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Cost-effectiveness of superabsorbent wound dressing versus standard of care in patients with moderate-to-highly exuding leg ulcers

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Cost-effectiveness of superabsorbent wound dressing versus standard of care in patients with moderate-to-highly exuding leg ulcers

Objective: To determine the cost-effectiveness/utility of a superabsorbent wound dressing (Zetuvit Plus Silicone) versus the current standard of care (SoC) dressings, from the NHS perspective in England, in patients with moderate-to-high exudating leg ulcers.
Method: A model-based economic evaluation was conducted to analyse the cost-effectiveness/utility of a new intervention. We used a microsimulation state-transition model with a time horizon of six months and a cycle length of one week. The model uses a combination of incidence base and risk prediction approach to inform transition probabilities. All clinical efficiency, health-related quality of life (HRQoL), cost and resource use inputs were informed by conducting a systematic review of UK specific literature.
Results: Treatment with the superabsorbent dressing leads to a total expected cost per patient for a six month period of £2887, associated with 15.933 expected quality adjusted life weeks and 10.9% healing rate. When treated with SoC, the total expected cost per patient for a six month period is £3109, 15.852 expected quality adjusted life weeks and 8% healing rate. Therefore, the superabsorbent dressing leads to an increase in quality-adjusted life weeks, an increase in healing rate by 2.9% and a cost-saving of £222 per single average patient over six months. Results of several scenario analyses, one-way deterministic sensitivity analysis, and probabilistic sensitivity analysis confirmed the robustness of base-case results. The probabilistic analysis confirmed that, in any combination of variable values, the superabsorbent dressing leads to cost saving results.
Conclusion: According to the model prediction, the superabsorbent dressing leads to an increase in health benefits and a decrease in associated costs of treatment.
Declaration of interest: Vladica M. Velickovic, Streit Iris, Adriana Bordeanu, Daniela Kaspar, Jörg Linder, and Hans Smola are full-time employees of the Hartmann Group.

cost-effectiveness • cost-utility • England • hard-to-heal wounds • superabsorbent polymer dressing

The reported findings of the Global Burden of Disease (GBD) study indicate a dramatic increase in the prevalence of skin and subcutaneous diseases of over 18% in the period 2005–2015.[1] A meta-analysis focusing on hard-to-heal wounds, estimated a global prevalence of hard-to-heal wounds of mixed aetiologies at 2.21 per 1000 population, and for hard-to-heal leg ulcers at 1.51 per 1000 population.[2] The high prevalence of hard-to-heal wounds is a public health problem causing a substantial individual, social and economic burden. According to findings, the National Health Service (NHS) in England manages 2.2 million wounds annually (2012–2013), which translates to direct healthcare spending of £4.5–5.1 billion.[3] Similar findings are also reported in other countries. In the US, Medicare spending for hard-to-heal ulcers is $1.8 billion USD annually.[4] According to a systematic review of cost-of-illness studies in hard-to-heal ulcers, average annual cost per patient from a third-party payer perspective was $44,200 USD for diabetic foot ulcers (DFU), $15,400 USD for pressure ulcers (PU) and $11,000 USD for leg ulcers with substantial annual out-of-the-pocket costs of $1000 USD per patient.[5]

Most hard-to-heal wounds are a consequence of systemic disease and/or poor overall health.[6–9] Many pathophysiological and molecular pathways that lead to wound occurrence and prolong the process of healing are well known and described.[10,11] Additionally, the clinical complexity of wound management remains a challenge due to high heterogeneity among affected patients.[12] Recommendations prescribe a holistic approach and personalised treatment in order to avoid

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Table 1. Major characteristics of patients from superabsorbent clinical study used for model[22]

Variable (n=39)					95% CI	
	Mean	SD	Range	SE	LB	UB
Age			46–98	1.81	72.06	79.42
Duration of wounds (months)	10.4	17.6	0.3–85.2	2.9	4.5	16.3
Wound size SoC (mm^2): baseline	3333	5783	35–33,000	926	1459	5208
Wound size (mm^2): after two weeks of the super absorbent dressing	3182	5819	16–33,000	932	1296	5069

n—number of observations; CI—confidence interval; SD—standard deviation; SE—standard error; LB—lower bound; UP—upper bound; SoC—standard of care

the 'one-fit-all' approach.[13] In such a situation, for achieving long-term clinical outcomes (wound healing and prevention of wound recurrence), different wound subtypes often have national and international guidance to support the best approach to management.[14] Among other recommendations, in line with the T.I.M.E. strategy (tissue management (wound bed preparation or debridement), inflammation and/or infection control, moisture balance, epithelial (edge) advancement) the wound bed should be physiologically humid; that is, not too dry but not too wet.[15]

In the case of venous leg ulcers (VLU), exudate level can be high consequently leading to maceration and breakdown of surrounding skin tissue, and a further increase in wound size and pain.[16] As a part of the optimum treatment of highly exudative wounds, an absorbent dressing is recommended, in order to adequately capture exudate and allow undisturbed wound healing with fewer dressing changes.[17] Polyacrylate superabsorbent polymer (SAP) dressings are the first-line recommendation for the treatment of moderate-to-high exudative wounds while alginates, hydrofibers, foams and hydropolymers are recommended as second-line dressings for these wounds.[12,18] Superabsorbent is a specific type of dressing material with high fluid retention capacity maintained even under compression, which additionally provides cushioning and high moisture vapour transmission rate.[18]

Polyacrylate superabsorber particles reduce factors that inhibit wound healing and the matrix metalloproteases (MMP) activity, through several distinct mechanisms, such as direct binding and inhibition of MMPs activity through competition for divalent ions.[19] Despite the high prevalence and significant economic burden of hard-to-heal wounds, as well as the vast number of different dressing solutions, the number of full health economic evaluations of wound specific treatments is very low. Full economic evaluations are a comparative analysis of two dressing alternatives, considering both resource use (with associated costs) and consequences (in terms of patient-related outcomes).[20] According to the most recent systematic review of economic models in leg ulcers, the total number of full economic evaluation models concerning leg ulcers in the UK is 15, with only six evaluating dressings as an intervention.[21]

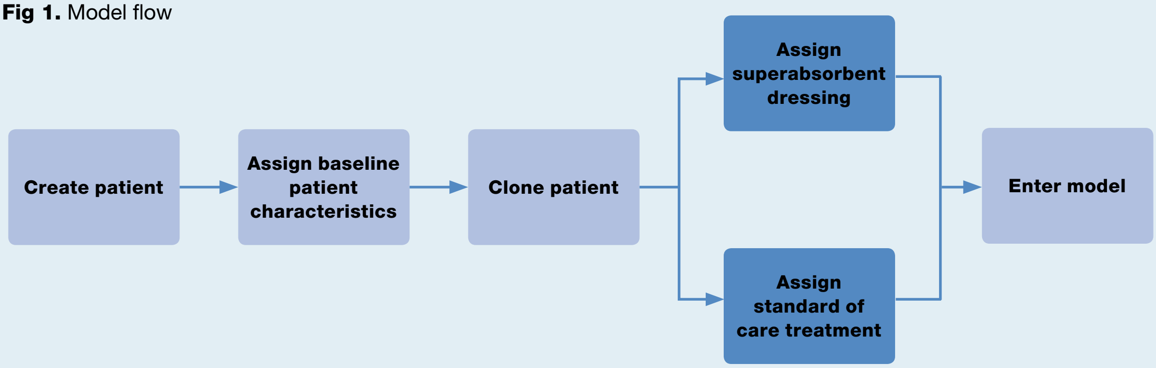
Recently, a superabsorbent dressing (Zetuvit Plus Silicone) was introduced onto the UK market. Adding a silicone wound contact layer to the superabsorbent dressing reduces tissue trauma during removal and allows for an undisturbed healing process. The aim of this study was to determine the cost-effectiveness/utility of the superabsorbent dressing versus the current standard of care (SoC), from the NHS perspective in England, in patients with moderate-to-high exudative

Table 2. Dressing specific resource use and associated costs (per week)

Product (dressing type)	Fraction of cohort	Source	n of dressing changes per week	Source	Price per dressing	Source
Intervention						NHS drug tariffs 2019[35] and Prescription cost analysis data[36]
Superabsorbent dressing	100%		2.80	Panca et al.[30]	£1.50	
Comparator (Standard of care)						
Other superabsorbents	36%	Data on file	2.80	Panca et al.[30]	£1.56	
Antimicrobials	30%		4.00	Assumed based on Panca et al.[30]	£6.87	
Foams	20%		4.00		£2.17	
Alginates	9%		4.00		£1.47	
Other dressings	5%		4.00		£1.47	

NHS—National Health Service; parameters in one-way sensitivity analysis (OWSA) varied ±20%; following distributions were used in probabilistic sensitivity analysis (PSA): fraction of cohort: dirichlet distribution, n of dressing changes: normal distribution and price: gamma distribution

Fig 1. Model flow



leg ulcers. Recent clinical data regarding the superabsorbent dressing[22] was used as the clinical basis for construction of an economic evaluation model.

Methods

The economic evaluation was conducted in line with good modelling practice recommendations,[23,24] reported in accordance with the CHEERS checklist[25] (quality of reporting) and additionally quality appraised with Drummond checklist[26] (quality of conducting).

Target population

Participants were male and female with moderately to highly exuding leg ulcers. Characteristics were taken from a superabsorbent dressing clinical study[22] in the UK (Table 1). Therefore, the baseline patient characteristics were based on individual patient level clinical data. The original clinical trial recruited 50 patients, of which 39 patients had complete outcome data, including wound size. The data from these 39 patients were used for the purpose of the health economic model. In order to achieve stability of the results, 1000 patient profiles were generated for the model by random sampling from the original dataset of 39 patients. Sampling number was determined based on analyses (material available on request to editor).

Study perspective

The economic evaluation is conducted from the NHS perspective in England. All cost data inputs used in the model are UK specific in GBP and therefore there was no need for conversion. Where applicable, cost was inflated to 2019 values using the hospital and community health services (HCHS) indices.[27] A discount rate for cost and outcomes was not applied given that the time horizon was shorter than one year. Societal perspective for scenario analysis was planned, however due to the lack of relevant data inputs it was not carried out.

Time horizon

The time horizon in the study was six months (24 weeks). Dressings are used for local treatment of leg ulcers and not for the treatment of underling chronic disease. Therefore, dressings cannot affect mortality, as well as cannot modify natural history of underlying disease (for example, varicose veins). For that reason, the life-time horizon is not adequate and a proper time horizon should capture wound/ulcer relevant outcomes (for example, healing rate). The most proper approach will be to also capture wound recurrence in the same localisation and, in that case, a proper time horizon should be between 1–2 years. However, current available data does not allow for reliable extrapolations up to one year or more for healing rate and inclusion of ulcer recurrence, and therefore a six month period was used. This time period is an optimal period to observe important health outcomes in patients with hard-to-heal wounds.

Comparators

The intervention used for the evaluation was a superabsorbent dressing (Zetuvit Plus Silicone, Hartmann, UK). The SoC was defined as a current intervention (dressing) for the treatment of leg ulcers with moderate-to-high exudate levels. To ensure fair comparison the exact mix of dressings (Table 2) from the superabsorbent dressing study[22] was used as a SoC.

Choice of model

Time invariant state-transition microsimulation model was developed with six health states relevant to leg ulcer treatment as recommended by Harding et al.[28] The patient-level simulation was selected due to the heterogeneity of the population at the start of the

Fig 2. Influence diagram

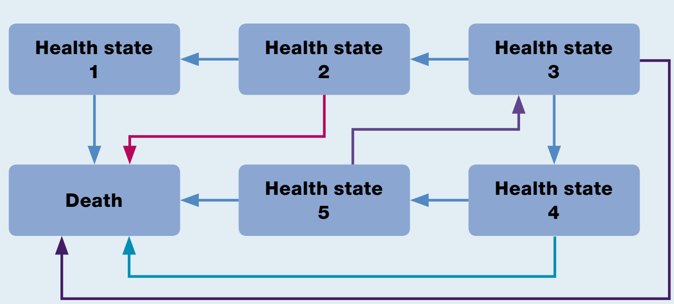


Table 3. Transition probabilities for state-transition model (weekly transitions)

Transition probability	Value	Range for OWSA	Parameters for PSA*	Source
Transition probability from HS1 to HS3	0.0000	±20%	NA	Assumption: no recurrence
Transition probability from HS2 to HS1	0.0250	±20%	97; 3,833 (beta)	Panca et al.[30]
Transition probability from HS3 to HS2	0.0367†	±20%	98; 3,939 (beta)	Shannon et al.[31]
Transition probability from HS3 to HS4	0.0188	±20%	98; 5,120 (beta)	Walzer et al.[40]
Transition probability from HS4 to HS5	0.0040	±20%	100; 24,799 (beta)	Shannon et al.[31]
Transition probability from HS5 to HS3	0.8000	±20%	19; 5 (beta)	Walzer et al.[40]
Transition probability from any HS to Death	Age-specific	±20%	100; 37,838 (beta)	UK life tables[32]

HS—health state; OWSA—one-way sensitivity analysis; PSA—probabilistic sensitivity analysis; NA—not applicable; *parameters: alpha and beta; †Adjusted for all patient using Margolis et al. risk prediction model

Table 4. Health-state specific utility values

Transition probability	Value	Range for OWSA	Parameters for PSA	Source
Utility associated with state HS1	1.000	–20%/1	4; 0.250	Clegg et al.[34]
Utility associated with state HS2	0.730	0.70–0.76	11; 0.0642 (gamma)	
Utility associated with state HS3	0.640	0.61–0.68	6; 0.0996 (gamma)	
Utility associated with state HS4	0.640	0.61–0.68	6; 0.0996 (gamma)	Assumption based on Clegg et al.[34]
Utility associated with state HS5	0.610	0.60–0.62	102; 0.0071 (gamma)	Estimation based on Matza et al.[43]

HS—health state; OWSA—one-way sensitivity analysis; PSA—probabilistic sensitivity analysis; NA—not applicable;

modelled period (Fig 1).[24] The patients have transited through the following health states (HS) (Fig 2):

- Healed: skin is intact (HS1)
- Unhealed grade 1 progressing: ulcer is progressing towards healing (HS2)
- Unhealed grade 1 static: ulcer is neither healing nor deteriorating (HS3)
- Unhealed grade 1 deteriorating: ulcer is deteriorating (HS4)
- Unhealed grade 2 severe: ulcer is infected or with other complications which may require hospital admission and/or surgical intervention (HS5)
- Death.

The model cycle length was one week, which reflects important clinical changes in the case of leg ulcers. Half-cycle correction was integrated in the Markov trace to take into consideration the possibility that patients can transit to a different health state at any time during the cycle. Due to the nature of wounds at the baseline in the clinical study,[22] all patients were entering the model in HS2 health.

For missing data, multiple imputations using mean values were used for the base case analysis and several other imputation methods were tested in the scenario analyses. Further details about the decision-analytic model and analytical approach are available on request to editor.

Clinical effectiveness inputs

The model uses a previously published risk prediction model by Margolis et al.[29] in order to quantify the risk that wound will not heal in six months based on following patient characteristics: (i) age, (ii) gender, (iii) number of wounds, (iv) duration of wound in months, (v) wound size in mm^2, and (vi) wound grade. Further details of the incorporation of risk prediction models into the structure of the decision-analytic model are available on request to the editor.

Transition probabilities for the health economic model were informed from published literature[30,31] and reported in Table 3. Considering that both the intervention and comparator cannot affect patient survival, age-specific survival was informed from the UK life tables,[32] with no difference between the two arms. As depicted in Table 3, transition probabilities are time-invariant and equal between the intervention and comparator. Only the transition from HS3 to HS2 was adjusted based on results of applied risk prediction model at the level of every single patient. Therefore, based on unique patient characteristics and depending on which therapy was applied, the patient will transit from HS3 to HS2 (from 'static wound' to 'wound progressing toward healing') at different rates. Difference in transition over time from static ulcer (HS3) to unhealed ulcer, progressing toward healing (HS2) between treatment arms will be a main driver of the final difference in healing rate.

Health-related quality of life inputs

Although, there is no difference in life expectancy between the two comparator arms in the model, quality of life (QoL) can differ and therefore quality-adjusted life-weeks (QALWs) were used to estimate the difference in

Table 5. Health-state specific costs

Health state Direct medical costs	Inflated costs	Range for OWSA	Parameters for PSA*	Source
Associated with state HS1	£7	±20%	187; 0.04 (gamma)	Harding et al.[28]
Associated with state HS2	£99	±20%	39,259; 0.003 (gamma)	
Associated with state HS3	£113	±20%	51,448; 0.002 (gamma)	
Associated with state HS4	£180	±20%	130,101; 0.001 (gamma)	
Associated with state HS5	£721	±20%	2,077,368; 0.0003 (gamma)	

HS—health state; OWSA—one-way sensitivity analysis; PSA—probabilistic sensitivity analysis

health-related QoL (HRQoL) between comparators. QALWs is an outcome measure that reflects life expectancy and QoL as a single outcome. QALWs is calculated by multiplying one week with the utility value for that period. The utility value can have a value range between zero (death) and one (perfect health), and the values for disease/state are empirically determined. In our model, HRQoL was modelled as health state-specific rather than treatment-specific, as suggested by good modelling practice recommendations.[33] In order to populate the model with the most adequate inputs, a literature review was conducted in line with Minimum Reporting Standards of Systematic Review of Utilities for Cost-effectiveness checklist.[33] The decision was made to use Clegg et al.[34] as a source for inputs since this study to determine the QoL is conducted in the UK with a robust methodological approach. The input values are presented in Table 4.

Cost and resource use inputs

Cost inputs can be divided into two categories: dressing specific costs and health state specific costs. Dressing specific costs are presented in Table 2. The average cost of dressing by dressing category is estimated by using 2019 NHS drug tariffs[35] and relevant market share for each dressing.[36] The average cost is then multiplied by the number of dressing changes to determine the weekly total cost. Health state specific costs were informed by Harding et al.[28] and inflated to 2019 values[27] (Table 5).

Analysis and uncertainty analysis

In line with National Institute for Health and Care Excellence (NICE) recommendations, the dressing was considered cost-effective if the incremental cost-effectiveness ratio (ICER) was below the lower-bound willingness-to-pay threshold of £20,000/QALY, or if the net monetary benefit (NMB) was positive.[37] ICER is an outcome measure that take in account costs, life expectancy and QoL in one single measure. It is calculated as:

$$\text{ICER} = \frac{(\text{Cost SA–Cost SoC})}{(\text{QALWs SA–QALWs SoC})}$$

where, SA is the superabsorbent dressing, SoC is a standard of care, and QALWs is Quality-Adjusted-Life Weeks. Net-monetary benefit (NMB) is outcome measure that combines cost, life expectancy and quality of life, and willingness to pay threshold in single unit. It is calculated as:

$$\text{NMB} = (\text{QALWs SA–QALWs SoC})\ \text{X WTP–(Cost SA–Cost SoC)}$$

where, SA is the superabsorbent dressing, SoC is a standard of care willingness-to-pay threshold (£20,000). Willingness-to-pay threshold is defined as a maximum value of money per health outcome that the NHS is willing to pay for a new intervention.

In standard health economic terminology, 'dominant treatment option' is used for situations where one intervention leads to better health outcomes for less costs.

In line with recommendations,[38] uncertainty about model structure and inputs were explored in both deterministic and probabilistic sensitivity analyses. One-way deterministic sensitivity analysis was conducted by a change of every input parameter, first to a minimum and then to maximum value, while keeping all other parameters fixed. Results are presented in the form of a Tornado diagram. Probabilistic sensitivity analysis was conducted as a Monte-Carlo simulation with 5000 iterations by randomly sampling parameter values from their probabilistic ranges in every iteration. Results are presented as a probabilistic cost-effectiveness plane. Several scenario analyses were conducted and reported. In cases when complete information of variability around data inputs was not reported in the literature, we have used arbitrary ranges of ±20% around mean value. Whenever variability information was presented in appropriate form, arbitrary ranges were not used.

Statistics analysis was performed using Stata 16 Special Edition (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, US The model was developed in Microsoft Office Excel 365 ProPlus (Microsoft Corp., US).

Model validation

In accordance with the good modelling practice recommendations,[39] the model was extensively validated through a process of model verification (for

Table 6. Economic evaluation base case results

Superabsorbent			Standard of care			Incremental Costs	Incremental QALWs	Incremental HR	ICER (QALW)	ICER (HR)	NMB
Cost	QALWs	HR	Cost	QALWs	HR						
£2887	15.933	0.1093	£3109	15.852	0.0797	–£221.97	0.08097	0.02960	Dominated by the superabsorbent dressing*		1841

QALWs—quality adjusted life weeks (outcome measure that reflect life expectancy and quality of life as a one single outcome); HR—healing rate, ICER—incremental cost-effectiveness ratio (outcome measure that take in account costs, life expectancy, and quality of life in one single measure); NMB—net monetary benefit; *dominated by superabsorbent dressing means that the superabsorbent dressing, when compared with standard of care, leads to more benefits (QALW, and healing rate) and less cost

Table 7. Scenario analysis results

Scenario	Base case input/ assumption	Scenario analysis input/assumption	Results of scenario analysis ICER (Incremental cost)
Increased number of wounds	One	Two	Dominates (–£196.86)
		Three	Dominates (–£194.79)
Wound grade	One	Three	Dominates (–£198.41)
		Five	Dominates (–£195.33)
Direct medical costs associated with state HS5	2,4 for SAP, 4 for others	±20%	Dominates (–£116.38)
Alternative source for utility values	HS1=1, HS2=0.73, HS3=0.64 HS4=0.64, HS5=0.61	HS1=0.63 HS2=0.534 HS3=0.525 HS4=0.534 HS5=0.13	Dominates (–£202.40)

HS—health state; OWSA—one way sensitivity analysis; PSA—probabilistic sensitivity analysis; NA—not applicable

internal validity) and cross-validation. Internal model validity was assessed using analysis of extremes and an in-house standardised quality checklist with the aim of identifying and resolving all potential programming bugs. Cross-validation was done by comparing results with other published models and using model structure to reproduce the results of the most similar models identified in the published literature.

Results

Base case analysis

The model predicts that the SoC dressing approach is dominated by superabsorbent dressing in leg ulcer patients with moderate-to-high exudate or, in other words, superabsorbent dressing leads to the increased health benefits for less costs when compared with SoC. As previously explained, dominance represents results

Fig 3. Tornado diagram of key parameters driving the model outcomes

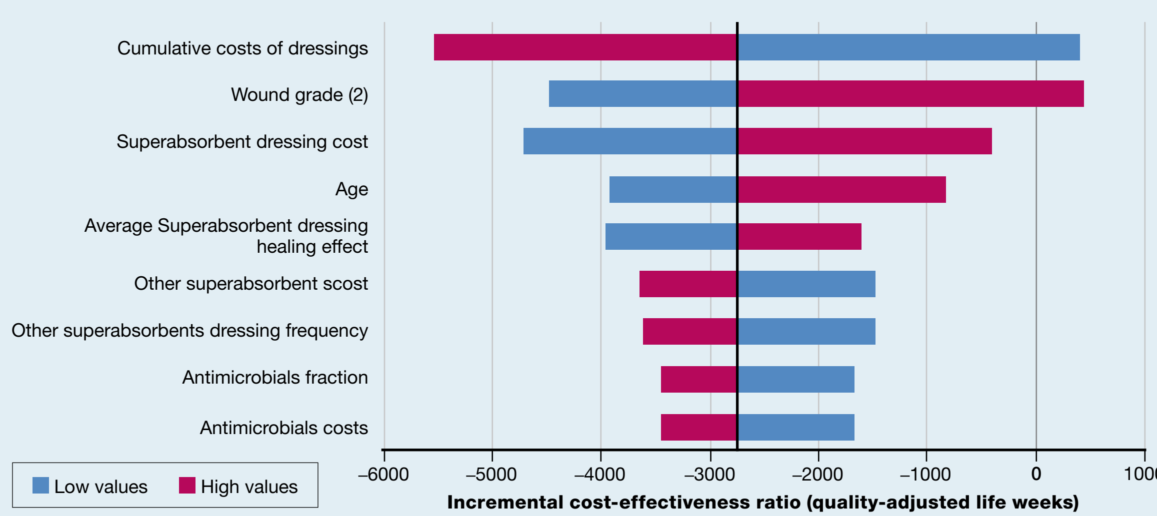
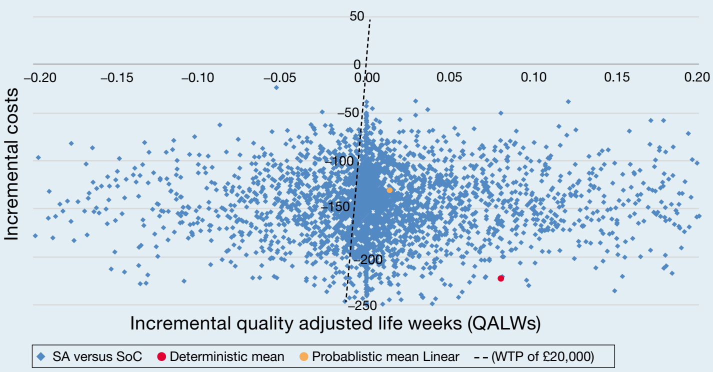


Fig 4. Probabilistic cost-effectiveness plane



SA—superabsorbent dressing; SoC—standard of care; WTP—willingness to pay threshold

of the economic evaluation in which one of the comparators is associated with more health benefits and fewer costs. As reported in Table 6, treatment with the superabsorbent dressing leads to a total expected cost per patient for a six month period of £2887, associated with 15.933 expected QALWs and 10.93% healing rate. When treated with the SoC, the total expected cost per patient for a six month period will be £3109, 15.852 expected QALWs and 7.97% healing rate. Therefore, the superabsorbent dressing leads to an increase in QALWs, an increase in healing rate by 2.96%, and a cost-saving of £222 per single average patient over six months.

Scenario analyses

To test the impact of different important assumptions on the main results, several scenario analyses were run, and results are presented in Table 7. As demonstrated, change of assumptions in scenario analysis does not have a substantial effect on base-case results. In addition, different methods for dealing with missing values do not change the results beyond inherent variability in results specific for the microsimulation models.

Sensitivity analysis

One-way deterministic sensitivity analysis identified cumulative costs of dressings in the standard of care, and superabsorbent dressing cost, as the two most influential parameters. Among other parameters, patient age and average superabsorbent healing rate are the two most influential parameters. The top 10 most influential parameters are presented in Fig 3.

Results of probabilistic sensitivity analysis (PSA) are reported in Table 8. Probabilistic sensitivity analysis demonstrates that Zetuvit Plus Silicone is a cost-saving option (Fig 4) and this cost-effectiveness persists when the willingness to pay threshold (WPT) is changed from GBP 0 to GBP 120,000 per QALY. Due to the nature of microsimulation modelling, every new analysis run of the base-case model leads to a change in the final results, as would be expected to happen if we ran a prospective study with the same inclusion/exclusion criteria several times, sampling from a hard-to-heal leg ulcer population in the UK. In addition, for the probabilistic analysis, we randomly sampled from all included variables in the analysis 5000 times in order to produce final PSA results. Therefore, in every 5000 iterations, we first randomly sample the population and then randomly sample all parameters. This point is emphasised in order to avoid confusion due to the difference between deterministic and probabilistic mean values in results tables.

Model validation

Internal model validation by using analysis of extremes and detailed quality checklist identified and eliminated all technical errors in the decision-analytic model.

Table 8. Results of probabilistic sensitivity analysis

Superabsorbent dressing			Standard of care			Incremental Costs (95% CI)	Incremental QALWs (95% CI)
Cost	**QALWs**	**HR**	**Cost**	**QALWs**	**HR**		
£2111	14.636	£2241	14.622	–£130 (–231, –66)	0.0140 (–0.062, 0.138)	SA dominates SoC	410

QALWs—quality adjusted life weeks (outcome measure that reflect life expectancy and quality of life as a one single outcome); HR—healing rate; ICER—Incremental cost-effectiveness ratio (outcome measure that take in account costs, life expectancy, and quality of life in one single measure); NMB—net monetary benefit; SA—superabsorbent dressing; SoC—standard of care

Table 9. Results of model cross-validation

CEA model	Total cost of treatment (£)	Model time horizon	Costing year	Average cost per month, inflated to 2019	Extrapolated to one year
Our model	From 2887 to 3109	Six months	2018/2019	500	6000
Walzer et al. 2018[40]	From 4699 to 4871	One year	NR	451	5412
Jemec et al. 2014[62]	From 1326 to 1468	Two months	2012/2013	734	8811
Guest et al. 2018[63]	From 3789 to 6328	Six months	2015/2016	862	10,341
Panca et al. 2013[30]	From 2453 to 5128	Six months	2003/2004	849	10,184

CEA—cost-effectiveness; NR—not reported

As part of cross-model validation, the results of our model were compared with the results of four model-based evaluations from the UK (Table 9), published after 2010 and identified in the most recent systematic review of model-based economic evaluations in leg ulcers.[21] We have compared the total cost of treatment of leg ulcers among comparators rather than ICERs or incremental costs/QALYs. To allow for comparison, we have inflated the cost for 2019 and conducted a rough approximation of all costs to annual level. The costs per patient range from £5412 to £10,341, and our results of £6000 are within the lower end of this range. The cross-model validation process demonstrates that our results are closest to an analysis by Walzer et al.[40] that used the same suggested model structure by Harding et al.[28] By simplifying our model structure, by switching to cohort simulation rather than patient-level simulation and changing the inputs, we were able to replicate Walzer et al.[40] results.

Discussion

Most hard-to-heal wounds are the expression of an underlying physiological condition or systemic disease, such as diabetes, chronic venous insufficiency or increased mechanical pressure. Systematisation of knowledge in relation to proper treatment dynamics at different phases of the hard-to-heal wound healing process has not yet been achieved at a satisfactory level.[41] Many different classes of treatment products are used simultaneously, and quantification of treatment specific contributions to the process of wound healing is largely unknown. Keeping in mind that any health economic evaluation is strongly dependent on precise estimates of treatment effect, such as situation in clinical research directly hinders health economic research.

After clinical recommendations unambiguously recommended using superabsorbers as a first line choice in moderate-to-high exudative leg ulcers,[18] this economic evaluation clearly indicates that the superabsorbent dressing used can be a cost-saving solution for the NHS when compared with SoC.

However, apart from clinical relevance, cost savings for the NHS are substantial per patient, keeping in mind a high prevalence and incidence of hard-to-heal wounds. Therefore, according to the results of the evaluation, the superabsorbent dressing should be used in the treatment of leg ulcers with moderate-to-high exudate levels due to the improved clinical benefits, increased QoL and cost-saving for the NHS. However, all results of this economic evaluation should be interpreted while bearing in mind all advantages and limitations of the analysis. The analysis and descriptions of all potential pros and cons have been transparently reported to the best of our knowledge. Not only do we report the limitations of our research and overall body of evidence, but we also suggest solutions and recommendations for future research efforts.

Deterministic sensitivity analysis results demonstrate that the superabsorbent dressing is cost-saving in almost all situations. Only in the extreme situation when the cumulative cost of all comparator dressings is lower than 20%, or the patient has a higher wound grade, the ICER could be positive; however, the superabsorbent dressing would still be highly cost-effective. In the probabilistic sensitivity analysis (PSA) with 5000 iterations the results were, in all cases, cost-saving for the superabsorbent dressing. However, the mean value results from PSA are lower in terms of cost-savings (incremental cost: £130) and QALW gained (0.0140), and deterministic mean results suggest that true cost and benefit mean value in the population can be lower, but still cost saving.

In this study we have applied two quality check lists[25,26] to ensure quality of conduct and good reporting. Model conceptualisation, method selection, and development follow appropriate health economic guidelines.[23,24] In terms of methodological novelty needed to ensure robust results, we selected the most appropriate modelling method and properly reported and justified our method choice. Selecting a state-transition (Markov) cohort model without providing justification, as done with previous economic evaluations, is not in line with good methodological practice,[26] and as we explain in many situations state-transition microsimulation will be the more adequate solution. According to our best knowledge, this is the first state-transition microsimulation model in health economics of wound care products. Furthermore, we have followed appropriate guidelines in identifying data inputs,[33] as well as estimating and adaptating data inputs for the model.[38] In the cases when identified data were not reported with variability measures with sufficient granularity, we were forced to apply arbitrary ranges ±20% for sensitivity analysis. In addition, we conducted model validation in line with recommendations.[39] In order to put our results into context, we compared them with the results of other model-based evaluations in the UK identified by recent systematic review.[21] Our results are comparable with similar cost-effectiveness comparisons among different types of dressings. Nonetheless, attention is needed to ensure standardisation of methods and therefore comparability of results between economic evaluations. We also followed and integrated UK specific recommendations,[37] wound specific consensus document recommendations,[18] and meta-critique from evidence synthesis papers.[21]

With regards to the results, it is evident that many products in economic evaluations of dressings have a dominant result in terms of evaluated cost-effectiveness of intervention. This arises from the fact that we potentially have publication bias when negative results are not reported, but it is also connected to the current pricing of dressings in the UK. Namely, the current tender process in the UK lead to the situation that the price of the dressing is taken into consideration, rather than opportunity cost and expected outcomes. In such situations, many companies, despite the overall quality of their product, do not apply value-based pricing, but rather, the price of the dressing is driven by tender requirements. In such situations, results of health economic evaluations should not come as a surprise. In addition, quality of clinical data direct affects quality of data inputs available for use in model-based economic evaluations, and therefore indirectly limits generation of more robust health economic evidence. Solutions to this are suggested in the section 'Recommendations for further research'.

Study limitation

Using model-based evaluations for analysis of the cost-effectiveness of new treatment options can potentially exclude some relationships between health and cost outcomes in a leg ulcer population. As for other indications, the most appropriate approach in these types of comparisons is to randomise patients to the superabsorbent dressing and SoC arms and follow relevant outcomes over time. However, in current practice, with the almost daily introduction of new dressings to the market, the SoC is a dynamic category which changes while planning, conducting and publishing results of any economic evaluation. For this reason, decision-analytic modelling should be considered as part of a standard approach for identifying the cost-effectiveness of dressings.

The current clinical evidence does not offer a satisfying level of short and middle-term outcomes among different types of dressings, even among different dressings categories.[41] In addition, only very limited data is available for specific populations (for example, patients with moderate-to-high exudative leg ulcers). Therefore, this analysis uses different non-randomised sources which are limited by moderate-to-high risk of bias.

As in other published economic evaluations,[21] the overall body of clinical evidence concerning dressings effectiveness does not offer sufficient inputs for time-dependent transition probabilities, and therefore time-invariant transition probabilities were used. Time-dependent probabilities can affect the time spent in different health states in the model and, therefore, can affect results. Further research is needed in the field of wound care to generate appropriate time-to-event evidence in this fashion.

The clinical study for the superabsorbent dressing[22] is a one arm study allowing for only a before/after comparison where the patient serves as his/her own control. The causal inference and determination of intervention attributable fraction from such a study design is not possible due to the temporal changes and regression toward the mean, irrespective of analytical methods applied.[42] Besides, one evident limitation is the low sample size in the clinical study for the superabsorbent dressing.[22] Therefore, the study has a higher likelihood of not accurately representing the population. For the reasons stated above, we have conducted cross-model validation and compared the results of our research with other cost-effectiveness studies in the leg ulcer population. Although the magnitude and direction of potential biases cannot be identified in this fashion, the results of cross-model validation demonstrate that our analysis does not have a substantial issue with representatives of the study population. On the other hand, we did not model reduction in pain during dressings changes with the superabsorbent dressing, which can affect final HRQoL results in favour of SoC.

Matza et al.[46] was used as a source for utility decrement due to wound infection for health state HS5 in the model. However, Matza et al.[43] was used for the analysis, despite the fact that in this study they measured utility decrement of infection of acute rather than hard-to-heal wounds. Currently, to the best of our knowledge, there is no adequate literature inputs for this purpose and Matza et al.[43] is the most appropriate proxy measure. In addition, we extensively tested this input in the sensitivity analyses.

Recommendations for further research

In order to determine the clinical effect of a single product, there is a need for background research that will determine exact disease/condition specific causal networks, with all relevant clinical factors and how they inter-relate. The determined causal network should preferably be developed using directed acyclic graphs (DAGs) or single-world intervention graphs (SWIGs),[44,45] and should serve as a basis for treatment comparisons and analyses, allowing for standardisation and comparison of results from many different types of research and geographies. The same standardisation effort is needed at the level of health economic studies. Future health economic research should collect and report resource use and associated costs in line with costing methodology by Harding et al.[28]

Use of real-world data is the future in this field. Several large, primary care databases exist in the UK, such as Clinical Practice Research Datalink (CPRD),[46,47] The Health Improvement Network (THIN)[48,49] and Qresearch,[50] that can support high-quality research. Whenever real-world data are used, good research practice recommendations must be followed to ensure relevance and validity.[51–54] However, transforming real-world data into real-world evidence, especially in highly heterogeneous populations, such as in wound care with many simultaneous and overlapping local and systemic treatments, is not a trivial task. In most cases, it will require applying the most advanced causal inference methods, such as marginal structural models[55,56] and target trial design.[57]

An effective approach would be organisation of a taskforce to standardise efforts and development of a wound management reference case model, which would include stakeholders from industry, universities, and the NHS. Simultaneously, there is a need for changes in the dressing tendering process by insisting on the most economically advantageous tender and

Reflective questions

- Do we need a reference case in the health economics of wound dressing to ensure the comparability of the results?
- Which modeling method is most appropriate for model-based economic evaluations considering high heterogeneity of the chronic wound population?
- How do we deal with a small sample size in prospective studies evaluating an intervention for chronic wounds?
- What are the advantages and disadvantages of using real-world data sources (Electronic Health records and registries) for comparative-effectiveness and cost-effectiveness in wound care?

ensuring that the best dressings will be offered for wound treatment, according to a demonstrated value for the patient rather than one purely based on price.[58]

An international consensus aimed at developing the reference case for cost-effectiveness in wound management was published in 2017.[59] An expert working group lead by Professor Keith Harding established the bridge between strict methodological requirements from key health economic professional organisations (such as International Society for Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making) and clinical practice in wound management, providing explanations and elaborations for health professionals. The resulting document is a huge step forward in establishing standardisation as mentioned above and preventing some common pitfalls in health economic evaluation reporting and conducting in the field of wound management. An important message from this consensus document relates to different types of health economic analyses and proper labelling of studies. Firstly, we need to be able to communicate using the same language—a prerequisite in any field of science. Secondly, we need consistent outcomes reporting in order to be able to make comparisons of results across the entire wound management field. Using consistent outcome measures and utilities/QoL in economic evaluations is underlined in the international consensus document.

In many situations, the new generation of simulation methods will be needed to determine health economic outcomes with more granularity and precision. Therefore, in future health economic research, advanced methods, such as agent-based modelling, system dynamics, discrete event simulation and multi-methods models (a combination of agent-based modelling, system dynamics, discrete event simulation) should be considered.[60,61]

Conclusion

The decision-analytic model was developed in order to compare cost-effectiveness and cost-utility of a superabsorbent dressing with SoC dressings from an NHS perspective in patients with moderate-to-high exudative leg ulcers. According to the model prediction, the superabsorbent dressing leads to an increase in health benefits and a decrease in associated costs of treatment. However, future research efforts are needed in order to standardise methods and outcomes in health economic studies of hard-to-heal wounds and make results across studies of various treatments more comparable. **JWC**

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