Cost-effectiveness of Debrichem in managing hard-to-heal venous leg ulcers in the UK

Objective: To estimate whether the topical debriding agent, Debrichem, could potentially afford the UK's National Health Service (NHS) a cost-effective intervention for the management of hard-to-heal venous leg ulcers (VLUs).

Method: A Markov model was constructed depicting the management of hard-to-heal VLUs with Debrichem plus standard care (SC) or SC alone over a period of 12 months. The model was populated with inputs from an indirect comparison of two propensity score-matched cohorts. The model estimated the cost-effectiveness of the two interventions in terms of the incremental cost per quality–adjusted life year (QALY) gained at 2019/20 prices.

Results: Addition of Debrichem to a SC protocol to treat hard-to-heal VLUs was found to increase the probability of healing by 75% (from 0.35 to 0.61) by 12 months, and to increase health-related quality of life over 12 months from 0.74 to 0.84 QALYs per patient. The 12-month cost of treatment with Debrichem plus SC (£3128 per patient) instead of SC alone (£7195 per patient) has the potential to reduce the total NHS cost of wound management by up to 57%. Hence, Debrichem was estimated to improve health outcomes for less cost. Sensitivity analysis showed that Debrichem plus SC remained a cost-effective (dominant) treatment with plausible variations in costs and effectiveness.

Conclusion: Within the limitations of the study, the addition of Debrichem to a SC protocol potentially affords a cost-effective treatment to the NHS for managing hard-to-heal VLUs.

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cost-effectiveness • Debrichem • debridement • venous leg ulcer • UK • wound • wound care • wound healing

Venous leg ulcers (VLUs) are a major cause of morbidity and decreased health-related quality of life (HRQoL).[1] The prevalence of VLUs in adults ≥18 years of age in the UK has been estimated at around 1 per 100 individuals in 2017/18.[2] VLUs arise from chronic venous insufficiency in the lower limbs, for which the main risk factors include family history, deep venous thrombosis, age and obesity.[3] These ulcers can heal within weeks or take up to several months.[4] Once healed, some VLUs recur and patients can experience a cycle of ulceration, healing and recurrence. Some VLUs fail to heal in a timely manner and they then become hard-to-heal.[5] Hard-to-heal ulcers, as with other hard-to-heal wounds, are subject to prolonged or excessive inflammation,[6] persistent infections,[7] and the inability of dermal and/or epidermal cells to respond to reparative stimuli.[8]

Biofilms are one of the causes of chronic infections in hard-to-heal wounds, thereby contributing to delayed wound healing.[9] Biofilms can be described as 'aggregates of microorganisms which may be embedded in a protective matrix, may attach to host tissue or in-dwelling medical devices or exist as aggregates in fluids adjacent to those surfaces'.[10] This may explain why biofilms can exhibit enhanced tolerance to antimicrobial agents. Furthermore, biofilms may be present in up to 80% of hard-to-heal wounds.[11]

Physical removal and/or disruption of biofilms by surgical or conservative sharp debridement are the mainstay of treatment. However, this can be timely and challenging in the community. Furthermore, the spatial distribution of microbial aggregates in tissue[12–14] also presents challenges in ensuring complete removal. Consequently, topical agents are being increasingly used for debridement. A recent systematic review reported that 90% of all topical wound agents tested for efficacy against biofilm were conducted in vitro.[15] Although there are acknowledged limitations of in vitro models, such as the absence of a model which truly mimics a human wound, in vitro analysis forms an integral component in screening for potentially beneficial agents.

Debrichem (DEBx Medical BV, The Netherlands) is a novel, topical wound desiccating agent containing methanesulfonic acid, dimethylsulfoxide and amorphous silica. It has a CE mark for a class IIb medical device and an ISO 13485:2016 certification,[16] and been shown to have demonstrable efficacy against in vitro biofilms.[17] When applied to the wound bed, its desiccating effect is thought to kill pathogens and denature any proteins present, thereby destroying any

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biofilm. The desiccated material in the wound bed can be partially washed out with saline and the remaining material digested by host macrophages. Debrichem does not affect healthy surrounding skin due to the low content of water in the external epidermal layer.

In a case series of 10 patients (mean age: 74.5 years) with a hard-to-heal ulcer of the lower limb (mean wound bed area: 65.7cm^2; mean wound duration: 15.8 weeks), the use of Debrichem resulted in all the wounds achieving granulation in a mean of 30.4 days.[18] None of the patients needed an additional application of Debrichem.[18] Of these wounds, five were hard-to-heal VLUs with a mean duration of 19.2 weeks and mean area of 52cm^2. Use of Debrichem on these wounds resulted in 100% granulation in a mean of 30 days.[18]

More recently, 61 consecutive patients with a hard-to-heal VLU attending a wound care clinic in Italy between March and December 2018 were enrolled in an observational study. Patients were excluded if they had any of the following:

- An ischaemic ulcer
- An unexplored fistula
- An abscess requiring drainage
- Cancer-related ulcers
- Systemic symptoms possibly correlated with an infection requiring parenteral antibiotic therapy.

Debrichem was applied to the wound bed for about 30 seconds and then washed with saline. Afterwards, the wound was dressed with wet gauze and ongoing ulcer management was left to the attending physician. The primary endpoint of the study was achievement of full granulation of the wound bed. Complete healing of the ulcer was a secondary endpoint. Patients were followed up for a mean of 7.5 months or until healing, if that happened sooner. Patients' age was a mean of 69.5 years, 50% were male, wound area was a mean of 92.9cm^2 and wound duration before the start of Debrichem was a mean of 7.8 months. During application of Debrichem, patients' pain score was a mean of 2.7 using a 0–5 visual analogue pain scale. On the day following the procedure their pain score was a mean of 0.0 and before the procedure their pain score was a mean of 1.7. Following application of Debrichem, all the wounds achieved full granulation in a mean of 1.7 months and 61% of the wounds healed in a mean of 3.9 months.[19] The aim of this health economic study was to use the findings from this Italian observational study to assess whether Debrichem affords the UK's National Health Service (NHS) a cost-effective technology with which to treat hard-to-heal VLUs.

Method

Study design

This was a modelling study based on a retrospective cohort analysis of the anonymised case records of patients with a hard-to-heal VLU.

Ethical approval

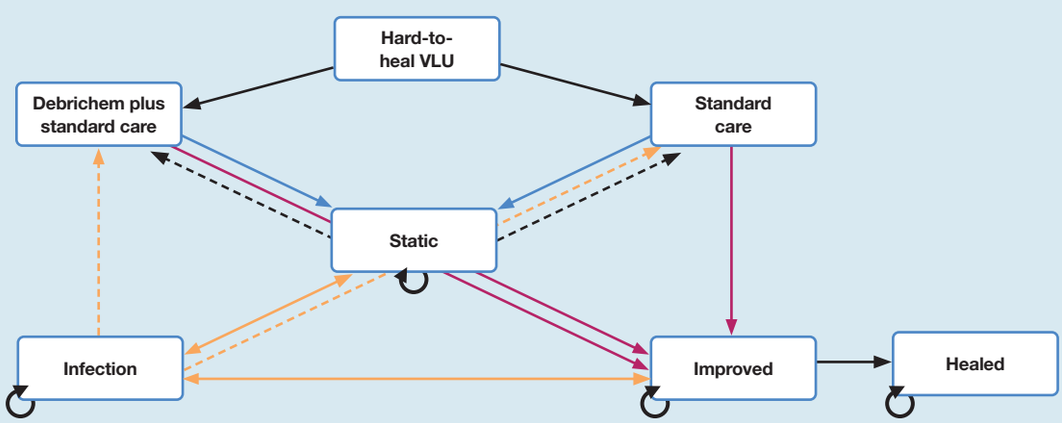
The observational study was conducted under the remit of a compassionate protocol and so ethics approval was not required. In addition, all of the patients provided informed consent.

Economic modelling

A Markov model was constructed in Excel (Microsoft Corp., US) depicting the management of hard-to-heal VLUs (Fig 1). The model considered the costs and consequences of the decision by a clinician to manage a VLU with Debrichem plus standard care (SC) or SC alone. The time horizon of the model was 12 months.

VLUs entered the model and were either managed with Debrichem plus SC or SC alone. They then transitioned to one of two health states (i.e., static ulcer (an ulcer that remains unchanged) or improved ulcer (followed by healed ulcer). The ulcers could either remain in their current health state or move to one of the other states and transition monthly for a total of 12 months. The model's health states were mutually exclusive and so each VLU represented in the model could be in only one of these health states at any given

Fig 1. Markov model



time during the time horizon of the model.

The model was populated with a combination of transition probabilities, clinical outcomes, resource utilisation estimates and utilities as described below.

Study population

The aforementioned Debrichem observational study in Italy had no comparator group.[19] Therefore, this model's population comprised the cohort of patients who participated in the Debrichem study and a matched sample of patients with a VLU obtained from the real-world evidence Health Improvement Network (THIN) database, who were managed with SC in clinical practice. (THIN is a registered trademark of Cegedim SA in the UK and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA.)

Propensity score matching

The Debrichem-treated patients were matched with patients from a cohort with a VLU managed with SC[2,4,20] on the basis of propensity scores.[21,22]

Propensity score matching (PSM) can be used to estimate the true treatment effect of an intervention and reduce group bias due to non-randomisation or indirect comparison of different cohorts of patients by controlling for confounding variables.[21,22] Accordingly, logistic regression was used to create a propensity score for each patient based on the following dependent variables:

- Patient's age at the start of treatment
- Sex
- Wound duration
- Cardiovascular symptoms
- Musculoskeletal symptoms.

Each patient's resulting propensity score was an estimate of the probability of them belonging to their respective treatment group. Patients in both groups were then individually matched according to their propensity score by subjecting them to 1:1 PSM using nearest-neighbour matching without replacement and a caliper width of 0.2.[23]

The resulting analysis was able to match 57 patients from the SC cohort with a VLU with 57 patients in the Debrichem data set (Table 1). The other four Debrichem-treated patients were excluded from the analysis since it was not possible to match them with a patient from the SC cohort. The PS score of the resulting 57 patients in the Debrichem data set was a mean of 0.41±0.13 and that of the 57 patients in the SC group was a mean of 0.39±0.12; p=0.214. No statistically significant differences were found between the two matched cohorts when tested with either a Mann–Whitney U-test or Chi-squared test.

The anonymised data sets of the propensity score-matched cohorts were used to construct the Markov model.

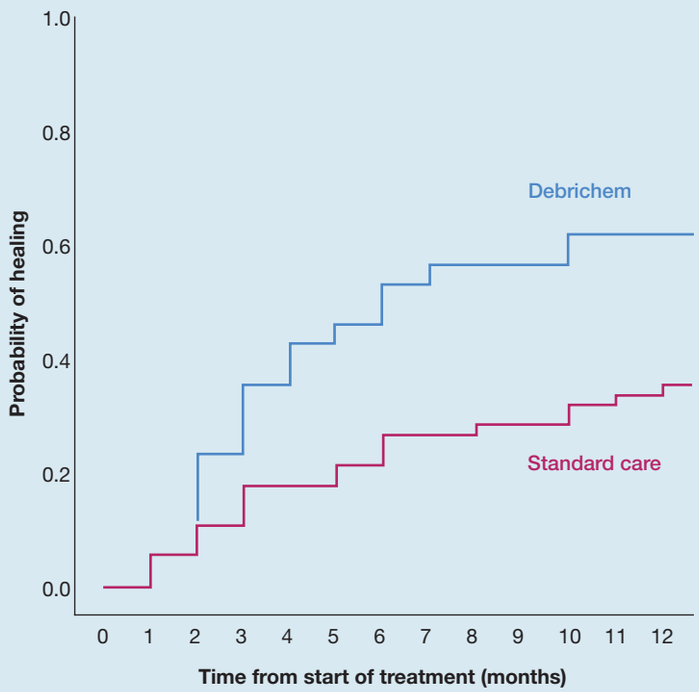
Kaplan–Meier analysis found the healing distributions of the two cohorts to be significantly different (Fig 2).

Table 1. Characteristics of the patients in the PS matched cohorts

Characteristic	Debrichem plus standard care	Standard care
Patients, n	57	57
Wounds, n	57	57
Propensity score per group, mean±SD	0.41±0.13	0.39±0.12
Age per patient, years, mean±SD	68.8±11.9	66.5±16.4
Sex: Female, %	39	39
Wound duration per VLU, months, mean±SD	7.8±6.2	8.2±6.1
Cardiovascular symptoms, %	46	46
Musculoskeletal disorders, %	18	30
Malnourished, %	2	0
Normal body mass index, %	30	27
Overweight, %	40	40
Obese/severe obesity, %	28	33

PS—propensity score; SD—standard deviation; VLU—venous leg ulcer

Fig 2. Kaplan–Meier time-to-healing analysis. The healing distribution between the two groups was significantly different (log rank (Mantel–Cox): p=0.003)



The monthly rates of wound healing, improvement, remaining static and infection over 12 months in these cohorts were used to estimate transition probabilities with which to populate the model (Table 2).

Table 2. Monthly transition probabilities in the Markov model

Month	Treatment	Static wound	Improved wound	Healed wound	Infected wound
0	Debrichem plus standard care	1.00	0.00	0.00	0.00
1	Debrichem plus standard care	0.37	0.60	0.02	0.02
2	Debrichem plus standard care	0.11	0.67	0.23	0.00
3	Debrichem plus standard care	0.07	0.56	0.37	0.00
4	Debrichem plus standard care	0.04	0.47	0.49	0.00
5	Debrichem plus standard care	0.05	0.39	0.56	0.00
6	Debrichem plus standard care	0.00	0.44	0.56	0.00
7	Debrichem plus standard care	0.00	0.44	0.56	0.00
8	Debrichem plus standard care	0.00	0.44	0.56	0.00
9	Debrichem plus standard care	0.00	0.39	0.61	0.00
10	Debrichem plus standard care	0.00	0.39	0.61	0.00
11	Debrichem plus standard care	0.00	0.39	0.61	0.00
12	Debrichem plus standard care	0.00	0.39	0.61	0.00
0	Standard care	1.00	0.00	0.00	0.00
1	Standard care	0.67	0.11	0.05	0.18
2	Standard care	0.75	0.11	0.11	0.04
3	Standard care	0.72	0.09	0.18	0.02
4	Standard care	0.68	0.11	0.18	0.04
5	Standard care	0.70	0.07	0.21	0.02
6	Standard care	0.61	0.09	0.26	0.04
7	Standard care	0.65	0.09	0.26	0.00
8	Standard care	0.63	0.07	0.28	0.02
9	Standard care	0.63	0.07	0.28	0.02
10	Standard care	0.65	0.04	0.32	0.00
11	Standard care	0.65	0.00	0.35	0.00
12	Standard care	0.65	0.00	0.35	0.00

Healthcare resource use

Documentation in the electronic records of the SC-treated cohort pertaining to number of clinician visits, hospital admissions, attendance at accident and emergency units plus the combination of dressings, compression therapy and other bandages that patients received,[2,4,20] constitutes SC and reflects real-world clinical practice for VLUs in the UK. This information was quantified over a period of 12 months from the start of treatment.

Each health state in the model was populated with relevant resource use estimates derived from this cohort. This enabled an estimation of the mean quantities of healthcare resources used to manage VLUs with SC over 12 months.

The model assumed that Debrichem would be administered in the following settings:

- 85% in a hospital outpatient clinic by a nurse specialist
- 5% in general practice by general practitioners (GPs)
- 5% in general practice by practice nurses
- 5% in the community by district nurses.

The model also assumed that 97% of patients treated with SC would undergo a mean of five mechanical debridements and cleansing, and 3% would undergo a mean of one conservative sharp debridement.

Utilities

Utility scores express patient preferences for specific health states, which can be used to estimate a patient's HRQoL in terms of the number of quality-adjusted life years (QALYs) gained by an intervention or service. HRQoL was not recorded in the Debrichem observational study nor in routine clinical practice. Hence, published utility scores for VLUs (0.64 for a static VLU, 0.73 for an improving VLU and 1.00 for a healed VLU),[24] obtained from the general public across the UK (some of whom had a VLU) using standard gamble methodology, were assigned to each health

state in the model. This enabled patients' HRQoL in terms of the number of QALYs at 12 months from the start of treatment to be estimated.

Unit costs

NHS unit resource costs at 2019/20 prices (Table 3)[25,26] were applied to the resources in the health states in the model to estimate the total healthcare cost of managing a VLU with Debrichem plus SC or SC alone over 12 months.

Model outputs

The primary measure of effectiveness was patients' HRQoL in terms of the number of QALYs at 12 months from the time patients entered the model. The secondary measure of effectiveness was the probability of healing by 12 months from the time patients entered the model.

The expected NHS cost of patient management over 12 months from the time patients entered the model was estimated at 2019/20 prices.

Cost-effectiveness analysis

The potential cost-effectiveness of including Debrichem in a SC protocol compared with SC alone was calculated as 'the difference between the expected costs of the two treatment strategies ÷ the difference in the number of QALYs between the two treatment strategies', and expressed as the incremental cost per QALY gained. If one of the strategies generated more QALYs for less cost, it was considered to be the dominant intervention.

Sensitivity analysis

Probabilistic sensitivity analysis was undertaken to evaluate uncertainty within the model. This involved 10,000 iterations of the model by simultaneously varying the different inputs. To estimate the random values of the inputs, the standard error was assumed to be 10% around the mean values, and relevant distributions were assigned to the deterministic values (beta distributions for probabilities and utilities, and gamma distributions for resource use and costs), enabling the distribution of costs and QALYs to be estimated. This analysis enabled an estimation of the probability of Debrichem plus SC being cost-effective compared with SC alone at different cost per QALY thresholds.

Deterministic sensitivity analyses were performed to assess the effect of independently varying the values of individual parameters within the model by 20% above and below the base case values, and varying the utility scores simultaneously by up to 10% above and below the base case values.

Budget impact analysis

The number of people ≥18 years of age across all 135 English Clinical Commissioning Groups (CCGs) was estimated to be a mean of 338,000 adults per CCG.[27] Comparable estimates for the 14 Scottish Health Boards and seven Welsh Health Boards were a mean of 387,000 and 360,000 adults, respectively.[28,29] The average of all the catchment areas was 340,000 adults.

Table 3. Unit costs at 2019/20 prices[25,26]

Resource	Unit cost, £
Practice nurse visit	21.00
District nurse visit	49.00
Healthcare assistant visit	30.00
General practitioner visit	76.99
Hospital outpatient visit	101.05
Hospital admission	3375.06
Accident and emergency attendance	166.70

An estimated 1.1% of adults ≥18 years of age were assumed to have a VLU.[2] Hence, the number of VLUs per catchment area of 340,000 adults was estimated to be 3740 ulcers. If the probability of a VLU being hard-to-heal is 0.63,[2] the number of hard-to-heal VLUs per catchment area of 340,000 adults is an estimated 2356 ulcers.

The budget impact analysis assumed that 2356 hard-to-heal VLUs would be eligible to be managed with Debrichem plus SC. Hence, an analysis was undertaken to assess the resource implications and budget impact to an average CCG/Health Board over 12 months by treating varying percentages of 2356 hard-to-heal VLUs with Debrichem plus SC and SC alone.

Results

Clinical outcomes and healthcare costs

Outputs from the model indicated that the probability of healing among the Debrichem-treated patients was 0.61 by 12 months, compared with 0.35 among the SC-treated patients (Table 4). Hence, treatment of hard-to-heal VLUs with Debrichem plus SC instead of SC alone was expected to increase the probability of healing by 12 months by up to 75%. Additionally, patients treated with Debrichem experienced a better HRQoL of 0.1 QALY per patient compared with those treated with SC alone (Table 4). Nevertheless, the time to healing was comparable in both groups.

The cost of VLU management over the 12 months was estimated to be £3128 per Debrichem-treated patient compared with £7195 per patient managed with SC (Table 4). The primary cost driver was district nurse visits, which accounted for up to 28% of the cost of managing VLUs in both groups. The secondary cost driver in both groups was healthcare assistant visits, which accounted for a further 17–18% of the cost of wound management. The cost of Debrichem accounted for 17% of the total NHS cost of wound management (Table 5).

Cost-effectiveness analysis

Outputs from the model showed that use of Debrichem plus SC, instead of SC alone, was expected to lead to a cost decrease of £4067 over 12 months and a corresponding increase of 0.10 QALYs (Table 6). Hence,

Table 4. Health outcomes and costs

	Debrichem plus standard care	Standard care
Time to 100% granulation per VLU, months, mean±SD	1.6±1.4	N/A
Healed at 12 months, probability	0.61	0.35
Improved at 12 months, probability	0.39	0.04
Static at 12 months, probability	0	0.61
Time to healing, months, mean±SD	5.5±2.7	6.0±3.5
Wound infected, probability	0.01	0.32
Number of QALYs per patient at 12 months, mean	0.84	0.74
Cost per patient at 12 months, £, mean	3128	7195

VLU—venous leg ulcer; SD—standard deviation; QALY—quality-adjusted life year

Table 5. Mean costs of healthcare resource use per VLU

Resource	Debrichem plus standard care	Standard care
	£ (%)	£ (%)
District nurse visits	840 (27)	2016 (28)
Healthcare assistant visits	534 (17)	1291 (18)
Hospital admissions	110 (4)	1195 (17)
General Practitioner visits	366 (12)	769 (11)
Wound care products	274 (9)	543 (8)
Prescribed medication	90 (3)	384 (5)
Hospital outpatient visits	142 (5)	476 (7)
Practice nurse visits	91 (3)	246 (3)
Other costs	144 (5)	197 (3)
Accident and emergency attendances	5 (<1)	78 (1)
Debrichem	532 (17)	0 (0)
Total	**3128 (100)**	**7195 (100)**

VLU—venous leg ulcer

including Debrichem into a SC protocol could potentially afford the NHS a dominant treatment, since it improves outcomes for less cost.

Sensitivity analyses

Probabilistic sensitivity analysis highlighted the distribution in the incremental costs and QALYs at 12 months between the two treatment strategies (Fig 3). The graph indicates that the majority of samples are located in the bottom right-hand (dominant) quadrant. Outputs from the analysis showed that at a cost-effectiveness threshold of £20,000 per QALY, up to 96% of a cohort is expected to be treated cost-effectively with Debrichem plus SC, compared with SC alone.

Deterministic sensitivity analyses in the form of a tornado diagram (Fig 4) showed that Debrichem's cost-effectiveness was potentially sensitive to changes in:

- Probability of healing
- Number of district nurse visits
- Number of hospital admissions
- Utility scores
- Unit cost of Debrichem.

Notwithstanding these findings, Debrichem remained a dominant treatment even when the value of these parameters were changed by 20% above and below the base case values and utility scores by up to 10%. Consequently, the use of Debrichem plus SC in the treatment of VLUs remained a cost-effective technology since its relative cost-effectiveness remained <£20,000 per QALY. Furthermore, changing the distribution of clinicians who administer Debrichem had negligible effect on the cost per patient and therefore had minimal impact on the debriding agent's cost-effectiveness (Table 7). A two-way sensitivity analysis found that as long as the 12-month healing rate among patients treated with Debrichem plus SC remained higher than that among SC-treated patients, then the incremental cost per QALY gained with this technology would be <£20,000 per QALY (Table 8).

When the PS-matched cohort of 57 Debrichem-treated patients in the model was expanded to include all 61 Debrichem-treated patients, the probability of healing and number of QALYs per patient remained unchanged at 0.61 and 0.84, respectively. The mean cost per patient at 12 months increased marginally from £3128 to £3159. However, this had minimal impact on Debrichem's cost-effectiveness, which remained a dominant intervention.

Budget impact of Debrichem

The budget impact analysis (Table 9) indicated that treating 2356 hard-to-heal VLUs with Debrichem plus SC instead of SC alone in an average CCG/health board

Table 6. Cost-effectiveness analysis

Intervention	NHS cost per patient over 12 months, £	QALYs per patient at 12 months, n	NHS cost-difference, £	QALY difference	Incremental cost per QALY gained, £
Standard care	7195	0.74			
Debrichem plus standard care	3128	0.84	–4067	0.1	–40,670

NHS—National Health Service; QALY—quality-adjusted life year

Fig 3. Scatterplot of the incremental cost-effectiveness of Debrichem plus standard care compared with standard care alone following 10,000 iterations of the model. QALY—quality-adjusted life year

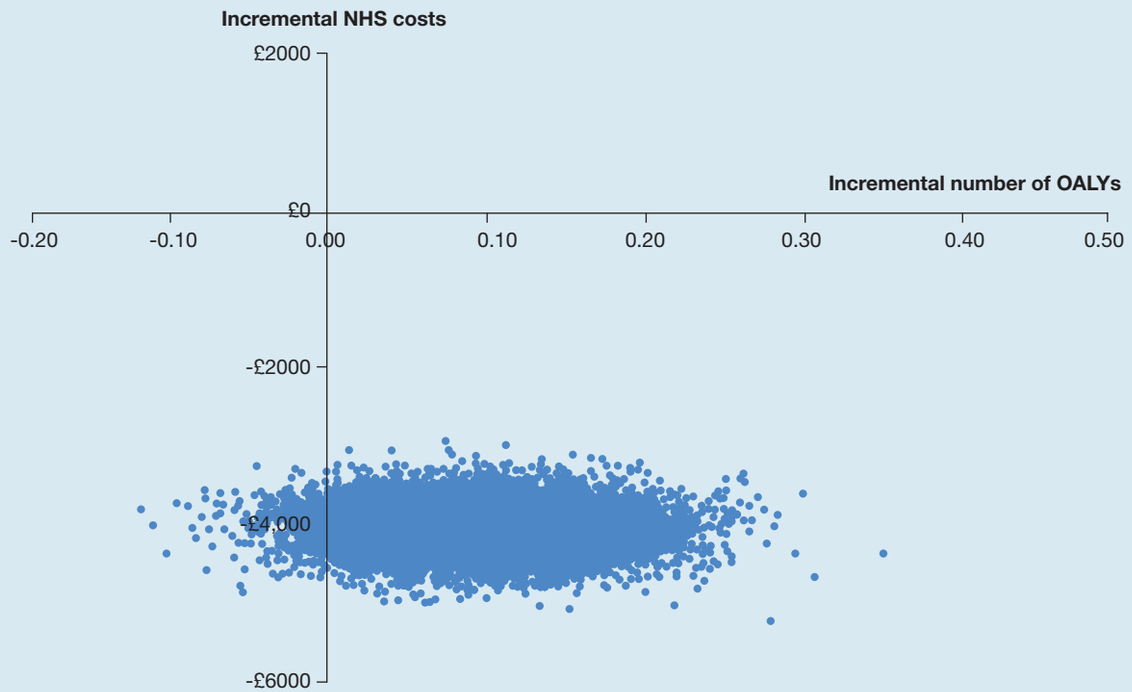
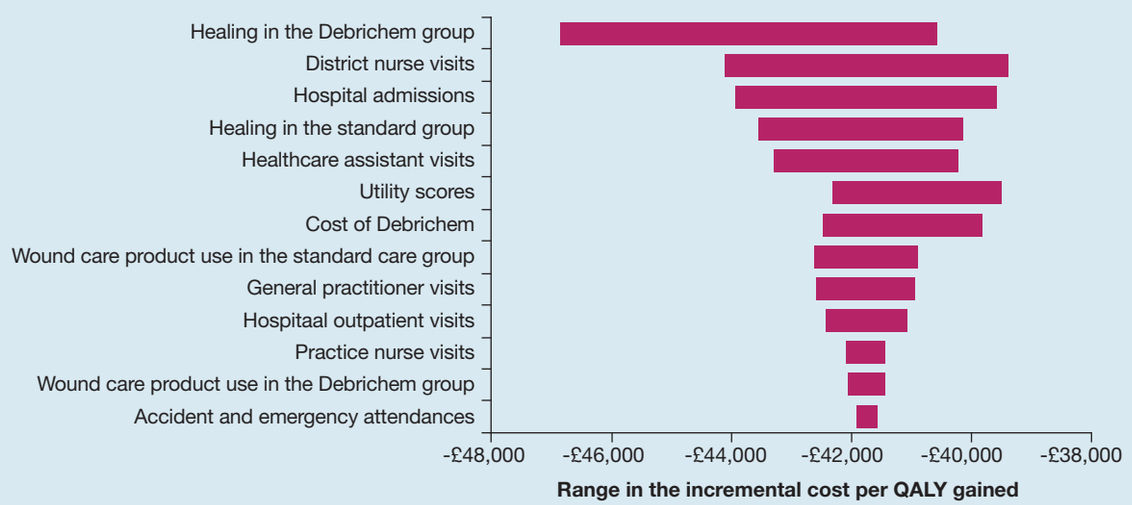


Fig 4. Tornado analysis showing the influence of increasing or decreasing key variables by up to 20% on the incremental cost per QALY gained with the use of Debrichem. QALY—quality-adjusted life year



over 12 months would potentially lead to:

- 75% improvement in healing (ie. 620 more healed patients)
- 59% reduction in total number of nursing and healthcare assistant visits (ie. 16,500 fewer practice nurse visits, 56,500 fewer district nurse visits and 58,900 fewer healthcare assistant visits)
- >90% reduction in hospital admissions (ie. 750 fewer hospital admissions)
- >90% reduction in accident and emergency attendances (ie. 1100 fewer attendances at accident and emergency units)
- 57% reduction in the total NHS wound management costs of £9.58 million.

Table 7. Sensitivity of changing the distribution of clinicians who administer Debrichem

Scenario	Practice nurses, %	District nurses, %	GPs, %	Hospital outpatient nurses, %	Total cost of wound care per patient, £
1	0	0	0	100	3136
2 (base case)	5	5	5	85	3128
3	10	10	5	75	3122
4	0	0	100	0	3122
5	20	20	10	50	3107
6	30	30	5	35	3095
7	0	100	0	0	3084
8	100	0	0	0	3056

GP—General practitioner

Table 8. Two-way sensitivity analysis showing the range in the incremental cost per quality-adjusted life year (QALY) gained using Debrichem plus standard care compared with standard care alone for simultaneous changes in the probability of healing in both groups. Combination of healing rates in the unshaded areas favour Debrichem plus standard care at the £20,000 cost per QALY threshold

		Probability of being healed with Debrichem plus standard care at 12 months					
		0.35	0.40	0.45	0.50	0.55	0.60
Probability of being healed with standard care at 12 months	0.25	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	0.30	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	0.35	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
	0.40	£15,851	Dominant	Dominant	Dominant	Dominant	Dominant
	0.45	-£17,625	£33,846	Dominant	Dominant	Dominant	Dominant
	0.50	-£25,422	-£16,134	£21,514	Dominant	Dominant	Dominant
	0.55	-£28,752	-£24,765	-£17,721	£9874	Dominant	Dominant
	0.60	-£30,273	-£27,777	-£24,409	-£17,624	£1670	Dominant

Table 9. Budget impact of treating 2356 non-healing VLUs with Debrichem plus standard care and standard care alone

	Percentage of patients treated with Debrichem plus standard care compared with standard care alone					
	100:0	80:20	60:40	40:60	20:80	0:100
Healed patients, n	1447	1323	1199	1075	951	827
Nurse and healthcare assistant visits, n	91,892	118,281	114,671	171,060	197,450	223,839
Hospital outpatient visits, n	2356	4241	6126	8011	9896	11,781
Hospital admissions, n	71	221	372	523	674	825
Accident and Emergency attendances, n	71	292	514	735	957	1178
Total NHS cost of VLU management (£ million)	7.37	9.29	11.20	13.12	15.04	16.95

NHS—National Health Service; VLU—venous leg ulcer

Discussion

Debridement includes any method that removes cell debris, dead fibrinous material, metabolic waste, exudate and infected or contaminated material.[30] These methods include surgical, sharp, enzymatic, mechanical, autolytic, chemical and biosurgical (larvae/maggots) techniques. The principal component of Debrichem is methanesulfonic acid, a hygroscopic molecule which readily absorbs water from its surroundings.[31] When in close proximity to cell membranes which are affected

by hydration, this agent can desiccate the membrane's lipid bilayers, thereby damaging the viability of its cells.[31] Hence, desiccation offers an alternative treatment option in the management of wounds with biofilm-driven infections.[31] Conventional wound care already incorporates various weak acidic formulations as a treatment.[31,32] Furthermore, honey-based formulations also possess hygroscopic properties resulting in dehydration.[33] There is also evidence to suggest that weak acids can eradicate biofilm through penetration of the matrix and cell membrane, which may be a similar mechanism to that of methanesulfonic acid.[34]

A systematic review concluded that there was limited evidence to suggest that actively debriding a VLU has a clinically significant impact on healing.[30] The low number of studies (only 10 randomised controlled studies) and study participants, and lack of meta-analysis, precluded any strong conclusions of benefit.[30] Notwithstanding this, the Italian observational study found that 61% of hard-to-heal VLUs with a mean duration of 7.8 months healed in a mean of 3.9 months following the application of Debrichem.[19] Furthermore, all the ulcers granulated in a mean of 1.7 months.[19] However, the extent to which Debrichem may offer the UK's NHS a cost-effective intervention was unknown.

The annual cost to the NHS of managing VLUs was estimated to be £3.20 billion in 2017/18.[2] An estimated 87% of this cost (£2.78 billion) was attributable to hard-to-heal VLUs.[2] Furthermore, the NHS cost (uprated to 2020/21 prices) of managing hard-to-heal wounds in clinical practice that had undergone a mix of mechanical and sharp debridement as well as larval debridement was £1374 per wound at one month and £2384 per wound at three months.[35] Due to the ever-increasing demand for healthcare and limited finance with which to fund it, healthcare managers require cost-effectiveness evidence to inform their decision-making. This assists them in deciding how to allocate resources and which agents should be granted market access. Hence, the choice of both debriding method and debriding agent should be based on the best available evidence, incorporating both cost and effectiveness data. Furthermore, any treatment that can facilitate the healing of a hard-to-heal ulcer can potentially reduce the health economic burden of wounds.

Against this background, this study estimated the relative cost-effectiveness of using Debrichem to treat hard-to-heal VLUs by adopting a Markov modelling approach. Markov modelling was considered the most representative way to simulate patients' transition between different health states over a 12-month period. Patients in the Debrichem observational study were followed up for a mean of 7.5 months or to healing, if that occurred sooner. Patients in the SC cohort were followed up for 12 months. Hence, it was decided to model VLU management over a time horizon of 12 months rather than 7.5 months, since that would allow sufficient time to better reflect a patient's journey in the real world. The beyond-study modelling was based on the assumption that Debrichem-treated patients who had not healed by 7.5 months remained unhealed.

The resulting model was based on an indirect comparison of the 57 patients who participated in the Debrichem observational study with 57 propensity score-matched patients extracted from a cohort of patients with a VLU who were managed in clinical practice in the UK[2,4] (since there was no comparator group in the observational study), in combination with published utilities derived from individuals with potentially differing characteristics to the modelled population.[24] The ensuing analysis indicated that use of Debrichem in combination with SC could potentially afford the NHS a cost-effective intervention for hard-to-heal VLUs, since it improved outcomes for less cost.

The small sample sizes may have increased uncertainty around the transition probabilities in the model. Furthermore, the inherent variation in patient characteristics and clinical management between the observational study and the SC cohort would have also created some uncertainties and limitations. In particular, patients who participated in the observational study were managed by specialist clinicians at a wound care centre, whereas the SC-treated patients were largely managed in the community by non-specialist nurses. Moreover, the observational study used a range of inclusion and exclusion criteria which would have resulted in a more homogenous population than in our SC cohort of patients who were managed in clinical practice. Consequently, the model may not necessarily reflect clinical outcomes associated with managing a large cohort of patients with a hard-to-heal VLU in clinical practice in the UK. Accordingly, the results should be viewed with some caution until more data become available, which can then be used to update the model, particularly the findings from a randomised controlled trial (RCT) assessing healing rates between Debrichem in addition to SC compared with SC alone. Nevertheless, sensitivity analysis showed that as long as the 12-month healing rate associated with the use of Debrichem plus SC exceeded that of SC alone, then including this desiccating agent into a SC protocol is likely to afford the NHS a cost-effective intervention, since the expected cost-effectiveness would be <£20,000 per QALY. Moreover, the budget impact analysis indicated that use of Debrichem in combination with SC has the potential to improve the healing rate of hard-to-heal VLUs while reducing costs and releasing healthcare resources for alternative use.

Since the study period was limited to 12 months, an estimation of the budget impact of Debrichem over a longer period would be subject to much uncertainty and be beyond the remit of this study. Nevertheless, at a time when the incidence of VLUs is rising,[2,36,37] and the health economic burden of wounds on CCGs and

health boards is predicted to increase,[37] this analysis would suggest that including Debrichem into a SC protocol for hard-to-heal VLUs would potentially facilitate a decrease in the annual prevalence of these wounds for no additional cost and thereby contribute to reducing the health economic burden of wounds. Notwithstanding this, if the time horizon of the model was extended beyond 12 months, Debrichem would become more cost-effective because there were more unhealed wounds in the SC group at 12 months.

A search of Medline found very few published cost-effectiveness studies on the use of debriding agents in the UK. In one such study, no difference between debriding sloughy or necrotic leg ulcers with larval therapy and hydrogel was found.[38] To the authors' knowledge, the present study is the first to show a debriding agent affording a cost-effective intervention to the NHS for use in the management of VLUs. However, it has been previously reported that a hydro-responsive wound dressing affords the NHS a cost-effective treatment for debriding both acute and hard-to-heal wounds.[35] Because the economic analysis was based on the results of a single observational study in hard-to-heal VLUs, it precludes generalisation of our findings to patients with other wound types. Nevertheless, the model structure should be generalisable to other countries that encompass similar patient pathways for hard-to-heal VLUs. Additionally, the clinical effectiveness of Debrichem would be expected to be similar in comparable cohorts of patients in other countries, if the patient pathways and standard of care were consistent across the countries. However, it cannot be implied that this study's estimate of Debrichem's cost-effectiveness would be transferable to other countries if those countries used different treatment pathways or reimbursement mechanisms to those in the UK, or if they had a privately funded healthcare system. The provision of wound care is heterogeneous between different settings and different management systems, and this variation can impact on Debrichem's level of cost-effectiveness.

Limitations

The study is subject to several other limitations. Patients in the Debrichem evaluation were indirectly compared with a cohort of SC-treated patients. They were matched according to their age, sex, wound duration and several comorbidities using propensity scores. While no statistically significant differences were found between the matched cohorts, the possibility that undetected significant differences existed cannot be excluded. In particular, it was not possible to match or compare wound sizes or wound bed information since this was not routinely documented in the records of the SC-treated patients. The analysis included all the NHS costs and outcomes associated with wound management over the study period. However, it did not consider the potential impact of those wounds that either remained unhealed or recurred beyond the study period. The analysis only considered NHS resource use and associated costs for the 'average patient', and excluded patients living in a care home, and direct costs incurred by patients and indirect costs incurred by society as a result of employed patients taking time off work. There were insufficient data to assess the relative cost-effectiveness of using Debrichem in particular subgroups or to stratify the analysis according to ulcer size. Similarly, the analysis was unable to consider the impact of other factors that may affect the results, such as the severity of underlying venous disease.

The analysis was unable to incorporate any intangible benefits that patients may have experienced following Debrichem, irrespective of whether their wound healed. Also, the analysis was unable to consider the level of a clinician's skills in administering Debrichem or the suitability of patients to receive Debrichem, or to discern the challenges clinicians may have in the community in using Debrichem. The Debrichem arm of the model was populated with estimates from a cohort of patients with VLUs in Italy who may not be representative of patients with VLUs in England. Additionally, there may be a selection bias as patients in the Debrichem observational study were not randomised to treatment but selected by their managing clinicians in accordance with a study protocol. The absence of a control group may have potentially compromised the internal validity of the observational study. However, patients entered the observational study with a wound of a mean duration of 7.8 months. After administration of Debrichem every wound achieved 100% granulation in a mean of 1.7 months and 61% healed in a mean of 3.9 months. Therefore, it seems highly probable that this effect was achieved by the application of Debrichem to the wound rather than due to a systematic error in the study design. The possibility that the cost-effectiveness analysis may not have identified all the confounding variables that could influence the effects of Debrichem cannot be excluded.

Conclusion

Within the study's limitations, the addition of Debrichem to SC potentially affords a clinically effective and cost-effective treatment to the NHS for managing hard-to-heal VLUs. **JWC**

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Reflective questions

- What types of debridement do you use? Why?
- How many debridements would an average wound usually require?
- Do you consider your debridement technique to be effective in improving granulation and healing? If so, why?
- Would you consider using Debrichem? What are the reasons for your answer?