Cost-utility of a biofilm-disrupting gel versus standard of care in chronic wounds: a Markov microsimulation model based on a randomised controlled trial

Objective: Analyse the cost-effectiveness and treatment outcomes of debridement (standard of care) plus BlastX, a biofilm-disrupting wound gel (group 1) or a triple-antibiotic, maximum-strength ointment (group 2), comparing a subset of patients who had not healed at four weeks using the ointment crossed-over to the biofilm-disrupting gel (group 3).
Methods: A series of Markov microsimulation models were built using health states of an unhealed non-infected ulcer, healed ulcer, and infected non-healed ulcer and absorbing states of dead or amputation. All patients started with unhealed non-infected ulcers at cycle 0. Complications and healing rates were based on a randomised controlled trial (RCT). Costs were incurred by patients for procedures at outpatient wound care clinics and hospitals (if complications occurred) and were in the form of Medicare allowable charges. Quality-adjusted life years (QALYs) were computed using literature utility values. Incremental cost-effectiveness ratios (ICERs) were calculated for group 1 versus group 2, and group 3 versus group 2. One-way, multi-way and probabilistic sensitivity analysis (PSA) was conducted.
Results: After one year, the base case ICER was $8794 per QALY for group 1 versus group 2, and $21,566 per QALY for group 3 versus group 2. Product cost and amputation rates had the most influence in one-way sensitivity analysis. PSA showed that the majority of costs were higher for group 1 but effectiveness values were always higher than for group 2. Average product use of 3.1ml per application represented 9.4% of the total group 1 cost (average $24.52 per application/$822.50 per group 1 patient). The biofilm-disrupting gel group performed substantially better than the current cost-effectiveness benchmarks, $8794 versus $50,000, respectively. Furthermore, when biofilm-disrupting gel treatment was delayed, as in group 3, the ICER outcomes were less substantial but it did remain cost-effective, suggesting the added benefits of immediate use of biofilm-disrupting gel. Also, when product cost assumptions used in the study were halved (Wolcott study usage), the model indicates important reductions in ICER to $966/QALY when comparing group 1 with group 2. It should be noted that product cost can hypothetically be affected not only by direct product purchase costs, but also by application intervals and technique. This suggests additional opportunities exist to optimise these parameters, maximising wound healing efficacy while providing significant cost savings to the payer.
Conclusion: The addition of the biofilm-disrupting gel treatment to standard of care is likely to be cost-effective in the treatment of chronic wounds but when delayed by as little as 9–12 weeks the ICER is still far less than current cost-effectiveness benchmarks. The implication for payers and decision-makers is that biofilm-disrupting gel should be used as a first-line therapy at the first clinic visit rather than waiting as it substantially decreases cost-utility.
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biofilm disruption agent • biofilm • chronic wounds • cost utility • health economics

Acute wounds progress through several phases to final healing. When factors interfere with this orderly progression, this causes healing to stop and the wound to become chronic,[1] and one of the most common factors for this is biofilm. Unlike planktonic bacteria, which exists as independent cells, biofilm is composed of microorganism aggregates protected by a non-crystalline extracellular matrix (ECM), extracellular polymeric substances (EPS), which is made of proteins, polysaccharides, lipids and other macromolecules.[2–5]

Biofilms frequently present without overt clinical symptoms of infection, are difficult to visualise except through imaging techniques due to their depth, and hard to eradicate by antibiotics because the tough EPS encapsulation makes penetration difficult. Moreover, with time, biofilm can adapt and evolve with cooperation of different species (quorum sensing), which provides further protection of bacteria from antibiotics and host defences. That said, the most important characteristics in wound healing impediment are the biofilm's virulence and pathogenicity,[6] which may be dependent on the prevalence of less common species and their ability to form polymicrobial colonies.[7–9]

Debridement is the chief means of biofilm removal. However, there is increasing clinician consensus that debridement cannot entirely remove biofilm associated with chronic wounds and that it can reform in a matter of days.[10–13] Attinger and Wolcott[14] suggest that even with weekly debridement, wound healing may still only occur for less than half of that week due to

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regrowth of biofilm, although the maturity (age) of the biofilm undoubtedly has a further mediating effect.[12]

The use of additional treatments to synergistically disrupt biofilm, particularly when it is most vulnerable, post-debridement, due to the need for increased metabolic activity for reconstitution, is becoming popular. One such product is a biofilm-disrupting gel, based on polyethylene glycol-based hydrogel with a pH buffer system and benzalkonium chloride surfactant that can destroy biofilms. This biofilm-disrupting gel was recently tested in a randomised controlled trial (RCT) in which patients with chronic wounds of at least one month's duration were randomised to either standard of care (SoC; weekly debridement, evaluation and 'personalised' treatment which consisted of a gel containing antibiofilm agents and antibiotics based on extensive testing), biofilm-disrupting gel only (BlastX, Next Science, US), or biofilm-disrupting gel plus SoC.[15] Healing was defined as a reduction in wound volume ≥50% over four weeks. The best result was the biofilm-disrupting gel plus SoC which, at 93%, had a statistically significant advantage over the other groups ($p<0.05$).

In another RCT, patients with chronic wounds of at least one month's duration were randomly assigned to SoC (weekly debridement and daily dressing change) or biofilm-disrupting gel plus SoC. Patients in the SoC arm who failed to respond to treatment were permitted to cross over to the biofilm-disrupting gel arm.[16] After 12 weeks' treatment, results showed a statistically significant improvement in complete wound healing in the biofilm-disrupting gel group versus the SoC group (52% versus 17%; $p<0.01$).

Wolcott reported that employing biofilm-based wound management strategies in treating diabetic foot ulcers (DFU) may also save health-care system costs. A retrospective analysis reported a reduction in total charges of 68% for patients with DFUs that were treated with biofilm-based wound management guided by molecular diagnostics, personalised gels and commercially available topical antibiotics versus conventional wound care.[17] Consequently, it was of interest to determine whether health economics were favourable for the biofilm-disrupting gel group compared with the SoC group in the most recent RCT.[16]

The objective of this study was to determine the cost-effectiveness of biofilm-disrupting gel by modelling the trial results using a Markov microsimulation approach for three groups.

Methods

Study participants, design and interventions

All data were taken from the biofilm-disrupting gel RCT.[16] In the original trial there were three groups:

- Intervention (daily application of biofilm-disrupting gel) plus SoC (group 1)
- Control (daily application of Neosporin, Johnson&Johnson, US) plus SoC (group 2)
- Patients from group 2 who received biofilm-disrupting gel after a delay (group 3).

Original randomisation was 1:1 for groups 1 and 2. In the original analysis of the RCT, groups 2 and 3 were combined. The numbers of participants in each group were: (group 1) 22; (group 2) 9; (group 3) 12.

Clinical outcomes

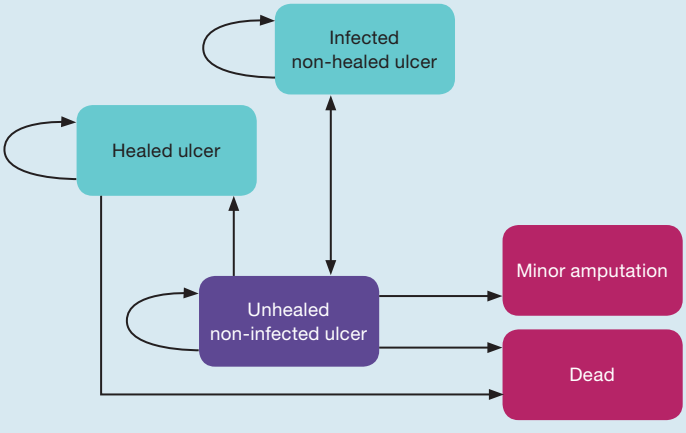
Complete wound healing was a secondary endpoint in the trial: the percentage of wounds closed was reported as 53% for group 1 versus 17% for groups 2 and 3 ($p<0.01$). Further analysis of this trial[16] showed that when three separate groups were created and outcomes extended to 20 weeks the proportion of wounds closed for group 1 was 9/22 (41%; all within 12 weeks); for group 2 it was 3/9 (33%; all within 12 weeks); and for group 3 it was 4/12 (33%; all within 20 weeks from randomisation).

Economic analysis

Health economic analysis carried out was group 1 versus group 2, and group 3 versus group 2. Withdrawals of patients in the trial were handled in an analogous manner to intention-to-treat; for example, a patient who withdrew consent was kept in the simulation. Complications that did not result in transitions to different health states were handled similarly by attaching costs at the appropriate point in time. Calibrating models at 12 weeks for percentages of wounds that actually healed in each group ensured that the wounds of such withdrawn patients were not healed within the primary time frame of the trial (12 weeks) and appropriate costs were captured. Modelling the trial out to one year required not only capturing healing of patients in group 3 (for which data were available for a further eight weeks) but developing appropriate healing rate curves for all groups and applying reasonable probabilities for complications and transitions to other health states besides a healed wound that were not based solely on small group statistics.

Cost-effectiveness analyses captured relevant wound-related costs[17] incurred by subjects at outpatient wound care clinics and in hospitals if complications occurred, using trial data. Costs were in the form of Medicare (US)

Fig 1. Health states used in Markov microsimulation models



allowable charges. Effectiveness units were quality-adjusted life years (QALY) computed by using literature utility values. Half cycle corrections were applied to cycle rewards. These corrections are used to compensate for the fact that in discrete, computer-based Markov models, transitions between states are usually modelled to occur at the beginning or end of a cycle, whereas, in reality, transitions occur in the middle of each cycle, on average.[18]

Patient Markov microsimulation models were built using Monte Carlo approaches to analyse cost-effectiveness using Treeage Pro software (2017; R2.1). The starting health state was an unhealed non-infected ulcer with other health states of healed ulcer, infected non-healed ulcer and the absorbing states, (a health state from which no transition to another health state is possible), of dead and minor amputation (Fig 1). In all models, subjects started with unhealed non-infected ulcers.

Model inputs: time horizon and perspective

Models were built with time horizons of one year. The perspective of the study was the payer,[19] which in this case is Medicare.

Health state transition probabilities

Probabilities of developing complications—i.e., amputation or infection—were calculated using data from the trial.

Epithelialisation rates

A logistic regression was performed using group 1 and groups 2 and 3 combined as a binary treatment variable, and the presence of peripheral arterial disease (PAD) (category) and initial wound age and area as additional covariates with healing after 12 weeks of treatment as the dependent variable. None of the covariates were even marginally significant (i.e. $p<0.1$) in the model. Model fit (Hosmer and Lemeshow) was also non-significant and Nagelkerke R^2 was 0.306. If the model had demonstrated that any of the covariates had been statistically significant—for example, as a result of imbalances between groups—this would have been grounds for adjusting the wound healing trajectory. Although it can be argued that the model may be statistically underpowered in regard to outcomes, we chose not to make any adjustment of initial healing rates (weeks 1–12) because there was insufficient information to do so.

Due to limitations of healing rate data in the first 12 weeks (and 12–20 weeks for group 3) a simple spline function could not be used. Instead, the healing rate curve for group 1 was initially constructed using a knot between weeks 12 and 13. Using healing rate percentages and time (unit of days), the equation developed for weeks 0 through 12 was $y=0.0032x2+ 0.226x$ ($R^2=0.937$). Using actual wound healing percentage points at 11 and 12 weeks and setting the percentage of healed wounds to 80% at one year based on the Kaplan-Meier data of Beckert et al.[20] with two additional estimated points at 48 and 50 weeks, resulted in a fitted curve of $y=–0.0002x2 + 0.248x + 16.1$ ($R^2=0.986$). This curve was used for weeks 13–52. The data between weeks eight and 18 was smoothed using a quadratic function.

Healing rates for group 2 for weeks 0–12 were constructed similarly to group 1 with the equation set at $y=4.5254\ln(x) – 4.2871$ ($R^2=0.815$). It was assumed that by week 20 healing rates for group 2 would be similar to group 1. Therefore, a curve was constructed using a figure of 13.9% healed at week 13 (proportionally weighted according to the second equation for group 2 at 12 weeks), using a final estimated percentage healed rate of 62% at one year based on the healing rate curves derived by Beckert et al.[20] The derived equation was: $y = –0.0004x2 + 0.348x – 11.7$ (R2=0.980).

For group 3, similar principles were used to derive an equation based on healing percentages at 12, 16.7 and 20 weeks (0, 8.3, and 33%, respectively), with a target percentage healed of 60% based on the data from Beckert et al.[20] and two additional interpolated points at 35.7 and 43.9 weeks (52% and 56%, respectively) to refine the equation. The final equation was $y = 4x10–6x3 – 0.0035x2 + 1.122x – 77.7$ ($R^2=0.966$).

Death

Mortality rates were modelled using age structure in five-year increments for each treatment group, based on the method of Carter et al.[21] and adjusted using national census data.[22] The percentage of patients in each age interval was calculated. To obtain a mean age-adjusted annual mortality rate for each treatment group, the following calculation was made:

$$\sum_{i=1}^{n} (Fi/100) \times Pi$$

Where F is the percentage of patients in the age *i*th group and P*i* is the probability of death in moving from the *i*th age group to the *i*th+1 age group, F1 is associated with the age group ≤20 years, and F_n is associated with the age group ≥95 years. The calculated annual mortality rates were: group 1: 8.6%; group 2: 14.0%; group 3: 6.4%. The values for each group were divided by 52 to obtain the nominal weekly mortality rate; these values were adjusted during model calibration. The weekly mortality rate for group 3 was the same as group 2 until week nine.

Amputation

One amputation (transmetatarsal) occurred in group 1 at four weeks. In group 2, two amputations occurred at four and 14 weeks and both involved hallux removal. All amputations occurred in DFUs. Because the numbers were small in each group, it was decided to initially model the incidence of amputations up to 14 weeks per trial results (i.e., 4.5% [1/22] at week four for group 1, 4.8% [1/21] at week four and 11% [1/9] at week 14 for group 2, and 4.8% [1/21] at week four for group 3). (Model calibration ensured that populations reflected

the true incidence of amputation at any given time). The alternative approach would have been to compute smoothed rates over the first 14 weeks but this would have required appropriate mathematical risk of amputation functions for each group that might not be linear and we had no useful data for these populations with which to work. After week 14, the probability of having an amputation was set at 0.7% per week (3/30 DFUs adjusted over a 14-week period), an implied assumption that amputation risk was equivalent across all groups, adjusted for the proportion of DFUs in each group using a reference of 70% as the proportion of DFUs in all groups (these are the wounds at risk for amputation).

Osteomyelitis

A case of worsening osteomyelitis was reported in group 3 at week 16 but no other details were available. The majority of cases of osteomyelitis do involve bone debridement and/or amputation[23] and given that further details were not available, it was decided not to model this disease state but assume that amputation modelling would account for it.

Cellulitis

A case of cellulitis was reported in group 1 at week three with a duration of 11 days in hospital; blood and wound cultures, magnetic resonance imaging (MRI) and X-rays were used for diagnosis and treatment involved IV antibiotics. The patient was not withdrawn from the study. It was modelled by incorporating into healing costs for group 1 at week three (i.e., 1/22 of the cellulitis costs).

Ruptured ulcer

About six months after randomisation, a DFU in group 1 'ruptured' and required bleeding control in the emergency room; the adverse event was resolved. Because this incident occurred long into trial follow-up, it was not modelled.

Vascular surgery

A patient in group 1 required vascular surgery at week four and was withdrawn from the trial. Because in real life patients would return to an outpatient wound care centre after recovery to continue wound treatment, it was decided include the costs of surgery and adjust these costs at week four (i.e., 1/22 of the surgery costs).

Infection

There were several incidences of wound deterioration that suggested serious cases of infection that were not formally described as cellulitis or osteomyelitis. In group 1, three patients had likely infection-related complications: one non-diabetic patient with an unknown wound type had an infection beginning at week three that lasted three weeks; this patient had also developed wound pain a week earlier and was withdrawn at week four for the latter reason. Another patient with a DFU developed a foot abscess at week three that lasted 29 days but was not withdrawn (treatment was unknown). The third non-diabetic patient with an unknown wound type was withdrawn at week four due to a 'deteriorating wound', with no further details given. In group 2 a patient was withdrawn at week 11 due to a deteriorating DFU that involved surgical intervention in hospital and application of Matristem a week later.

All these incidents were treated as an infection-related episode over the first 12 weeks. Because these events clustered around weeks 3–4 for group 1, it was decided to model these wounds using a tunnel parameter of four weeks and a probability of 1 for infection resolution at three weeks. The probability at week three for infection was calculated as 3/22 (13.6%). To simplify the modelling process for both groups 2 and 3, a similar approach was used at week 11 for group 2 only with a probability of 1/9 (11.1%).

For infection episode modelling after 12 weeks the same approach was used as for 12 weeks except that the overall incidence was set to 0.23% per week (9.3% [4/43] divided by 40) for all groups. Wounds were not permitted to become infected more than once.

Wound pain

There were three patients who experienced wound pain, two in group 1 and one in group 2. In group 1 these involved one DFU in which a patient was withdrawn at four weeks (this patient also had a wound infection) and was treated for pain for two weeks, and an unknown wound type in which the patient had ongoing pain but was not withdrawn. The single patient in group 2 with a DFU withdrew consent at two weeks, presumably due to pain.

Such pain is often treated with opioids or neuropathic pain medication. To model pain, the cost of pain medications was applied to cost of unhealed ulcers weekly for the first 12 weeks using a weekly incidence factor of 0.07 (3/42).

Peripheral arterial disease (PAD)

A patient in group 1 was reported to have worsening PAD at week two but the patient was not withdrawn and no treatment details were available. Consequently, as no surgery was reported this complication was not modelled.

Resource use: outpatient clinic visits

The model assumption based on the trial was that subjects had a weekly outpatient clinic visit until healed within the first 12 weeks unless they had a complication lasting more than one week or reached an absorptive state. After 12 weeks, subjects with unhealed wounds were modelled as having an outpatient visit every two weeks per recent findings in regard to outcomes.[24]

Resource use: debridement

In the trial, all wounds had weekly debridement for the first 12 weeks. Data from the largest wound debridement study to date[25] suggest that debridement might occur at least every two weeks for unhealed wounds, and thus a

Table 1. Unit costs (US dollars)

Category	Item	CPT/HCPCS/ (MS-DRG Code)	Medicare allowable charges or cost ($)**	Source
Initial clinic visit*†	(a) Evaluation	G0463	184.49	CMS[24,25]
	(b) Debridement, surgical, cutaneous	11042	356.14	
	(c) Additional 20cm^2 with 11042	11045	26.92	
Established clinic visit*†‡	(a) Evaluation	G0463	158.29	CMS[24,25]
	(b) Debridement, selective	97597	176.81	
	(c) Additional 20cm^2 with 97598	97598	11.13	
Intervention product	(a) Wound gel		235.00	(a) Commercial price, hospital
	(b) Neosporin		6.67	(b) Red Book¶
Offloading	Walking boot (DFU/other wound, foot)	L4386	151.45	CMS[26]
	Group 1 gel pressure mattress pad (PU)	E0185 NU mod	172.89	CMS[26]
Compression‡	High compression bandaging (VLU)	29581	138.43	CMS[24,25]
Dressings¶¶	Non-adherent dressing	—	2.50	ASP
Infection management	Bacterial organism identification			
	(a) Culture, disk method	87184	9.34	CMS[27]
	(b) Nucleic acid quantification, each organism	87799	57.40	CMS[27]
	Antibiotics (outpatient management):			Red Book¶
	(a) Cephalexin 500mg capsule		1.64	
	(b) Amoxicillin clavulanate 500mg tablet (+125mg clavulanic acid]		4.37	
	(c) Levofloxacin 500mg		27.50	
	(d) Wound infection (hospitalised)			
	• Without any complications	(594)	4,776.13	CMS[28]
Cellulitis management	Hospitalisation (no complications)	(603)	5,028.15	CMS[28]
Amputation	Toe, or transmetatarsal	(618)	7,760.61	CMS[28]
Vascular surgery	Lower extremity, popliteal, no complications	(254)	10,711.38	CMS[28]
Wound-related pain	Medications for wound-related pain:			Red Book¶
	(a) Gabapentin, 600mg tablet		2.53	
	(b) Extended release oxycodone (37mg)		11.50	

CPT—current procedural terminology; HCPCS—healthcare common procedure coding system; MS-DRG—Medicare Severity Diagnosis Related Groups; *A 'clinic' is a hospital-based outpatient wound care department; **Where appropriate, values include physician components as well as facility components; †The clinic visit included everything except debridement. Level 3 complexity was assumed for evaluation and management at all visits; ‡If any debridement was performed at an established clinic visit, separate billing for evaluation and management charges or compression was not permitted. If there is no debridement, for VLU patients, compression codes are used and no E/M billing is permitted; ¶Average wholesale price of all manufacturers, all packages offered;¶¶Nominal pricing for a week based on daily dressing (except at clinic) for a typical non-adherent dressing such as Adaptic or Mepitel

debridement rate of 0.5 per week was applied for all unhealed wounds after 12 weeks.

Resource use: offloading

Although offloading or high-compression bandaging data were not available from the trial,[16] it was assumed that all DFUs and other wounds located on the foot plantar surface or heel should have received offloading of the wound. Likewise, pressure ulcers (PU) should have been offloaded and all venous leg ulcers (VLU) received high-compression bandaging. To simplify cost calculations, all offloading devices were assumed to be boots.

In group 1, 15/22 wounds (68%) were offloaded, while in groups 2 and 3, 19/21 wounds (90%) were offloaded. In group 1, 3/22 wounds (14%) received high compression, while 1/21 wounds (5%) in groups 2/3 received high compression.

Resource use: product applications

Biofilm-disrupting gel and Neosporin came in 1oz tubes (29.57ml). Weekly application totals for each group were based on the mean area of unhealed wounds at each week multiplied by 0.3 cm and converted to days of usage; for example, at week two

Table 2. Cycle costs (US dollars) for unhealed non-infected ulcers

Cycle Number	Group 1	Group 2	Group 3
0	817.85	744.88	744.88
1	341.23	213.92	213.92
2	347.06	214.14	214.14
3	575.61	214.14	214.14
4	833.94	214.38	214.38
5	353.34	214.73	214.73
6	361.84	214.73	214.73
7	371.26	214.73	214.73
8	396.47	214.73	214.73
9	396.47	201.28	236.61
10	396.47	201.28	236.61
11	396.47	201.28	236.61
12	422.57	212.91	342.18
13	124.50	85.72	253.78
14	85.60	85.72	253.78
16	85.60	85.72	253.78
17	85.60	85.72	267.79
19	85.60	85.72	301.80
20	85.60	85.72	266.65
24	85.60	85.72	266.65
25	85.60	85.72	86.28
52	85.60	85.72	86.28

in group 1, the mean area was 9.2 cm^2, so the percentage of a 1oz tube used on average for one week would be (7x9.2x0.3): 65%. Biofilm-disrupting gel or Neosporin was applied from week zero through week 12 for groups 1 and 2, respectively. Biofilm-disrupting gel was also applied from week nine onward for two patients in group 3 and the remainder at 12 weeks, for 12 weeks.

Resource use: costs

Costs were calculated for groups 1 and 2 for each cycle starting with cycle 0 for both cohorts (based on numbers of patients of 22 and 21, respectively); group 3 costs were initially the same as group 2 and started at cycle 0 but were adjusted on week nine when two patients crossed over, and for the full cohort (n=12) at 12 weeks. Costs for group 2 were also adjusted based on the crossing over of patients in time to group 3.

Resource use: unit costs

Unit costs included visits at hospital-based outpatient department wound care clinics (including selective debridement, compression and dressing changes although these are typically bundled into visit costs); offloading devices; intervention products; dressings; infection management as an outpatient or hospital inpatient; and lower extremity amputation or cellulitis treatment as a hospital inpatient. All of these costs were associated with the non-epithelialised state.

The basis for unit cost calculations is provided in Table 1. All costs were based on the 2017 Medicare national average reimbursement rates, with the exception of diagnostic-related grouping (DRG) Medicare payments, which were reported for 2015, and the cost of antibiotics and pain medications, which were obtained from the Red Book.

Resource use: cycle costs

The initial visit cost (cycle 0; equivalent to day of randomisation in the trial) for groups 1 and 2 included the initial visit cost, cutaneous debridement, the offloading device (if appropriate), and apportioned costs for intervention products and dressings. Subsequent visit costs included established visit cost, an apportioned cost due to debridement, and an apportioned cost for compression for VLUs, and an apportioned cost for intervention products as appropriate.

In group 1, two wounds were >20cm^2 at randomisation (22.4cm^2 and 114cm^2), which is the break point for additional billing, in 20cm^2 increments. In group 2, 5/21 wounds were >20cm^2 (24.2cm^2, 34.9cm^2, 50.8cm^2; 46cm^2 and 48cm^2 for two wounds that became part of group 3). Calculations for debridement costs reflected the additional costs for larger wounds, adjusted for the number of these wounds as a proportion of all unhealed wounds in each group week by week for the first 12 weeks. Adjustments were not made beyond 12 weeks because some of the larger wounds might have reduced in size and not all the wound area may have required debridement.

Calculations for each cycle took into account the mix of wound types. For example, for cycle 1 the total cost for a wound-gel treated DFU would be (20/22 x US$176.81) + (2/22 x (US$176.81 + (6 x US$11.13))) + (7/7.1 x US$235) + $2.50 + US$7.65 = US$341.23. Costs per cycle for each group are shown in Table 2.

Resource use: amputations

The transition cost of moving from an infected unhealed wound to amputation was US$7760.61.

Resource use: cellulitis

The cost of cellulitis (US$5,028.15/22: US$228.56) was added to cycle three costs for group 1 only.

Resource use: vascular surgery

The cost of vascular surgery (US$10,711.38/22: US$486.88) was added to cycle four costs for group 1 only.

Resource use: death

No costs were added for death.

Resource use: infection

Costs of a single infection episode lasting three weeks were based on four office visits, bacterial organism identification, plus three weeks of treatment of cephalexin, amoxicillin clavulanate or levofloxacin (these costs were averaged at the level of a unit dose) (Table 1) or hospitalisation. Costs for group 1 (weeks 3–12) were calculated at three weeks (transition cost when moving to a health state of non-infected unhealed ulcer) based on an equally weighted treatment of oral antibiotics plus diagnostic/office visit costs or hospitalisation without complications, whereas costs for group 2 (weeks 11 and 12) was based on hospitalisation without any complications. After 12 weeks, costs for all groups were based on equally weighted treatment of oral antibiotics as well as the other costs or hospitalisation without complications.

The transition cost for infection for group 1 (weeks 3–12) was US$2972.59; for group 2 (11 or 12 weeks) it was US$4776.13. After 12 weeks, it was US$2972.59 for all groups.

Pain medications

Costs were based on a daily dosage of 1.8g gabapentin (3x600mg) or a daily dose of oxycodone extended release formulation (2x27mg) (Table 1).

Effectiveness

Although there were a few VLUs in groups 1 and 2 and one PU in group 1, the differences in utility between unhealed and healed states are similar for these wounds compared to DFUs.[17] (The difference between unhealed and healed DFU/VLUs is 0.09 and 0.115 for PUs.) Moreover, there are some chronic wounds of ambiguous aetiology on the foot and two wounds not on the lower extremity for which it would be hard to assign utility values. Consequently, rather than attempt to create uncertain utility value sets for each group for unhealed and healed wounds it was decided to use utility values for health states taken from Redekop et al.[31] in their study of DFUs: unhealed infected ulcer: 0.75; infected unhealed ulcer: 0.70; healed ulcer: 0.84: minor amputation: 0.74. QALY rewards for each cycle were calculated as the utility values for each health state divided by 52.

Sensitivity analysis: one-way

Based on model input variables, three sets were chosen in the categories of cost, probabilities and utility values (Table 3). Changes in costs and probability values were based on possible 'round-number' capitations or provider policies or limits for extension of the trial population, or specific metrics of interest to test the basic model and its assumptions. To better present the results, these were calculated at one year using 1,000,000 patients and displayed as tornado diagrams based on the relative changes to the baseline case (i.e. the centre point would be US$0 per QALY).

Sensitivity analysis: multiple ways

Additionally, a three-way analysis of cost variables (1–3)

Table 3. Variables used in sensitivity analysis, rationale for using them and values used in the analysis

Variable	Rationale	Values
	Costs	
(1) Healing an ulcer	Represents more generous reimbursement or more severe capitation scenarios	±25%
(2) Infection episode	Represents more or less severe infections on average	±50%
(3) Amputation	Represents higher levels of amputations or lower percentage of DFUs in wound mix	±50%
(4) Product cost	Represents different reimbursement scenarios	±50%
	Probabilities	
(5) Healing rates	Represents more or less severe wounds, smaller/larger wounds, and wound type mix	±25%
(6) Infection rates	Represents populations with higher or lower infection rates	±50%
(7) Amputation	Represents populations in which wounds are more or less severe and patients have more or less serious comorbidities	±50%
(8) Death	Represents a much older population	Mortality rate at population mean of 75 years
(9) Higher healing rate group 3	Represents uncertainty in group 3 versus group 2 analysis in constructing healing curves for group 3 due to small numbers of healed wounds in group 3	+25%
	Utility values	
(10) Change in utility value on healing	Represents uncertainty of assigned utility value changes in healing of different wound types (mixes)	±10%*

*Change in utility value for healing a wound; DFU—diabetic foot ulcer

Table 4. Cycle probability rates for absorbing health states and infected non-healed ulcers for all study groups

Cycle number	Dead	Amputation	Initial infection
Group 1			
0–2; 5–10; 12	0.00184	0	0
3	0.00184	0	0.15
4	0.00184	0.0635	0
11	0.00184	0	0
13, 14	0.00184	0	0.0023
15–52	0.00184	0.007	0.0023
Group 2			
0–3; 5–10; 12	0.00343	0	0
4	0.00343	0.054	0
11	0.00343	0	0.0143
13	0.00343	0	0.0023
14	0.00343	0.184	0.0023
15–52	0.00343	0.007	0.0023
Group 3			
0–3; 5–10; 12	0.00343	0	0
4	0.00343	0.054	0
9	0.0009	0	0
13, 14	0.0009	0	0.0023
15–52	0.0009	0.007	0.0023

Table 5. Cycle probability rates for healing rates for all study groups. Note cycle 0 corresponds to the day of randomisation in the trial; cycle 12 corresponds to week 12 in the trial

Cycle	Group 1	Group 2	Group 3
0	0.0221	0.0011	0.0011
1	0.0272	0.0513	0.0513
2	0.0320	0.0000	0.0000
3	0.0371	0.0550	0.0550
4	0.0427	0.0579	0.0579
5	0.0488	0.0000	0.0000
6	0.0555	0.0000	0.0000
7	0.0629	0.0000	0.0000
8	0.0714	0.0220	0.0220
9	0.0812	0.0000	0.0000
10	0.0854	0.0000	0.0000
11	0.0366	0.0000	0.0000
12	0.0794	0.0336	0.0140
14	0.0283	0.0733	0.0432
16	0.0243	0.0672	0.0413
18	0.0576	0.0673	0.0391
20	0.0588	0.0673	0.0366
22	0.0601	0.0670	0.0339
24	0.0614	0.0666	0.0311
26	0.0627	0.0660	0.0283
28	0.0641	0.0652	0.0256
30	0.0655	0.0641	0.0230
32	0.0669	0.0627	0.0207
34	0.0684	0.0610	0.0188
36	0.0699	0.0589	0.0174
38	0.0714	0.0565	0.0166
40	0.0730	0.0537	0.0165
42	0.0745	0.0504	0.0171
44	0.0760	0.0467	0.0185
46	0.0775	0.0426	0.0210
48	0.0790	0.0381	0.0245
50	0.0804	0.0332	0.0293
52	0.0814	0.0266	0.0348

was carried out using values as for one-way sensitivity analysis, representing overall cost capitation or more generous payer reimbursement, or more or less costly wound complications. Another three-way analysis was conducted for probability variables (5–7) with (a) 25% higher healing rates and 50% lower rates of infection and amputation, representing less severe or smaller wounds and patients with less serious comorbidities; and (b) 25% lower healing rates and 50% higher rates of infection and amputation, representing more severe or larger wounds and patients with more serious comorbidities.

Probabilistic sensitivity analysis (PSA)

PSA was carried out via a two-dimensional approach with an outer loop for parameter uncertainty (sampling) and an inner loop for individual variability (trials) using 1,000 samples and 1,000 trials. For parameter uncertainty, costs used gamma distributions, probabilities used beta distributions, and utility variables normal distributions. Standard deviation estimates were initially estimated from examination of the results at one year with calibrated models; standard deviations were set at 50% of the mean for costs, 25% of the mean for probabilities and 10% of the value of utility variables. All cost and probability variables were employed, as well as mortality rate and utility values themselves, with the exception of tunnel probabilities (in infection resolution and time for ulcer healing).

Fig 2. Group 1 versus group 2: tornado diagram showing influence of increasing or decreasing key cost and health state transition rate variables over the base case incremental cost-effectiveness ratios (ICER) using units of quality-adjusted life years (QALY). Note: units are expressed as the relative expected change in ICER

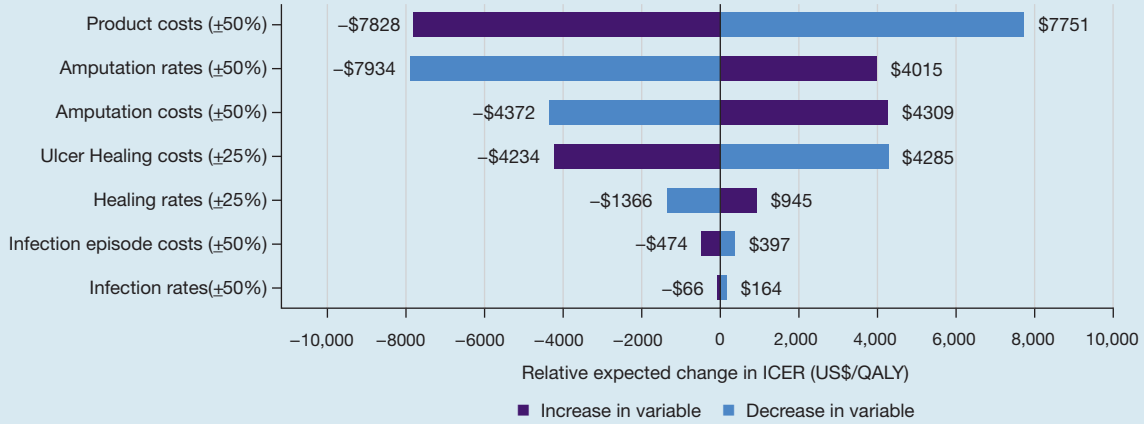
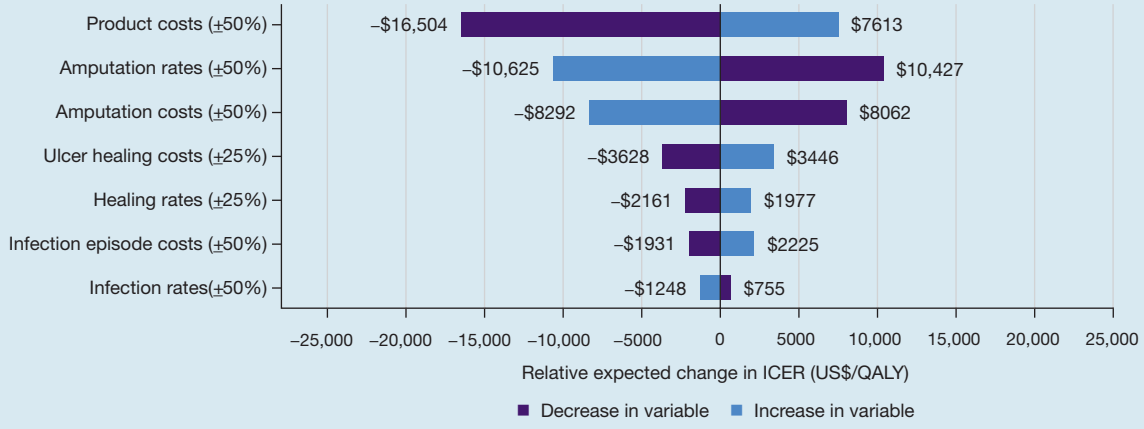


Fig 3. Group 3 versus group 2: Tornado diagram showing influence of increasing or decreasing key cost and health state transition rate variables over the base case incremental cost-effectiveness ratios (ICER) using units of quality-adjusted life years (QALY). Note: units are expressed as the relative expected change in ICER



Model validation

Models were built initially with dummy figures to ensure that their overall structures corresponded with desired outputs. A tracker variable was added to the temporary health state of infected ulcers to count the number of infection episodes. Additional tracker variables were also added in model building to calculate health state percentages and validate that tunnel states were working correctly and that probabilities associated with permanent tracker variables were correct.

For this study, two separate models were used: group 1 versus group 2, and group 2 versus group 3. In the calibration of group 1, which was an iterative process, Monte Carlo simulations of 1,000,000 patients were run; it was determined that this number provided results of reasonable accuracy. First, the calibration for the health state of dead was completed after 53 cycles, followed by calibration of amputation and infected ulcer using trackers for both health states and number of infections after 13 cycles. Calibration of the health state of healed ulcer was done after 13 and 53 cycles. This calibration sequence was repeated until all population targets were within specification. Calibration was required to achieve an accuracy of ±0.2% regarding target population percentages for healed ulcers, and ±0.1% for absorbing states and infected ulcers (sum of ulcers that had been infected or were still infected). Calibration of group 2 was similar to group 1 except that calibration of amputations needed to be done in stages after 13 and 16 cycles. Calibration of group 3 was done after 53 cycles after incorporating incidence of amputation at four weeks only. The final cycle probability rates for all health states except healed ulcers are shown in Table 4; the final cycle probability rates for healed ulcers are shown in Table 5.

Results

Health state distributions and events

At four weeks, 14.1% of ulcers had healed in group 1 versus 15.3% in group 2 and none in group 3; at 12

weeks, the figures were 45.3%, 18.8% and 1.6%, respectively; at one year the figures were 80.2%, 62.1%, and 59.9%, respectively. By the end of one year much higher rates of amputation were observed in group 2 (20.0%) and group 3 (14.4%) versus group 1 (9.0%); 5.0% of wounds had been infected once in group 1 compared with 12.1% in group 2 and 4.0% in group 3.

Cost-effectiveness: base case

For group 1 versus group 2, after one year, the calculated incremental cost-effectiveness ratio (ICER) was $8794 per QALY (($6280.43 – 5408.46)/(0.7541 – 0.6550)). For group 3 versus group 2, the ICER was $21,566 per QALY ((6803.96–5410.61)/(0.7198–0.6551)).

One-way and multiple-way sensitivity analysis

For group 1 versus group 2, product cost was the most influential variable (–$7828 to $7751 per QALY), followed by amputation rates ($4015 to –$7934 per QALY) (Fig 2). Amputation costs and healing costs had a similar albeit lesser (and opposite) influence with relative expected ICER changes of $4309 to –$4372 and –$4234 to $4285 per QALY, respectively (Fig 2). When the assigned utility values to the various health states were changed ±10%, the resultant ICER was $8055 to $9768. At one year, when mortality rates were changed to simulate a population with a mean patient age of 75 years for both groups, the ICER was $13,766/QALY. When the three cost variables were changed simultaneously, the calculated ICER was $8526 to $9030 per QALY. A much larger ICER range occurred when the three health transition rate variables were changed according to the sensitivity plan compared with any one-way sensitivity analysis: $4,255 to $19,090/QALY).

For group 3 versus group 2, product cost remained the most influential variable (–$16,504 to $7613 per QALY), also followed by amputation rates (–$10,625 to $10,427 per QALY), and amputation costs (–$8292 to $8062) (Fig 3). While amputation rates and costs had a very similar albeit lesser influence with relative expected ICER changes to product costs, the patterns were opposite to this variable. When the assigned utility values to the various health states were changed ±10%, the resultant ICER was $19,672 to $24,376. At one year, when mortality rates were changed to simulate a population with a mean patient age of 75 years for both groups, the ICER was $39,074/QALY. When the three cost variables were simultaneously changed the calculated ICER was $18,966 to $24,324 per QALY. Simultaneous changes in the three health transition rate variables resulted in an ICER of $12,717 to $39,662 per QALY—again, a much larger range compared with the results of the one-way sensitivity analysis for product costs.

Probabilistic sensitivity analysis

The ICER scatterplot showed that 71.6% of the cost values were higher in group 1 compared with group 2, but group 1 always has increased positive incremental effectiveness (Fig 4). (The 95% CI [confidence intervals] ellipse encompasses incremental cost boundaries of

Fig 4. Incremental cost-effectiveness (ICER), group 1 versus group 2

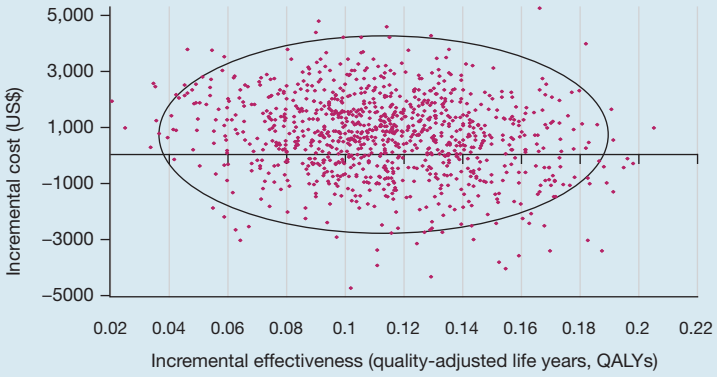


Fig 5. Cost-effectiveness acceptability curve, quality-adjusted life years (QALYs)

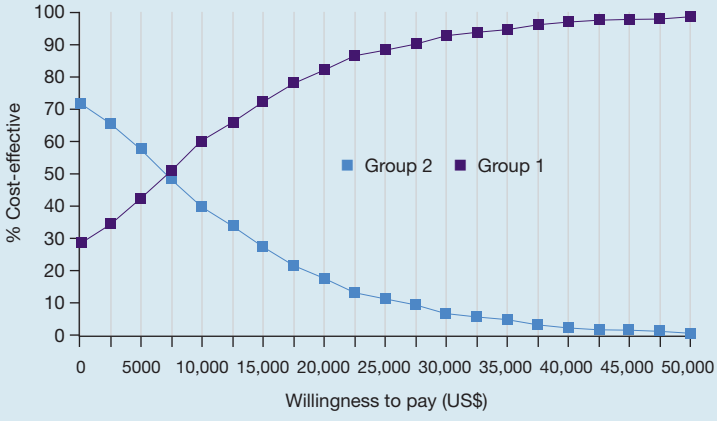


Fig 6. Incremental cost-effectiveness (ICER), group 3 versus group 2

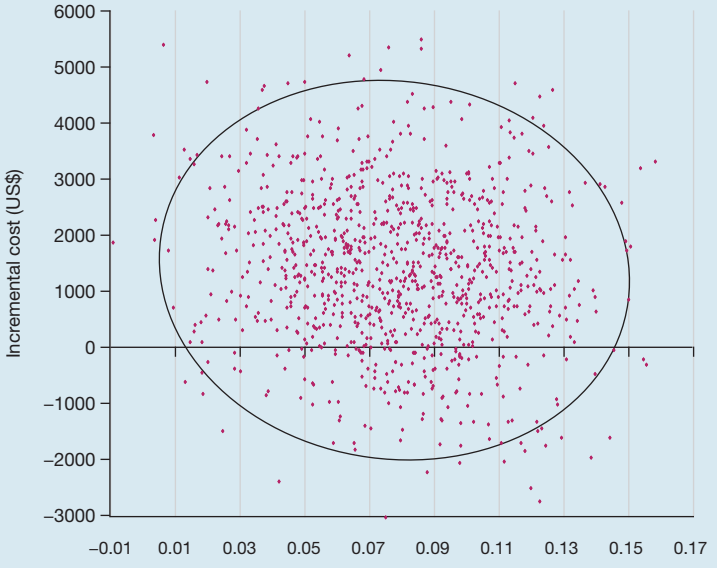
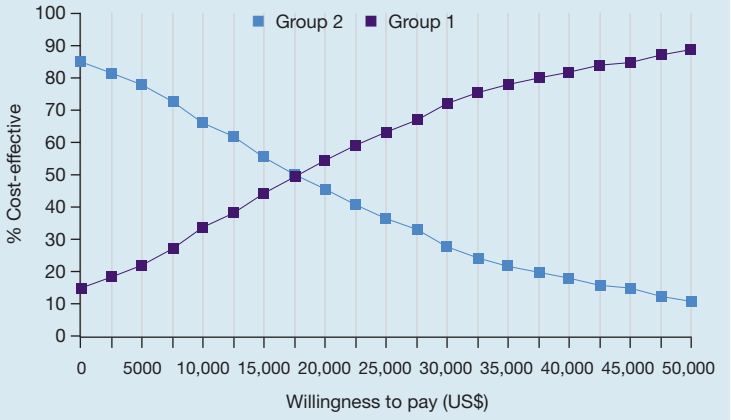


Fig 7. Cost-effectiveness acceptability curve for one quality-adjusted life year (QALY) (group 3 versus group 2)



about –$2800 to $4200 and incremental effectiveness boundaries of 0.038–0.190 QALYs.) The 'willingness to pay' (WTP) curve also demonstrated that about 28% of interventions were cost effective for group 1 when no money was paid, increasing to 99% at a WTP of about $50,000 per QALY (Fig 5). Conversely, about 72% of group 2 interventions were cost-effective when no money is paid, reducing to 1% at the same WTP; the crossover point (about 50% of interventions cost-effective) was reached at a WTP of $7,500 per QALY.

For group 3, the ICER scatterplot showed that while 84.8% of cost values were higher than group 2, increased positive incremental effectiveness occurred for virtually all values (99.7%) (Fig 5). The 95%CI ellipse encompasses incremental cost boundaries of about –$2000 to $4700 and incremental effectiveness boundaries of 0.006–0.150 QALYs. The WTP diagram also demonstrated that about 15% of interventions were cost effective for group 3 when zero dollars are paid, increasing to 89% at a WTP of about $50,000 per QALY (Fig 7). Conversely, about 85% of group 2 interventions were cost-effective when no money is paid reducing to 15% at the same WTP; the crossover point was attained at a WTP of $17,500 per QALY.

Discussion

In the US, clinical practice guidelines emphasise examining the wound healing trajectory at about four weeks after the wound has first been seen in the wound care clinic. These guidelines are based on accumulating evidence that a high proportion of chronic wounds respond to good wound care, including appropriate debridement.[32–35] Consequently, adjunctive treatment for non-responsive wounds is frequently delayed for at least four weeks. However, given the high prevalence of biofilm in chronic wounds[36] it makes no sense to delay introduction of any product that can be used synergistically with debridement to control or eradicate biofilm that is delaying healing. Consequently, it make sense not only to evaluate the cost-effectiveness of immediate treatment but also compare it with the scenario in which it is delayed—in this instance by approximately 12 weeks.

The baseline results show that the calculated ICER was $8794 per QALY after one year for group 1 versus group 2, and $21,566 per QALY for group 3 versus group 2. The QALY was designed to be an effectiveness outcome that can be universally applied to all medical conditions and disease. Although there is ongoing debate as to what constitutes a cost-effective intervention based on cost per QALY,[37,38] both QALY ICERs meet the much-discussed $50,000 per QALY benchmark that constitutes a 'cost-effective intervention', and the higher thresholds that Neumann et al.[38] have advocated. However, it can be clearly seen that delaying the biofilm-disrupting gel intervention, which for most patients in group 2 was 12 weeks, causes the ICER to be two-and-half times more expensive compared with no delay. It is also important to understand that delay should not be interpreted as acceptable just because the ICER is still relatively cost-effective. Also, as a caveat, because the numbers of patients in the clinical trial are small (especially group 3) it is possible that the ICER could be considerably higher in some populations (i.e., group 3) despite the extensive sensitivity analysis.

Both the one– and multiway sensitivity analysis suggest that product costs (i.e., the cost of the biofilm-disrupting gel) and amputation rates have the most influence on results for the ICERs based on QALYs. The assumptions for the calculation of product costs include a 2mm depth of product in the wound and daily application and study costs were heavily influenced by several large wounds. In populations of smaller wounds, costs would be proportionately less. Since amputation costs are high, in a small group, even a single amputation can affect the overall results considerably and the amputation rates in the study were on the high side, indicating that many of the patients' wounds were relatively severe.

PSA, which represents the most comprehensive form of sensitivity analysis, indicates that both ICERs fall in quadrant two in which costs are higher but effectiveness is always higher.[39] WTP plots also reflect that delay in administering biofilm-disrupting gel carries a penalty; for example, the intersection of both groups, approximately at the point in which 50% of the interventions are cost-effective, is more than double for group 3 versus group 2 compared with group 1 versus group 2. Also, while the amount of money required to reach 90% of interventions being cost-effective is about $27,500 for group 1, it is at least $50,000 for group 3, which is crossing the first threshold guideline for cost-effective interventions.

The population under study had different characteristics to the other RCT[15] in which the antibiofilm agent was evaluated. In particular, the mean wound area was much higher (9.8cm^2 versus 3.1cm^2 for the biofilm-disrupting gel group plus SoC) and the proportion of DFUs was slightly higher (55%

versus 47% for the biofilm-disrupting gel group plus SoC). In terms of overall healing trajectory, the mix of wound types in the current study precludes comparisons with most other wound care RCTs and any health economic studies derived from them as the vast majority of study populations are based on single wound types and many include only non-severe wounds.

Strengths of this trial-based health economics study include using sophisticated models that followed the International Society for Pharmacoeconomics and Outcomes' (ISPOR) best practices for Markov modelling, including transparency and validity.[40,41] In addition, compared with many other RCTs in the literature, the patients had a much higher proportion of serious comorbidities and more severe wounds, as evidenced from the demographics of the original clinical trial.[16] Consequently, the results of this study would be more generalisable to a 'real-world' wound care population[42] than other health economic studies based on RCTs with less sick patients and less severe wounds.

Limitations

This study also had a number of limitations. First, the sample size of the trial[16] was relatively small, and groups 2 and 3 were particularly small. This creates some uncertainty in the wound healing trajectory and rate of complications, such as amputation, when using the data to extrapolate to very large populations. Had the sample size of the original trial been much larger, this uncertainty would have been much reduced. The use of one-way analysis can illustrate what happens to the results when wound-related parameters in the model were changed but it is not a substitute for more precise data.

Second, while the majority of wound-related complications were captured, the incidence of these complications, such as vascular surgery, or amputation can considerably change both costs and effectiveness for any group. It is also challenging to decide what procedures should be included in any health economics study; for example, vascular surgery is often required for ischaemic wounds to heal but may not be seen as a wound-healing-related expense. Third, the complexity of trial results had to be reduced to a manageable model; for example, wound infection episodes are limited to a certain period of time with a simple probability distribution of time-related infection resolution and severity of infection modelled with only approximate costs and no possibility to transition to another health state (i.e., all infection is resolved without any further complications). We also used the base health state of uninfected non-healed ulcer rather than considering the majority of ulcers to have a biofilm because eligible wounds were not tested in time in the clinical trial[16] to identify whether:

- Biofilm was present
- Whether the biofilm was pathological in nature.

A model based on biofilm characteristics would also add several layers of complexity.

Fourth, extension of trial results to one year was predicated on several assumptions, especially wound healing rates. Although these issues were partially mitigated by incorporating the values of percentage of wounds healed at one year into our study equations from a large cohort study of diabetic foot ulcers,[20] as well as sensitivity analysis, there still remains some uncertainty when extrapolating wound healing trajectories with small sample size studies. Fifth, lack of data meant that certain pathologies could not be modelled as a natural progression of health states; for instance, while the majority of osteomyelitis cases can be successfully managed with antibiotics alone a substantial proportion of such cases will result in amputations at various levels. Finally, the payer perspective does not cover societal costs, those incurred by patients, their caregivers, and society. Consequently, cost-effectiveness results may in fact may be an underestimate.

Conclusion

Based on a small RCT that compared a biofilm-disrupting gel to treat biofilm with SoC in patients with chronic wounds, as well as permitting SoC patients who were treatment failures to access biofilm-disrupting gel, cost-utility analysis showed that addition of biofilm-disrupting gel to SoC is likely to be cost-effective. Delay of the intervention (about 12 weeks) was still cost-effective, although the ICER was much larger. The addition of this antibiofilm biofilm-disrupting gel to SoC should be considered by payers and decision-makers as a procedure to be incorporated into the SoC of chronic wounds from the time when they are first seen to avoid the costly effects of biofilm rather than waiting for a period of time to see if the wound is on a reasonable healing trajectory. JWC

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Reflective questions

- What benchmarks area available to help decide whether one product is more cost-effective than another?
- What was the most influential factor in the modeling of this study?
- Was infection management modeled solely on an outpatient basis?
- What would happen to the base case incremental cost-effectiveness ratios (ICER) if on average treated wounds were smaller in area?

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