-case)

colleagues modelled the cost-effectiveness of HBOT up to 12 years.[38] There was an observed incremental cost per QALY of $27 310 (US dollars) at 1 year, and this incremental cost effectiveness ratio decreased to $2255 by year 12. An economic evaluation from the Canadian Agency for Drug and Technology in Health reported that HBOT in a 12-year model resulted in reduced costs and improved outcomes when compared with standard care.[39] A more recent evaluation of HBOT compared with standard care by Health Quality Ontario observed a similar result for a lifetime model (lower cost and better outcomes).[35] However, sensitivity analyses suggest that there is a high level of uncertainty with the results.

Several studies have examined the health care cost of DFU. In a US study published in 2014, the health care costs for individuals in the Medicare programme with DFU was $28 031 in the first year post-ulcer.[11] Individuals on private insurance cost $26 881.[11] Extrapolating this over 5 years, the cost would be $140 000 (US dollars) for individuals in the Medicare programme and $134 400 (US dollars) for individuals on private insurance. This is much higher than our results. However, first-year costs after ulcers are expected to be higher than the following years, and a straight extrapolation of first-year costs is an overestimate. The cumulative health care cost of DFU for individuals treated in Canada has been evaluated using health care administrative data by Hopkins and colleagues. The total cumulative average cost in the first 3 years for individuals with DFU was observed to be $52 360 Canadian dollars or $43 540 US dollars. Extrapolating the 3-year cost, the 5-year cost would be approximately $72 600 US dollars ($87 300 Canadian dollars). This is slightly lower than the 5-year cumulative costs modelled in our cost-effectiveness analyses. The difference is likely due to the difference in the chronicity of the foot ulcer in this study. The study by Hopkins and colleagues evaluated all individuals admitted to an acute hospital with a primary diagnosis of diagnosis foot ulcer through International Classification of Diseases codes regardless of severity.[40] The cohort evaluated in our cost-effectiveness analysis were screened to select for hard to heal foot ulcers. Thus, we expect that the study cohort in the cost-effectiveness analysis is more severe and would cost more.

Several conservative assumptions were made that biased the results towards better outcomes to the comparator. For instance, it was assumed that there were no major or minor amputations, cellulitis, osteomyelitis for NPWT. In clinical studies, several cases of cellulitis, osteomyelitis, major and minor amputations were observed in participants receiving NPWT during an observation period of 112 days. The additional of these adverse events in the NPWT would lead to higher costs for NPWT. CDO therapy was developed to deliver oxygen to a moist wound dressing that can be replaced by the individual with the foot ulcer. This was indeed observed in the clinical trial by Niederauer and colleagues, where all but one individual in the CDO arm replaced the moist wound dressing without assistance.[22] Thus, dressing changes can occur as needed from the convenience of home. On the other hand, NPWT requires the insertion of a foam dressing into the wound with a film applied on top. The difficulty in removing the foam necessitates the assistance of a home care nurse for re-dressing. For individuals receiving HBOT, dressing changes occur concurrently with treatment sessions at HBOT clinics with the help of the physician or nurse. On the other hand, some benefits may also be lost with self-administered wound dressing changes. For one, self-administered wound dressing changes decreases the number of contacts an individual has with a health care provider. This reduces the number of checkpoints that a nurse would have with the patient potentially impacting the health of the individual. The total number of sessions HBOT requires may also be a barrier to treatment access. Individuals receiving HBOT travel to a hyperbaric facility and remain in the chamber for a period of 90 minutes per session for a total of 40 to 45 sessions.[35] The cost to access treatment in terms of the individual's time, travel, caregiver assistance were not incorporated in the economic evaluation. The additional barriers to treatment access may impact treatment compliance reducing the real-life effectiveness of NPWT and HBOT from those observed in efficacy trials.

The results presented in our analysis should be interpreted with caution given the various limitations associated with our analysis. First, there was no direct comparison of CDO to NPWT. Instead, a clinical trial conducted in the US was selected as the study comparator since it had a similar follow-up period in a study in the same country. However, the follow-up periods were

not identical between studies, and there may be differences in the cohort characteristics entering the different study clinics. For instance, NPWT is generally used for individuals with complex wounds that may be larger and more severe than those recruited in the CDO trial. The percentage of individuals in the moist wound therapy healed in the intent-to-treat cohort (excluding surgical closure) between the two studies were similar (CDO study = 16.7%, NPWT study = 20.5% [48 healed - 14 surgically healed/166 cohort size]) suggesting the cohorts may be similar. If the study cohorts are not truly similar, the healing rates from the moist wound therapy arm for both clinical studies suggest that the NPWT study cohort may consist of individuals with less severe ulcers (higher healing rate), and this would bias results towards NPWT. This may be explained by the run-in period included in the CDO therapy clinical trials to exclude individuals with acute wounds and thus including only chronic ulcers. This, to the author's knowledge, was not included in the clinical trials for NPWT. A scenario analysis was also conducted to examine the change in the primary outcomes of our economic evaluation using CDO therapy clinical trial subgroup data stratified by ulcer size at recruitment. The larger ulcer sizes showed greater cost reductions and improvements in outcomes compared with the base-case analysis. Second, evaluation of the wounds healed associated with CDO treatment has been limited to a 12-week follow-up. A subsequent 12-week follow-up for individuals healed during the original observation window suggests that ulcer healing is sustainable. However, without evidence of longer-term follow-up of CDO treatment, the impact of this treatment beyond the first half-year remains uncertain. Third, the lack of long-term outcomes data in general in the chronic DFU population limited the analysis to a 10-year time horizon. Long-term DFU healing rates have been reported in several studies with percentage healing ranging from 44.5% to 77%.[41-44] However, these studies were based on all presenting DFU compared with the more severe chronic foot ulcer cases evaluated in our analysis. A study of long-term healing rates in a similar cohort has not been evaluated. As a result, the percentage of individuals healed in the comparator arm of our analysis was assumed to reflect annual long-term healing rates beyond 1 year for the duration of the model. A fourth, similar limitation to our analysis is related to the heterogeneous nature of the model inputs. Study results consistent with the perspective of the analysis (Canadian provincial public health care payer) were included in the model inputs. Unfortunately, some Canadian-specific model inputs were not available. For instance, the primary clinical outcome data were collected from a US study cohort.[22,26] The clinical outcomes of CDO and NPWT treatment may differ in a Canadian cohort given the differences in health care delivery and population characteristics between the two countries. However, in the absence of Canadian-specific clinical outcomes, this study assumed that the results of the US clinical trials included in the model would be similar in the Canadian context. Fifth, the incremental change in QALYs resulting from the use of CDO therapy was 0.025. This is a very small incremental difference between the two treatment options suggesting that there is little health-related quality of life improvement with CDO therapy estimated in the model. In the scenario analysis, incremental QALYs ranged between −0.004 and 0.077. This would suggest that there may be some uncertainty on the change in QALYs between CDO therapy and the comparator depending on the model assumptions. This range also suggests that even with changes to the model assumptions, in most cases, there is a very slight improvement in health-related quality of life between CDO therapy and comparators. There was only one scenario where CDO therapy QALYs were lower than the comparator. In this scenario, the healing outcomes of NPWT reported by Blume and colleagues were included in the model without adjustment. In the advanced moist wound therapy arm of the study by Blume and colleagues, 20.5% experienced closure without surgery (34 of 166 individuals).[26] This is higher than the percentage healed with advanced moist wound therapy observed in the study by Niederauer and colleagues.[22] Without adjustment, the outcomes are biased towards a more favourable outcome for NPWT resulting in a small incremental outcome of −0.004 QALYs or 1.5 days in favour of NPWT. Sixth, our economic evaluation was based on the results of published clinical trials. Ideally, these clinical trials could have collected data for an economic evaluation prospectively. This data would include a more detailed exploration of the cost of intervention, follow-up health care utilisation, and health-related quality of life using tools such as the EQ5D or SF-36 to calculate QALYs during the trial period. The impact of a prospective economic evaluation would be greater accuracy of the immediate cost and QALYs of the intervention and comparator. However, clinical outcomes and long-term outcomes will remain unaffected. Thus, the magnitude and direction of the impact of including a prospective analysis to the overall results are unknown.

Despite the limitations, our analysis also has several strengths. Many economic evaluations of interventions for DFU have similar methodological limitations, including inadequate evidence of treatment efficacy through systematic reviews, RCTs or large sample observational studies, limited quality of life outcomes, lack of uncertainty analyses, and short-term timeframes.[36] Our analysis evaluating CDO for DFU addressed these limitations.

The primary efficacy outcome for CDO was based on an RCT that enrolled a total of 146 individuals with a chronic DFU.[22] The screening of participants included a two-week assessment of the percentage of wound healing to exclude individuals expected to have full wound healing within weeks. Thus, the RCT evaluated individuals who had chronic ulcers that were not expected to heal. This is true to the anticipated population that would receive CDO outside the clinical trial setting. The primary outcome for the cost-effectiveness analysis was QALYs. This measure considers both the difference in duration in life adjusted for the quality of life.[45] Scenario and probabilistic sensitivity analyses were included to examine the impact of parameter uncertainty on the results. The results show that different model inputs did not markedly change the observation that CDO resulted in lower costs compared with NPWT with very little difference in QALYs. The base-case time horizon for the analysis was 5 years; selected because it was anticipated to be long enough to capture relevant clinical outcomes. A long-term time horizon of a 10-year time horizon was also examined in scenario sensitivity analyses.

Future clinical studies comparing CDO to NPWT and HBOT directly would be valuable in evaluating the differences between the treatment options. This would allow for a more accurate comparison of healing rates between the treatment options in a similar study cohort. As well, evaluation of long-term healing outcomes of CDO beyond the 12-week period would provide a better understanding of the recurrence of ulcer after treatment with CDO. Current evidence suggests that CDO wound healing may have a durable effect (12 weeks after ulcer closure).[22] If this durability persists at and beyond 1 year, the incremental cost reductions and improvement in QALYs with CDO treatment would be greater. Furthermore, an evaluation of changes to health-related quality of life with the use of CDO therapy in the context of the clinical trial would allow for a more accurate estimation of the changes in QALYs. Finally, epidemiological studies examining the long-term risk of secondary complications associated with a persistent DFU would also allow for a more accurate longer timeline projection of the economic full impact of the different treatment options. These studies would reduce the number of assumptions required in the economic evaluation and provide a better understanding of the cost-effectiveness of CDO in the treatment of hard to heal DFU.

Individuals with hard to heal DFU face an increased risk for secondary complications, amputation, and death associated with the unhealed wound. Treatment for this population includes interventions that are costly, time-consuming, inconvenient, and/or unavailable. CDO provides a potential treatment option that may be less costly than other treatment options using a device that is portable and allows for individuals to conduct dressing changes on their own.

ACKNOWLEDGEMENTS

Funding for the economic analysis was provided by EO_2 Concepts Inc. as an unrestricted grant. EO_2 Concepts Inc. was provided with an earlier version of the manuscript for review. The primary author had independent control over model development, analysis, and interpretation of the results. EO_2 Concepts Inc. did not have editorial control over the content presented in the manuscript.

CONFLICT OF INTEREST

Funding for the economic analysis was provided by EO_2 Concepts Inc. as an unrestricted grant. Karen Campbell is a paid consultant for EO_2 Concepts Inc.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Brian C.-F. Chan https://orcid.org/0000-0001-5037-0446

REFERENCES

1. Margolis DJ, Malay DS, Hoffstad OJ, et al. Prevalence of diabetes, diabetic foot ulcer, and lower extremity amputation among medicare beneficiaries, 2006 to 2008: Data points #1. In: *Data points publication series*. Rockville (MD), 2011. NBK63602 [bookaccession].
2. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. *Diabetes Care*. 2020;43(5):964-974.
3. Brownrigg JR, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. *Diabetologia*. 2012;55(11):2906-2912.
4. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in europe. Baseline results from the eurodiale study. *Diabetologia*. 2007;50(1):18-25.
5. Bridges RM, Jr DEA. Diabetic foot infections. Pathophysiology and treatment. *Surg Clin North Am*. 1994;74(3):537-555.
6. Maharaj D, Bahadursingh S, Shah D, Chang BB, Darling RC 3rd. Sepsis and the scalpel: anatomic compartments and the diabetic foot. *Vasc Endovascular Surg*. 2005;39(5):421-423.
7. Morbach S, Furchert H, Groblinghoff U, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care*. 2012;35(10):2021-2027.
8. Izumi Y, Satterfield K, Lee S, Harkless LB. Risk of reamputation in diabetic patients stratified by limb and level of

amputation: a 10-year observation. *Diabetes Care*. 2006;29(3):566-570.
9. Izumi Y, Satterfield K, Lee S, Harkless LB, Lavery LA. Mortality of first-time amputees in diabetics: a 10-year observation. *Diabetes Res Clin Pract*. 2009;83(1):126-131.
10. Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. *J Foot Ankle Res*. 2020;13(1):16.
11. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care*. 2014;37(3):651-658.
12. Chan BCF, Cadarette SM, Wodchis WP, Mittmann N, Krahn MD. Lifetime cost of chronic ulcers requiring hospitalization in Ontario, Canada: a population-based study. *Wound Med*. 2018;20:21-34.
13. Barshes NR, Sigireddi M, Wrobel JS, et al. The system of care for the diabetic foot: objectives, outcomes, and opportunities. *Diabetic Foot Ankle*. 2013;4. https://doi.org/10.3402/dfa.v4i0.21847.
14. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. *World J Diabetes*. 2015;6(1):37-53.
15. Moura LI, Dias AM, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment – a review. *Acta Biomater*. 2013;9(7):7093-7114.
16. Chadwick P, Edmond M, Fox A, Leigh R, Stang D, Vig S. Expert panel report. The role of topical oxygen therapy in the management of diabetic foot ulcers. *Diabetic Foot J*. 2019;1-12.
17. Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. *Am J Surg*. 2003;186(3):259-263.
18. Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. *Br J Dermatol*. 2010;163(2):257-268.
19. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Datab Syst Rev*. 2015;2015(6):CD004123.
20. O'Reilly D, Pasricha A, Campbell K, et al. Hyperbaric oxygen therapy for diabetic ulcers: systematic review and meta-analysis. *Int J Technol Assess Health Care*. 2013;29(3):269-281.
21. Dissemond J, Kroger K, Storck M, Risse A, Engels P. Topical oxygen wound therapies for chronic wounds: a review. *J Wound Care*. 2015;24(2):53-4, 56-60, 62-63.
22. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *J Wound Care*. 2018;27(Sup9):S30-S45.
23. Canadian Institute for Health Information. How does canada's health spending compare internationally? https://www.cihi.ca/en/how-does-canadas-health-spending-compare-internationally. Updated 2019. Accessed September 11, 2019.
24. Feldmeier JJ, Hopf HW, Warriner RA 3rd, Fife CE, Gesell LB, Bennett M. UHMS position statement: topical oxygen for chronic wounds. *Undersea Hyperb Med*. 2005;32(3):157-168.
25. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care*. 1998;21(5):855-859.
26. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care*. 2008;31(4):631-636.
27. Canadian Agency for Drugs and Technology in Health. Guidelines for the economic evaluation of health technologies: Canada. 4th ed.; 2017.
28. Statistics Canada. Life tables, canada, provinces and territories, 1980/1982 to 2015/2017. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011401. Updated 2019. Accessed December 23, 2019.
29. Canadian Coordinating Office for Health Technology Assessment. Issues in emerging health technologies: vacuum assisted wound closure therapy. 2003;44:1-6.
30. Rosella LC, Lebenbaum M, Fitzpatrick T, et al. Impact of diabetes on healthcare costs in a population-based cohort: a cost analysis. *Diabet Med*. 2016;33(3):395-403.
31. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*. 1999;22(3):382-387.
32. Redekop WK, Stolk EA, Kok E, Lovas K, Kalo Z, Busschbach JJ. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. *Diabetes Metab*. 2004;30(6):549-556.
33. Organisation for Economic Co-operation and Development. PPPs and exchange rates. http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4. Updated 2019. Accessed May 13, 2019.
34. Bank of Canada. Inflation calculator. https://www.bankofcanada.ca/rates/related/inflation-calculator/. Updated 2019. Accessed June 1, 2019.
35. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers. A health technology assessment. *Ont Health Technol Assess Ser [Internet]*. 2017;17(5):1-142.
36. Tricco AC, Cogo E, Isaranuwatchai W, et al. A systematic review of cost-effectiveness analyses of complex wound interventions reveals optimal treatments for specific wound types. *BMC Med*. 2015;13:90.
37. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg*. 2003;25(6):513-518.
38. Guo S, Counte MA, Gillespie KN, Schmitz H. Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. *Int J Technol Assess Health Care*. 2003;19(4):731-737.
39. Hailey D, Jacobs P, Perry DC, Chuck A, Morrison A, Boudreau R. Adjunctive hyperbaric oxygen therapy for diabetic foot ulcer: an economic analysis. *Can Agency Drugs Technol Health*. 2007;75:1-19.
40. Hopkins RB, Burke N, Harlock J, Jegathisawaran J, Goeree R. Economic burden of illness associated with diabetic foot ulcers in Canada. *BMC Health Serv Res*. 2015;15:13.
41. Ndosi M, Wright-Hughes A, Brown S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. *Diabet Med*. 2018;35(1):78-88.
42. Prompers L, Huijberts M, Schaper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers.

Prospective data from the eurodiale study. *Diabetologia*. 2008; 51(10):1826-1834.
43. Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and the outcome of foot lesions in a UKpopulation with diabetes. *Diabet Med*. 2007;24 (9):977-981.
44. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. *Diabetes Care*. 2006;29(8): 1784-1787.
45. Prieto L, Sacristan JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes*. 2003;1:80-7525-1-80.
46. Lind M, Garcia-Rodriguez LA, Booth GL, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UKfrom 1996 to 2009: a population-based study. *Diabetologia*. 2013;56(12):2601-2608.
47. Al-Rubeaan K, Almashouq MK, Youssef AM, et al. All-cause mortality among diabetic foot patients and related risk factors in Saudi Arabia. *PLoS One*. 2017;12(11):e0188097.
48. Ontario Ministry of Health and Long-term Care. Schedule of benefits: physician services under the health insurance act. 2019:1-752.
49. Wodchis W, Bushmeneva K, Nikitovic M, et al. Guidelines on person-level costing using administrative databases in Ontario. 2013.
50. Kim JJ, Franczyk M, Gottlieb LJ, Song DH. Cost-effective alternative for negative-pressure wound therapy. *Plast Reconstr Surg Glob Open*. 2017;5(2):e1211.
51. Lavery LA, Niederauer MQ, Papas KK, Armstrong DG. Does debridement improve clinical outcomes in people with diabetic foot ulcers treated with continuous diffusion of oxygen? *Wounds*. 2019;31(10):246-251.
52. Armstrong DG, Lavery LA. Diabetic foot study consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet*. 2005;366(9498):1704-1710.
53. Liu Z, Dumville JC, Hinchliffe RJ, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2018;10(10): CD010318.
54. Apelqvist J, Ragnarson-Tennvall G, Larsson J, Persson U. Long-term costs for foot ulcers in diabetic patients in a multidisciplinary setting. *Foot Ankle Int*. 1995;16(7):388-394.
55. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375.

How to cite this article: Chan BC-F, Campbell KE. An economic evaluation examining the cost-effectiveness of continuous diffusion of oxygen therapy for individuals with diabetic foot ulcers. *Int Wound J*. 2020;17:1791–1808. https://doi.org/10.1111/iwj.13468

APPENDIX A.

APPENDIX TABLE 1 Additional model inputs (base-case)

Variable	Value	Distribution Shape for Sensitivity Analysis	Source
Cost of amputation			
Major amputation surgical cost (hospital cost)	$28 581 (standard deviation $43 532)	Log normal	Health Quality Ontario report,[35] Canadian Institute of Health Information – cost per hospital visit
Major amputation surgical cost (physician costs)	$2067	Not applicable	Hopkins 2015[54] (supplementary Table S8)
Increase in costs for individuals with major amputation relative to individuals with diabetes alone (1st year)	4.54	Not applicable	Apelqvist 1995[54]
Increase in costs for individuals with major amputation relative to individuals with diabetes alone (2nd + year)	2.77	Not applicable	Apelqvist 1995[54]
Minor amputation surgical cost (hospital cost)	$16 747 (standard deviation $15 321)	log normal	Health Quality Ontario report,[35] Canadian Institute of Health Information – cost per hospital visit
Minor amputation surgical cost (physician costs)	$1683	Not applicable	Hopkins 2015[54] (supplementary Table S8)
Increase in costs for individuals with minor amputation relative to individuals with diabetes alone (1st year)	2.22	Not applicable	Apelqvist 1995[54]
Increase in costs for individuals with minor amputation relative to individuals with diabetes alone (2nd + year)	2.23	Not applicable	Apelqvist 1995[54]
Annual cost of diabetes			
Annual cost of care for women with diabetes <65 years of age	$10 167 (standard deviation: $72 547)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for women with diabetes 65 to 74 years of age	$19 471 (standard deviation: $94 645)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for women with diabetes 75 to 84 years of age	$40 298 (standard deviation: $142 891)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for women with diabetes >84 years of age	$77 464 (standard deviation: $160 067)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for men with diabetes <65 years of age	$11 110 (standard deviation: $85 307)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for men with diabetes 65 to 74 years of age	$23 836 (standard deviation: $114 944)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for men with diabetes 75 to 84 years of age	$48 425 (standard deviation: $158 575)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)
Annual cost of care for men with diabetes >84 years of age	$93 740 (standard deviation: $202 225)	Log normal	Rosella 2016[30] (costs inflated to 2019 Canadian dollars)

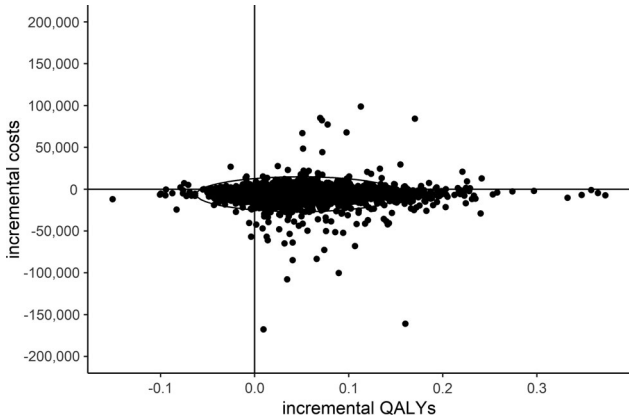
(Continues)

APPENDIX TABLE 1 (Continued)

Variable	Value	Distribution Shape for Sensitivity Analysis	Source
The relative increase in costs for individuals with diabetes with ulcer compared to those without ulcer (1st year)	2.67 (standard deviation: 0.68)	Log normal	Ramsey 1999[31]
The relative increase in costs for individuals with diabetes with ulcer compared to those without ulcer (2nd year+)	1.56 (standard deviation: 0.68)	Log normal	Ramsey 1999[31]
Transitions between health states			
Probability of ulcer recurrence (short-term) (1 year post-healed)	40%	Not applicable	Armstrong 2017[55]
Probability of ulcer recurrence (medium-term) (2-3 years post-healed)	10%	Not applicable	Armstrong 2017[55]
Probability of ulcer recurrence (long-term) (4+ years post-healed)	5%	Not applicable	Armstrong 2017[55]
Probability of a minor amputation (below ankle) with presence of DFU (1st year)	10.7% (539/5015)	Beta	Hopkins 2015[40]
Probability of a minor amputation (below ankle) with presence of DFU (2nd year)	3.9% (196/5015)	Beta	Hopkins 2015[40]
Probability of a minor amputation (below ankle) with presence of DFU (3rd + year)	2% (100/5015)	Beta	Hopkins 2015[40]
Probability of a major amputation (below ankle) with presence of DFU (1st year)	10.0% (502/5015)	Beta	Hopkins 2015[40]
Probability of a major amputation (below ankle) with presence of DFU (2nd year)	4.9% (252/5015)	Beta	Hopkins 2015[40]
Probability of a major amputation (below ankle) with presence of DFU (3rd + year)	2.3% (118/5015)	Beta	Hopkins 2015[40]
Probability of DFU infection requiring hospitalisation (1st year)	7.5% (377/5015)	Beta	Hopkins 2015[40]
Probability of DFU infection requiring hospitalisation (2nd year)	3.8% (192/5015)	Beta	Hopkins 2015[40]
Probability of DFU infection requiring hospitalisation (3rd + year)	2.8% (142/5015)	Beta	Hopkins 2015[40]
Probability of major re-amputation after minor amputation (1st year)	22.8%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after minor amputation (2nd year)	8.4%	Not applicable	Izumi 2006[8]

APPENDIX TABLE 1 (Continued)

Variable	Value	Distribution Shape for Sensitivity Analysis	Source
Probability of major re-amputation after minor amputation (3rd year)	8.4%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after minor amputation (4th year)	6.4%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after minor amputation (5th year)	6.4%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after minor amputation (1st year)	3.5%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after minor amputation (2nd year)	7.7%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after minor amputation (3rd year)	7.7%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after minor amputation (4th year)	5.4%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after minor amputation (5th year)	5.4%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after major amputation (1st year)	4.7%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after major amputation (2nd year)	3.6%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after major amputation (3rd year)	3.6%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after major amputation (4th year)	0.8%	Not applicable	Izumi 2006[8]
Probability of major re-amputation after major amputation (5th year)	0.8%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after major amputation (1st year)	11.6%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after major amputation (2nd year)	16.3%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after major amputation (3rd year)	16.3%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after major amputation (4th year)	4.6%	Not applicable	Izumi 2006[8]
Probability of minor re-amputation after major amputation (5th year)	4.6%	Not applicable	Izumi 2006[8]



APPENDIX FIGURE 1 Probabilistic sensitivity analysis on the cost-effectiveness plane for 10-year model timeframe