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Cost effectiveness of topical wound oxygen therapy for chronic diabetic foot ulcers

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ABSTRACT

Aims: To estimate the cost effectiveness of Topical Wound Oxygen therapy (TWO2) for chronic diabetic foot ulcers.

Methods: A Markov model was created to estimate the cost effectiveness of TWO2 over 2 years. Clinical outcome probabilities were estimated from a recent multi-national randomised controlled trial. Diabetic footcare costs were estimated for the National Health Service in England, based on national cost collections, published literature and expert opinion. Model inputs were varied in sensitivity analyses.

Results: Base case results indicate that at a weekly TWO2 price of £650 for up to 12 weeks, total diabetic footcare costs over 2 years are £5038 lower for a patient treated with TWO2 than for standard care, and QALYs are 0.07 higher. Probabilistic sensitivity analysis estimates an 81 % likelihood that the treatment is cost effective at a willingness to pay threshold of £25,000 per QALY.

Conclusions: Base case results indicate that if the clinical outcomes in the RCT are replicated in routine care, TWO2 is a dominant treatment, with lower cost and improved outcomes relative to standard care. Sensitivity analysis shows a high probability that the treatment is cost effective at a willingness to pay threshold of £25,000 per QALY.

1. Introduction

Foot disease is one of the most feared complications of diabetes, and a major cause of disability.[1] It has been estimated that globally 4.8 % of people with diabetes have a current foot ulcer, around 26 million people based on 2021 diabetes prevalence estimates.[2] Incidence is elevated in people who are Black, Hispanic or Native American and in those of low socioeconomic status.[3] Many ulcers persist for months; some never heal, and some lead to amputation. Five-year mortality after diabetic foot ulcer (DFU) has been estimated at 40 %.[4] Patients with diabetic foot disease often have severe comorbidities such as renal disease which contribute to this high mortality rate.[5] However, ulceration and amputation are independent risk factors for premature death.[6,7]

As well as the human costs, diabetic foot ulcers entail substantial financial costs. In the United States, the annual cost of diabetic foot disease has been estimated at around US$80 billion.[8] In England, the estimated cost is almost 1 % of the National Health Service (NHS) budget.[9] Severe ulcers of long duration are a major cost driver. In the Eurodiale study, the mean cost of 12 months of care for an ulcer that remained unhealed, based on data from seven European countries, was €18,790 in 2005, (around €31,444 in 2024 prices, equivalent to £26,647 or US$33,708).[10]

For many years, international reviews have pointed to the dearth of robust evidence on effective treatments for these chronic ulcers, and the low quality of evidence for many current treatments.[11,12] However, a recent American Diabetes Association compendium has sounded a more optimistic note, identifying topical oxygen therapy as a treatment supported by high-quality RCTs and meta-analyses.[13] A 2023 guideline from the International Working Group on the Diabetic Foot (IWGDF) recommended that this therapy should be considered as an adjunct treatment for diabetes-related foot ulcers where standard care has failed.[14] However, the guideline pointed to a lack of evidence on cost

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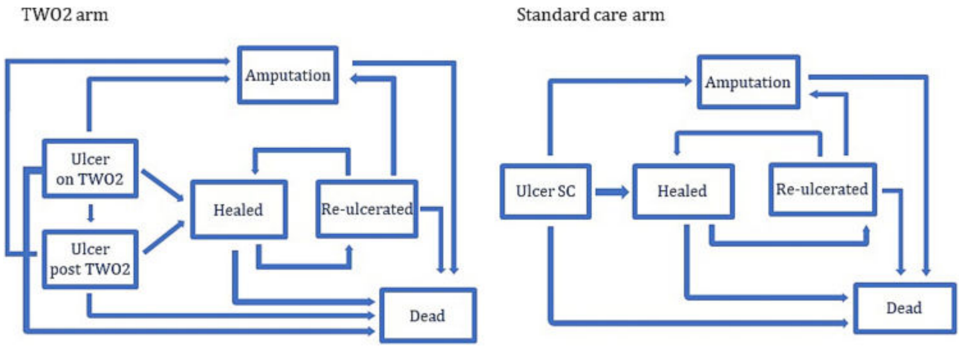

Fig. 1. Markov model states and transitions.

effectiveness and stated that therefore only a conditional recommendation was made.

The purpose of this paper is to address the evidence gap identified by the IWDGF, estimating cost effectiveness for topical oxygen relative to standard care, so decision makers can understand the potential clinical gain and longer-term financial savings in relation to the up-front costs of the treatment. It focuses on a multi-modality cyclically pressurised topical wound oxygen (TWO2) therapy provided by Advanced Oxygen Therapy Inc. (AOTI), San Diego, CA, USA.

TWO2 combines cyclical pressure oxygen, non-contact compression and humidification. It is patient-administered and designed for use in a patient's own home. A recent multinational double-blinded randomised control trial reported that 41.7 % of chronic DFUs treated with TWO2 were healed after 12 weeks, compared with 13.5 % in the control arm (hazard ratio 4.66 (97.8 % CI 1.36, 15.98), $P = 0.004$ after adjustment for University of Texas Classification ulcer grade).[15] At 12 months post-enrolment, 56 % of intervention arm ulcers were closed compared with 27 % of control arm ulcers ($P = 0.013$).

In this paper, the results of the RCT are used to develop an economic model estimating the cost effectiveness of TWO2 treatment relative to standard care over 2 years. Results over 1 year are also presented.

Estimation of cost effectiveness in relation to diabetic foot care is challenging as care is often provided by multiple organisations and clinical disciplines, and data on both activity and unit costs are generally incomplete. In this paper, costs are estimated using data for the NHS in England. Measurement of activity and costs is somewhat easier in England than in many other health economies owing to the existence of a universal healthcare system which collects national data on hospital activity and costs. There are also other resources, including a National Diabetes Footcare Audit, which provide information on ulcer duration, severity and outcomes. Even so, these datasets do not cover all aspects of care, and some costs for the economic model have been based on peer-reviewed economic literature and expert opinion.

2. Methods

A Markov model was constructed to simulate care pathways, outcomes and costs for a cohort of patients with hard to heal diabetic foot ulcers. Markov models are frequently used in health economics to model the impact of alternative treatments on clinical outcomes and costs. They contain two or more treatment arms, and in each arm there is a finite set of health states in which an individual can be found. Time is represented by cycles of a defined length and in each cycle patients can move between states or stay in the same state, with movements defined by transition probabilities. Unit costs and utilities are attached to each health state and are allocated in each cycle. Utilities are summed to estimate quality-adjusted life years (QALYs). At the end of the model, cost effectiveness results are generated by comparing costs and QALYs accrued in each arm.

In this model, there are two arms. All patients start with a hard to heal diabetic foot ulcer. In one arm, patients start TWO2 care at the beginning of the model and in the other arm patients receive standard care. The cycle length is one week. Costs and QALYs are discounted at 3.5 % a year. Markov states and transitions are shown in Fig. 1.

2.1. Probabilities

Probabilities for the model were estimated from the TWO2 RCT.[15] As probabilities were reported over longer time frames than a week, source probabilities were first converted into rates and then into weekly probabilities. Healing probabilities for weeks 1–12 and 13–52 were calculated for each arm of the model based on the proportion of ulcers closed at 12 and 52 weeks in the RCT. The weekly healing probabilities for each arm were scaled to take account of re-ulceration, amputation and death, which impact the number of patients ulcerated in each week of the model. Weekly probabilities of re-ulceration were estimated for each arm using the mean number of weeks in the healed state. For amputation and death there was no statistically significant difference between arms in the RCT. Probabilities for these outcomes were therefore based on pooled values from the RCT and applied to both arms. As the model allows amputation only while ulcerated, the calculation of the weekly probability of amputation was based on the mean number of ulcerated weeks estimated in the model (Table 1).

As the RCT followed patients for 12 months and the model runs for 2 years, there is uncertainty over transition probabilities in year 2. It is assumed that the weekly probabilities of healing and re-ulceration for standard care in year 2 are equal to those for weeks 13–52. In the base case it is assumed that the benefit of TWO2 diminishes linearly over weeks 53–78, converging with standard care probabilities in week 78, and that from weeks 79–104 the probabilities are the same for both arms. In sensitivity analysis TWO2 and standard care probabilities are set equal throughout year 2. The probabilities of amputation and death are the same in years 1 and 2, and the same for both arms.

2.2. Costs

Costs were estimated from the perspective of the healthcare funder (in England, the NHS) and expressed in 2024–25 UK pounds. Where costs were derived from earlier years, these were adjusted for inflation using factors derived from Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care.[16] While all costs in the model were sourced from the UK, the paper refers also to costs in other countries. These were inflation-adjusted using local healthcare inflation indices and converted to pounds using the exchange rate on 28/06/24 (£1 = US$1.26 and €1.18).

The price of the intervention (supplied by AOTI) is £650 a week, provided for a maximum treatment period of 12 weeks. Healing is assessed weekly and, for patients who heal within 12 weeks, the total cost of TWO2 care is calculated pro rata on a weekly basis. No charge for TWO2 is made after the end of the week in which healing occurs.

Table 1
Markov model inputs.

	Value	Source/Notes
Weekly probabilities		
Ulcer to healed, weeks 1–12: standard care	0.0132	Frykberg et al.[15]
Ulcer to healed, weeks 1–12: TWO2	0.0459	
Ulcer to healed, weeks 13–104: standard care	0.0089	
Ulcer to healed, weeks 13–52: TWO2	0.0110	
Ulcer to healed, weeks 53–104: TWO2	See note	Linear convergence with standard care weeks 53–78; equal to standard care weeks 79–104. Varied in sensitivity analysis.
Ulcer to amputation: standard care and TWO2	0.0022	Combined results of TWO2 and standard care reported in Frykberg et al.[15] adjusted to apply to ulcerated period only.
Healed to re-ulcerated: standard care	0.0124	Frykberg et al.[15]
Healed to re-ulcerated, weeks 1–52: TWO2	0.0016	
Healed to re-ulcerated, weeks 53–104: TWO2	See note	Linear convergence with standard care weeks 53–78; equal to standard care weeks 79–104. Varied in sensitivity analysis.
Re-ulcerated to amputation: standard care and TWO2	0.0022	Assumed equal to probability for ulcer to amputation
Death	0.0011	Frykberg et al.[15]
Weekly costs		
Ulcer: standard care (weekly)	£457, reduced to £171 in the last 3 weeks before healing	Kerr et al.,[9] NDFA,[26] NHS Reference Costs.[27] Weighted average cost based on 60 % severe ulcers. Costs scaled on assumption that all ulcers have less severe ulcer costs in last 3 weeks before healing.
Ulcer: during TWO2 treatment (weekly)	£1061, reduced to £804 in the last 3 weeks before healing	AOTI cost of £650 a week, plus 90 % of standard care costs. Costs (other than those for TWO2 treatment) scaled in last 3 weeks before healing, as for standard care.
Ulcer: post-TWO2 (weekly)	£457, reduced to £171 in the last 3 weeks before healing	As for ulcer: standard care
Re-ulcerated (weekly)	£457, reduced to £171 in the last 3 weeks before healing	As for ulcer: standard care
Amputation: one-time cost including inpatient rehabilitation	£14,148	NHS Cost Collection for surgical admission: HRGs YQ21–22 (major) and YQ23–26 (minor).[17] Foot Care Profiles for ratio of major to minor amputations.[18] Expert opinion for proportion of major amputees discharged to specialist rehabilitation centre/community hospital. Day rates from HRG VC14Z for specialist rehabilitation,[17] cost of standard NHS bed day for community inpatient care.[25]
Post-amputation: weekly	£22	Kerr et al.[9] for unit costs. Foot Care Profiles for ratio of major to minor amputations.[18] 2-year costs calculated and distributed weekly.
Utilities		
All ulcer and re-ulcerated states	0.44	Tennvall et al.[30]
Healed	0.6	
Amputation and post-amputation	0.53	Tennvall et al. for major and minor amputation.[30] Weighted using proportion of major amputations in Diabetes Foot Care Profiles.[18]

For ulcer care in inpatient settings and acute amputation care, NHS datasets provide details of activity and costs. These were assessed for completeness, analysed, and supplemented where necessary. For the other two elements, ulcer care in community, primary and outpatient settings and post-amputation care, no relevant national datasets were identified. Costs were estimated from the literature. Expert opinion was sought to identity any areas of current practice not captured in national data or the literature. Unit costs and sources are summarised in Table 1.

2.2.1. *Acute amputation care*

Each year, the NHS publishes data on mean costs in acute hospitals in England for inpatient admissions and other activities. Inpatient care is classified using Healthcare Resource Groups (HRGs). Activity is allocated to HRGs using diagnosis (ICD-10) and procedure (OPCS-4) codes. Each HRG is designed to cover activity that is clinically related and similar in cost. For the model, surgical admission costs for major (above ankle) amputation were estimated from the weighted average cost in HRGs YQ21 and YQ22 (Amputation of single limb with or without other blood vessel procedure, sub-divided by complication and comorbidity score) in the 2021–22 National Cost Collection. Costs for minor (below ankle) amputation were estimated from the weighted average cost in HRGs YQ23–26 (Multiple/Single amputation stump or partial foot amputation procedures for diabetes/arterial disease). The weighted average cost (inflation-adjusted) is £18,935 for HRGs YQ21–22 and £10,156 for HRGs YQ23–26.[17] The NHS also regularly publishes Diabetes Foot Care Profiles, which provide counts of major and minor amputations in diabetes in England over a 3-year period. In 2018–21, 27 % of these amputations were major and 73 % were minor.[18] Using these proportions, the mean cost of a hospital admission for amputation surgery was estimated at £12,525.

2.2.2. *Post-amputation care*

Inpatient rehabilitation after amputation is associated with increased survival and mobility.[19–21] In some health economies, around a third of patients receive inpatient rehabilitation after amputation, with typical lengths of stay of 4–9 weeks.[22,23] In England, routine datasets do not provide details of this care, and there are regional disparities in provision.[24] We assume here, based on advice from surgical and rehabilitation experts from a number of centres in England, that 6.7 % of patients who have undergone amputation receive inpatient rehabilitation (25 % of those who have had major amputation and none of those who have had minor amputation). It is estimated that care is provided in a specialist centre for 2.7 % and in a community hospital for 4 %, with mean length of stay of 7 weeks. The cost of a bed day in a specialist centre is taken from the NHS National Cost Collection, HRG VC14Z Rehabilitation for amputation of limb (£612.46 after inflation adjustment),[17] and the cost of a standard NHS bed day without treatment costs is used for care in a community centre (£409.89).[25] Apportioning these additional costs across all amputations adds £1622.80 to the mean cost, taking the total mean cost of acute amputation care to £14,148. These assumptions are tested in sensitivity analysis. Costs for other post-amputation care, including prosthetics, wheelchairs and physiotherapy

Table 2
Mean healthcare costs and QALYs per patient over 1 and 2 years, TWO2 and standard care, base case.

		TWO2		Standard Care		Net impact of TWO2	
		Cost	QALY	Cost	QALY	Cost	QALY
Year 1	TWO2	£6002		£0		£6002	
	Ulcer care	£11,266		£17,469		-£6204	
	Amputation	£850		£1242		-£392	
	TOTAL	£18,118	0.50	£18,711	0.46	-£593	0.04
Year 2	TWO2	£0		£0		£0	
	Ulcer care	£7527		£11,651		-£4124	
	Amputation	£592		£913		-£321	
	TOTAL	£8119	0.48	£12,564	0.45	-£4445	0.03
2-year cumulative	TWO2	£6002		£0		£6002	
	Ulcer care	£18,793		£29,121		-£10,328	
	Amputation	£1442		£2155		-£713	
	TOTAL	£26,237	0.98	£31,275	0.91	-£5038	0.07

are taken from Kerr et al.[9] The mean cost of these elements of care is estimated at £2142 per patient over 24 months, equivalent to £21.98 per week.

2.2.3. Inpatient ulcer care

The weekly cost of ulcer-related hospital admissions was estimated based on National Diabetes Foot Care Audit (NDFA) activity data and NHS Reference Costs. The NDFA reports that the mean number of inpatient bed days per ulcer within 6 months of first expert assessment was 1.49 for less severe ulcers and 6.91 for severe ulcers (based on 33,155 ulcers in England and Wales in 2015–18).[26] We estimated mean ulcer duration during the 6 months after first expert assessment at 12.1 weeks for less severe ulcers and 16.7 weeks for severe ulcers, based on reported healing rates at 12 and 24 weeks in NDFA. Using the weighted average bed day cost from HRGs KB03C-D (Diabetes with lower limb complications) in NHS Reference Costs 2017–18 (inflation-adjusted), £541.54, the average cost of inpatient care per ulcerated week is estimated at £66.65 for less severe ulcers and £224.15 for severe ulcers.[27] (These mean costs are across all ulcers, not just those that necessitated a hospital admission. 2017–18 Reference Costs are used as more recent National Cost Collection publications do not provide bed day counts.)

2.2.4. Ulcer care in outpatient, community and primary care settings

The weekly cost of outpatient, community and primary ulcer care was estimated from Kerr et al. at £104.70 for less severe ulcers and £351.85 for severe ulcers, after inflation adjustment.[9]

2.2.5. Weighting costs for ulcer severity

Ulcer severity in the NDFA and in Kerr et al. is measured at first expert assessment, and this approach is adopted in the model. Around 43 % of all ulcers recorded in NDFA are severe at first assessment. Amongst ulcers eligible for treatment with TWO2 the proportion that are severe (at first expert assessment) will be higher than the proportion amongst all ulcers registered in NDFA, as ulcers eligible for TWO2 have duration of at least 4 weeks plus a run-in period of 2 weeks in which they have not reduced in size by ≥30 %, and less severe ulcers are more likely to have healed or reduced in size during that time. Supplementary modelling was undertaken to estimate the proportion of ulcers at 6 weeks from first expert assessment that would have been categorised as severe at first assessment, based on healing data from NDFA for severe and non-severe ulcers in the first 12 weeks, and assuming a constant weekly probability of healing for each ulcer type during that period. The estimate produced was 60 %, and this proportion was used to calculate a mean weekly ulcer care cost.

2.2.6. Scaling of severe ulcer costs as ulcers heal

Ulcers that are severe at the outset are likely to become less severe as they approach healing. For example, area and depth are likely to reduce, and there is less likely to be infection.[28,29] The estimated total cost of a severe ulcer of mean duration was therefore redistributed over the period of ulceration so that in the final three weeks before healing the costs are equivalent to those for less severe ulcers. Severe ulcer costs for the earlier weeks were adjusted upwards so total costs for an ulcer of mean duration were unchanged.

2.2.7. Ulcer costs during TWO2 care

Expert opinion suggests that ulcer care costs are likely to be reduced while patients are receiving TWO2 (over and above the reduction in costs as patients approach healing, outlined above). As patients are receiving an evidence-based treatment with support provided by AOTI, they may need fewer podiatry clinic visits. The likelihood and duration of hospital admission may also be reduced. There is uncertainty regarding the scale of these impacts. In the base case, other ulcer care costs were reduced by 10 % while patients are receiving TWO2. This reduction was varied in sensitivity analysis.

2.3. Utilities

Utility values for the model were taken from Tennvall et al.[30] (Table 1).

2.4. Validation

Tests of technical, face and predictive validity were conducted on model structure, inputs and outputs. Projected clinical outcomes including active ulcer, amputation and death were validated against year 1 endpoints reported in the RCT. Year 2 outcomes were checked for clinical plausibility. All inputs to the model were varied across plausible ranges and with extreme values to test the robustness of model behaviour, and both clinical and cost outputs were found to respond appropriately.

2.5. Sensitivity analyses

Deterministic and probabilistic sensitivity analyses were performed on all key variables to explore the robustness of base case results to parameter uncertainties and modelling assumptions. In deterministic analysis, (1) all key parameters were altered by ±20 %; (2) the probabilities of healing and re-ulceration in TWO2 patients were (a) set equal to those for standard care from week 53 and (b) diminished linearly from week 53 to converge with standard care probabilities in week 104 - this sensitivity analysis was undertaken for healing and re-ulceration separately and for the two outcomes combined; (3) the change in the costs of other ulcer care during TWO2 treatment was set at (a) zero and (b) -20 %, and (4) the relative risks for healing and re-ulceration with TWO2 versus standard care were altered to the bounds of the 95 % confidence intervals, estimated from log normal distributions.

In probabilistic analysis, a Monte Carlo simulation was used with

Table 3
Deterministic sensitivity analysis, net QALYs and costs per patient over 2 years, TWO2 relative to standard care.

Parameter	Sensitivity	Net QALYs, TWO2	Net cost, TWO2
Probability of healing: standard care	20 % below base case	0.08	-£6712
	20 % above base case	0.06	-£3517
Probability of healing in year 1: TWO2	20 % below base case	0.05	-£2045
	20 % above base case	0.08	-£7592
Time at which ongoing weekly probability of healing in TWO2 patients matches standard care	At start of year 2	0.07	-£4924
	By end of year 2	0.07	-£5121
Probability of re-ulceration: standard care	20 % below base case	0.07	-£4702
	20 % above base case	0.07	-£5325
Probability of re-ulceration: TWO2	20 % below base case	0.07	-£5201
	20 % above base case	0.07	-£4878
Time at which ongoing weekly probability of re-ulceration in TWO2 patients matches standard care	At start of year 2	0.06	-£4127
	By end of year 2	0.07	-£5716
Time at which ongoing weekly probability of **both** healing and re-ulceration in TWO2 patients match standard care	At start of year 2	0.06	-£4009
	By end of year 2	0.07	-£5795
Probability of amputation	20 % below base case	0.07	-£5106
	20 % above base case	0.07	-£4971
Probability of death	20 % below base case	0.07	-£5139
	20 % above base case	0.07	-£4940
Cost of ulcer care	20 % below base case	0.07	-£2972
	20 % above base case	0.07	-£7103
Reduction in ulcer care cost during TWO2 treatment	No reduction	0.07	-£4649
	20 % reduction	0.07	-£5427
Cost of amputation inpatient care including inpatient rehabilitation	20 % below base case	0.07	-£4906
	20 % above base case	0.07	-£5170
Cost of other post-amputation care	20 % below base case	0.07	-£5027
	20 % above base case	0.07	-£5049
Utility - ulcerated	20 % below base case	0.11	-£5038
	20 % above base case	0.03	-£5038
Utility - post healing	20 % below base case	0.01	-£5038
	20 % above base case	0.13	-£5038
Utility - post amputation	20 % below base case	0.07	-£5038
	20 % above base case	0.06	-£5038
Relative risk of healing weeks 1–12, TWO2:standard care	95 % CI lower bound	0.03	£2597
	95 % CI upper bound	0.16	-£20,725
Relative risk of healing weeks 13–52, TWO2:standard care	95 % CI lower bound	0.05	-£2604
	95 % CI upper bound	0.11	-£11,601
Relative risk of re-ulceration, TWO2:standard care	95 % CI lower bound	0.07	-£5820
	95 % CI upper bound	0.05	-£1854

parameter inputs (treatment effects, costs and utilities) drawn by random sampling from probability distributions around the point estimate. Log normal distributions were used for relative risks, beta distributions for inputs bounded by 0 and 1, and gamma distributions for costs. Standard errors for relative risks for healing and re-ulceration were calculated from the RCT results. For other variables, we assumed standard errors of 10 % of the point estimate. Results were simulated over 5000 runs, after which cost-effectiveness outcomes had stabilised.

3. Results

The base case model clinical outcomes at 12 months closely match those observed in the RCT, with 55.6 % of TWO2 patients and 27.0 % of standard care patients alive and ulcer free. The model projects that after 24 months, 43.5 % of TWO2 patients and 30.4 % of standard care patients are ulcer-free; 8.9 % of TWO2 patients and 13.4 % of standard care patients have had an amputation. Further details are provided in supplementary material.

The base case results indicate that overall diabetic foot costs for patients who receive TWO2 are likely to be lower than for standard care patients; the net saving per patient is estimated at £5038 over 2 years and £593 over 1 year (Table 2). The mean per patient cost of the TWO2 intervention itself is £6002 (based on a weekly cost of £650 and mean treatment time of 9.2 weeks, estimated from the healing reported in the RCT). Most of the savings arise through averted ulcer care owing to earlier healing. TWO2 treatment is estimated to generate a QALY gain of 0.07 per patient over 2 years. (A QALY gain indicates that a treatment improves quality of life and/or survival relative to the alternative. In this instance the QALY gain arises because more TWO2 patients experience healing, and the healed state has higher quality of life and lower mortality than the ulcerated state. The absolute value of the QALY gain is constrained by the 2-year model duration - many economic models adopt a lifetime perspective.)

3.1. Sensitivity analyses

The model predicts that TWO2 increases QALYs relative to standard care in all deterministic sensitivity analyses undertaken (Table 3). The relative probability of healing between TWO2 and standard care and the cost of standard ulcer care have the greatest impact on cost effectiveness.

If the year 1 probability of healing with standard care is increased by 20 %, or the probability with TWO2 is reduced by 20 %, both the net QALY gain and the financial benefit of TWO2 are reduced, but TWO2 remains QALY increasing and cost saving. If the probabilities of healing and re-ulceration are both set equal for the two arms from the end of year 1, again TWO2 remains QALY increasing and cost saving. In relative risk sensitivity analysis, TWO2 remains QALY increasing and cost saving at the boundaries of the 95 % confidence intervals for both healing in weeks 13–52 and re-ulceration. At the lower bound of the confidence interval for healing in weeks 1–12, TWO2 increases QALYs but is cost incurring (£2597). If the cost of standard ulcer care is 20 % lower than base case, TW02 remains cost effective and cost saving.

In probabilistic sensitivity analysis, the average results align with the deterministic base case. 97 % of iterations show a QALY gain for TWO2, and 76 % of iterations show a cost saving. The treatment is cost effective in 81 % of iterations at a willingness to pay threshold of £25,000 per QALY, and in 85 % of iterations at a threshold of £50,000 (Fig. 2).

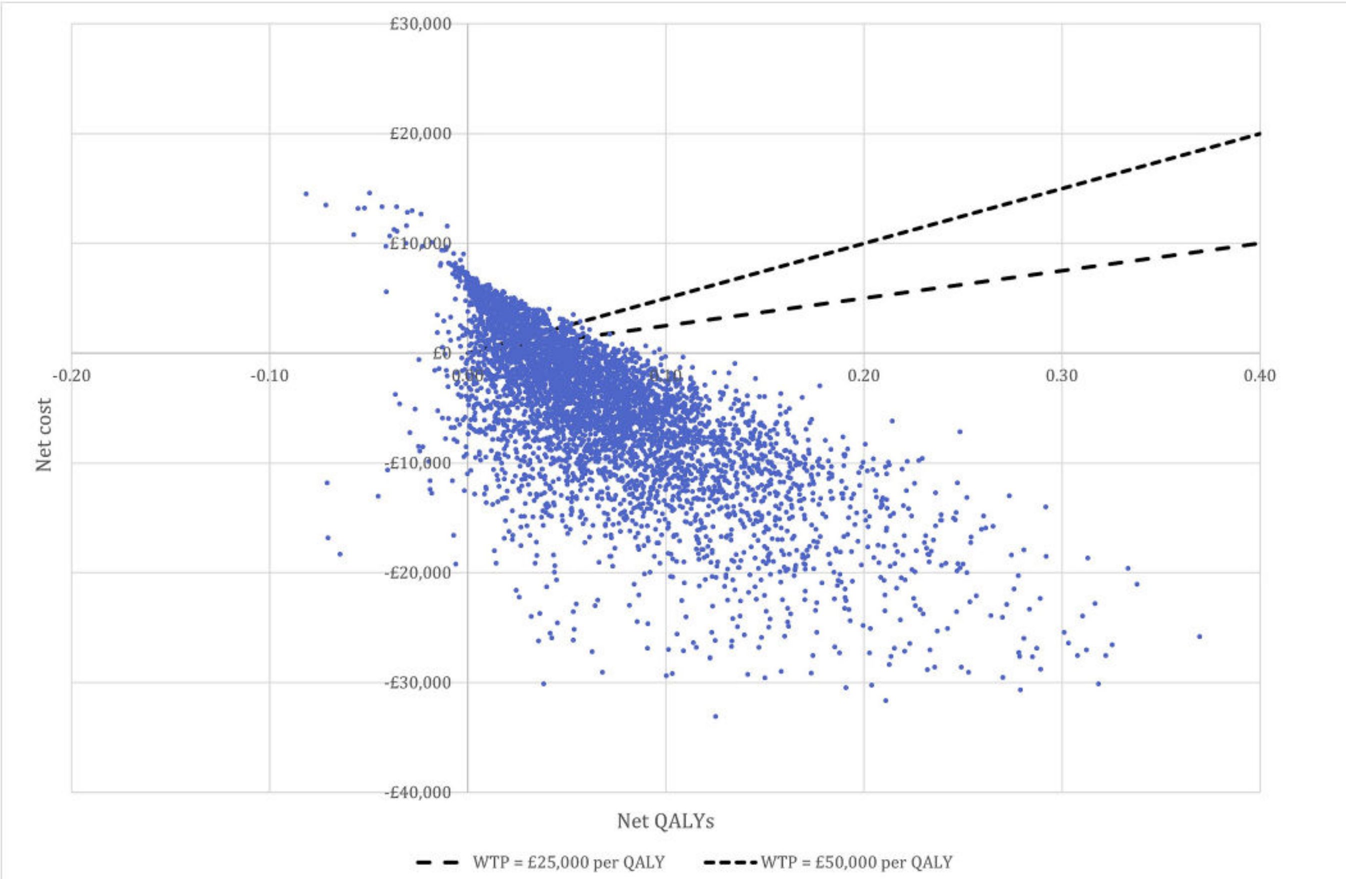

Fig. 2. Probabilistic sensitivity analysis results, net QALYs and costs per patient.

4. Discussion

This is, to our knowledge, the first published estimation of the cost effectiveness of topical wound oxygen treatment for chronic diabetic foot ulcers. Our study estimates that TWO2 results in a per patient saving of £5038 over 2 years at a weekly price of £650 for a maximum treatment period of 12 weeks, if routine care treatment effects match those observed in the RCT. As the IWGDF has indicated, informed decision-making on adoption of new treatments requires information on cost effectiveness, as healthcare systems seek value for money and equity in the allocation of finite healthcare budgets. It is hoped that our estimates of costs and offsetting savings will support clinicians and budget holders considering adoption of topical oxygen therapy.

While the clinical inputs to our model are taken from the multinational TWO2 RCT (with participating centres in France, Germany, Luxembourg, UK and US), the cost inputs are specific to England. Both patterns of care and unit costs may vary considerably across health economies, and this may limit the application of cost effectiveness findings across jurisdictions. The model indicates that the costs of standard ulcer care, in particular, are likely to impact cost effectiveness, as these represent the majority of diabetic foot care costs. The higher the cost of standard ulcer care, the more likely that an intervention that increases healing will be cost effective at a given price. While the unit cost of amputation is high, amputations are relatively rare events and have a much smaller impact on cohort-level costs, as shown in Table 2.

The weekly cost of care for non-healing ulcers estimated across seven European countries in the Eurodiale trial (Czech Republic, Denmark, Italy, Netherlands, Slovenia and the UK) was €361 in 2005 (€605 after inflation adjustment, equivalent to £512).[10] This is somewhat higher than the weekly ulcer care cost estimated for this model (£457), but nonetheless the model may provide a good starting point for assessment of cost effectiveness in Europe, with appropriate validation of cost inputs using country-specific data. In the United States, care costs are very much higher than in Europe. A 2019 US study estimated the average weekly cost of ulcer care at more than twice the estimate used in the model, suggesting that if the price of topical oxygen were the same as in the model, cost effectiveness may be much greater in the US.[31]

In lower income countries, available resources, treatment plans and unit costs are likely to differ substantially from those in the model. In 2012, the cost of care for severe ulcers in Tanzania was estimated at one sixtieth of the cost in the US, after adjustment for differences in purchasing power.[32] The likelihood that a treatment will be cost effective at a given price is of course much smaller where standard care costs are relatively low.

The lack of trial data for the second year after treatment is a limitation to our study. In the base case we assumed that healing and re-ulceration probabilities for TWO2 and standard care patients converge linearly over months 13–18 and are equal thereafter. However, in sensitivity analysis we explored the impact of no TWO2 advantage in healing or re-ulceration rates in the second year (i.e. the probabilities for both outcomes are equal to those for standard care patients from the end of year 1), and the intervention remains cost saving. It is the differential in the percentage of patients healed at the end of year 1, as observed in the RCT, that accounts for most of the cost difference in year 2; 59 % of standard care patients remained ulcerated at this point and thus require ongoing ulcer care, compared with 33 % of TWO2 patients.

A further limitation is uncertainty regarding the likely reduction in standard care costs during the TWO2 treatment period. In the base case we estimate a reduction of 10 % in these costs, based on expert advice. In sensitivity analysis we set this reduction at zero, and topical oxygen remains cost saving.

As TWO2 is adopted for routine care it is recommended that further research is undertaken on clinical outcomes outside the trial setting, and on cost impacts relative to standard care in jurisdictions other than the UK.

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CRediT authorship contribution statement

Marion Kerr: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Daisy Wild:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Michael Edmonds:** Writing – review & editing. **Andrew J.M. Boulton:** Writing – review & editing, Conceptualization.

Author statement

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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Declaration of competing interest

This study was funded by AOTI Inc., USA (see details under Funding Source). MK and DW have no other interests to declare. ME: Advisory Boards: Convatec, IsomAb, AJMB: Advisory Boards: Nevro Inc., Bluedrop Ltd., Diabetis jsc, AOTI Inc., Viatris, Worwag. Speakers Bureau: Urgo (France), Diabetis jsc, AOTI Inc., Nevro Inc.

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