Cost-effectiveness of using adjunctive porcine small intestine submucosa tri-layer matrix compared with standard care in managing diabetic foot ulcers in the US

Objective: To estimate the cost-effectiveness of using tri-layer porcine small intestine submucosa (SIS; Oasis Ultra) as an adjunct to standard care compared with standard care alone in managing diabetic foot ulcers (DFUs) in the US, from the perspective of Medicare.
Method: A Markov model was constructed to simulate the management of diabetic neuropathic lower extremity ulcers over a period of one year in the US. The model was used to estimate the cost-effectiveness of initially using adjunctive SIS compared with standard care alone to treat a DFU in the US at 2016 prices.
Results: At 12 months after the start of treatment, the use of adjunctive SIS instead of standard care alone is expected to lead to a 42 % increase in the number of ulcer-free months, 32 % increase in the probability of healing, a 3 % decrease in the probability of developing complicated ulcers and a 1 % decrease in the probability of undergoing an amputation. Health-care resource use is expected to be reduced by 11–14 % among patients who are initially managed with adjunctive SIS compared with those initially managed with standard care alone, with the exception of debridement, which is expected to be reduced by 35 %. Hence, the total health-care cost of starting treatment with adjunctive SIS instead of standard care alone was estimated to reduce payer costs by 1 % (i.e. $105 per patient) over 12 months following the start of treatment.
Conclusion: Within the study's limitations, the use of adjunctive SIS instead of standard care alone improves outcome for less cost and thereby affords a cost-effective use of Medicare-funded resources in the management of neuropathic foot ulcers among adult patients with type 1 or 2 diabetes mellitus in the US.
Declaration of interest: The authors certify that they have no affiliation with or financial involvement in any organisation or entity with a direct financial interest in the subject matter or materials discussed in this manuscript, although CRW is an employee of the sponsor, Smith and Nephew, Inc. JLF, AG and CJA are speakers and/or clinical trial investigators in the field of diabetes, all of which are independent of this current study. Additionally, JLF and AG have provided consultancy/advisory services to Smith and Nephew Inc., and received research funding independently of this current study. The authors have no other conflicts of interest that are directly relevant to the content of this manuscript.

cost-effectiveness • diabetic foot ulcer • Oasis Ultra • porcine small intestine submucosa tri-layer matrix • United States

Diabetic foot ulcers (DFUs) are a frequent and serious complication of diabetes mellitus with an annual incidence of 0.01–0.04 and a lifetime risk of 0.15–0.25.[1–3] DFUs are often difficult to heal, and may become chronic, substantially increasing the risk of becoming infected leading to hospital admissions and possibly a lower limb amputation.[4]

The goal of DFU management is to promote rapid and complete re-epithelialisation to minimise the risk of ulcer complications and to restore a patient's health-related quality of life to a 'pre-ulcer' status. Good standard care for DFUs comprises debridement of necrotic tissue, infection control, off-loading and maintenance of a moist wound environment.[5] One advanced therapy that can be used adjunctively with standard care is tri-layer porcine small intestine submucosa (SIS; Oasis Ultra; Cook Biotech, Inc., West Lafayette, IN; exclusively marketed by Smith and Nephew, Inc., Fort Worth, TX). SIS is a three-dimensional biomaterial ~0.3 mm thick consisting of a biocompatible, acellular, collagen-based (predominantly types I, III, and V) extracellular matrix.

Single-layer porcine SIS has been used successfully in the management of many types of cutaneous wounds, including venous/arterial ulcers, pressure ulcers and DFUs.[6–8] SIS has recently been evaluated in a randomised, parallel-group, open-label, multicentre, 16-week study (including a 12-week treatment period).[9] A total of 82 patients, 18 years of age or older, with a diagnosis of type 1 or 2 diabetes mellitus requiring medications to control

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Table 1. Model inputs

Variables	Value	Source
Monthly transition probabilities		
Uninfected ulcer (standard care alone) → healed ulcer	0.100	[9]
Uninfected ulcer (adjunctive SIS) → healed ulcer	0.164	[9]
Uninfected ulcer → infected ulcer	0.048	[10]
Infected ulcer → uninfected ulcer	0.425	[11]
Infected ulcer → gangrene	0.084	[10]
Infected ulcer → amputation → post amputation	0.018	[10,11]
Infected ulcer → amputation → infected ulcer	0.046	[10,11]
Gangrene → amputation → post amputation	0.033	[10,11]
Gangrene → amputation → gangrene	0.196	[10,11]
Healed ulcer (standard care alone) → uninfected ulcer	0.158	[9]
Healed ulcer (adjunctive SIS) → uninfected ulcer	0.158	[9]
Healed ulcer → deceased	0.009	[13]
Uninfected ulcer → deceased	0.009	[13]
Infected ulcer → deceased	0.013	[13]
Gangrene → deceased	0.013	[13]
Post amputation → deceased	0.017	[13]
Management of an uninfected ulcer with standard care alone (per month)		
Number of visits to a physician	4.00	[9]
Proportion of patients receiving debridement	0.77	[9]
Number of occasions of sharp debridement	4.00	[9]
Proportion of patients receiving silver dressing	0.32	[9]
Number of silver dressings	4.00	[9]
Proportion of patients receiving hydrogel	0.24	[9]
Number of hydrogel dressings	4.00	[9]
Proportion of patients receiving wet-to-dry dressing	0.22	[9]
Number of wet-to-dry dressings	4.00	[9]
Proportion of patients receiving alginate dressing	0.10	[9]
Number of alginate dressings	4.00	[9]
Proportion of patients receiving Manuka honey	0.07	[9]
Number of Manuka honey dressings	4.00	[9]
Proportion of patients receiving triple antibiotic dressing	0.05	[9]
Number of triple antibiotic dressings	4.00	[9]
Number of padding/soft roll bandages	4.00	Clinician estimates
Number of gauze bandage rolls	4.00	Clinician estimates
Number of compression bandages	4.00	Clinician estimates
Management of an uninfected ulcer with adjunctive SIS (per month)		
Number of sterile saline applications	4.00	[9]
Number of SIS applications	4.00	[9]
Number of non-adherent dressings	4.00	[9]
Number of foam dressings	4.00	[9]
Number of self-adherent wrap bandages	4.00	[9]
Management of an infected ulcer with standard care alone (per month)		
Proportion of patients with infected ulcers as outpatient	0.73	Clinician estimates
Number of visits to a physician	4.00	Clinician estimates
Proportion of patients receiving debridement	0.77	[9]

blood glucose levels and who had a neuropathic foot ulcer were randomised to receive either SIS in combination with standard care or standard care alone (n=41 per group). All 82 patients were considered evaluable for the intention to treat (ITT) analysis. Patients' wound duration was a mean 21.8 weeks, with a mean area of 2.3 cm^2. There were no significant baseline differences between the two groups. During the study, patients returned weekly for 12 weeks for ulcer assessment/measurement, recording of any adverse events that may have occurred, debridement (for standard care patients only) and application of SIS or the assigned standard care.

The study showed that a significantly greater proportion of ulcers were closed by 12 weeks in the SIS group than in the standard care group (54% versus 32%; p=0.021). There were no significant differences in adverse events between the two groups.

The comparative health-economic impact of SIS and standard care is unknown, and therefore treatment choices are based largely on their clinical value, safety and purchase cost. Hence, the objective of this study was to use data from the patients who participated in the aforementioned trial[9] to estimate the cost-effectiveness of using adjunctive SIS compared with standard care alone in managing DFUs in the US, from the perspective of Medicare.

Methods

Study design

This was a decision-modelling study based on patient-level data obtained from the aforementioned clinical trial,[9] supplemented with information pertaining to patient management obtained from the clinical authors, who are involved in managing diabetic foot ulcers in the US, and published literature.

Literature review

A systematic literature review was performed by searching Embase and PubMed databases for relevant publications on the management of DFUs in the US, published up to July 2015. The search terms focused on diabetic foot ulcer, management, resource use, costs and quality of life. The search was restricted to human subjects and the English language. After applying various related search terms in the databases, 498 abstracts were obtained. Of these, 386 studies were excluded because of duplication or lack of relevance. This generated 112 publications to review in full. During the review process various guidelines and publications on the management of diabetic foot ulcers in the US were identified. A manual literature search was subsequently conducted using citations in the papers.

Management of diabetic foot ulcers with standard wound care and adjunctive SIS

Patients in the clinical trial with uninfected ulcers received an offloading device (Darco shoe) and had a weekly dressing change in an outpatient clinic, irrespective of treatment.[9]

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Patients in the standard care group were treated with one of the following dressings: silver dressing, hydrogel, wet-to-dry dressing, alginate dressing, Manuka honey and triple antibiotic dressing, as shown in Table 1. Between the weekly outpatient clinic visits, patients also had dressing changes at their home every 1–2 days. Furthermore, an estimated 76.7% of patients underwent debridement during each clinic visit.

Patients in the SIS group received a weekly application of SIS during their outpatient clinic visit.

Patients in both treatment groups received a secondary dressing on top of either the primary standard care dressing or SIS. Recurrent ulcers could be treated with the same dressings and bandages that were used to treat their original ulcer.

If a DFU becomes infected or develops gangrene, wound management becomes more intense, and an amputation may become necessary to salvage the foot or limb. Infected ulcers are not eligible for treatment with SIS (since they are contra-indicated). Hence, an infected ulcer would only be treated with standard care dressings and offloading; debridement might also be performed. According to the clinical authors, an estimated 72.5% of patients with an infected ulcer would be treated on an outpatient basis and the other 27.5% would be hospitalised for approximately 10 days. In addition to treatment with standard care, patients with infected ulcers may be prescribed antibiotics and undergo various imaging and diagnostic tests, as well as negative pressure wound therapy. Patients might also be referred to other physicians (for example, to internal medicine, vascular surgery) and an estimated 55% of patients would undergo vascular surgery. Patients who develop gangrene would undergo similar tests and treatments to those with an infected ulcer, but wound care products would not be applied. The majority of patients with gangrene would be hospitalised for approximately two weeks, and an estimated 55% of them would undergo some form of vascular surgery. Complicated ulcers may also require home care or attendance at a nursing facility for treatment, depending on the severity of the ulcer. For some infected ulcers and those with gangrene, an amputation may be required. Such amputations are generally minor and performed below the ankle (for example, toe, ray, metatarsal).

Patients with a healed ulcer and those post-amputation would generally receive monthly follow-up visits and therapeutic shoes in order to prevent further ulceration/recurrence.

Markov model

A Markov model (Fig 1) was constructed to simulate the management of diabetic neuropathic lower extremity ulcers over a period of one year in the US, based on the aforementioned clinical trial.[9] The model structure and health states were based on a comparable model constructed by Persson et al.,[10] which simulated the management of diabetic neuropathic lower-extremity ulcers in Sweden. The model comprises the following six

Table 1. Model inputs continued

Number of sharp debridements	4.00	Clinician estimates
Number of bacterial cultures	1.00	Clinician estimates
Proportion of patients receiving silver dressing	0.32	[9]
Number of silver dressings	4.00	Clinician estimates
Proportion of patients receiving hydrogel	0.24	[9]
Number of hydrogel dressings	4.00	Clinician estimates
Proportion of patients receiving wet-to-dry dressing	0.22	[9]
Number of wet-to-dry dressings	4.00	Clinician estimates
Proportion of patients receiving alginate dressing	0.10	[9]
Number of alginate dressings	4.00	Clinician estimates
Proportion of patients receiving Manuka honey	0.07	[9]
Number of Manuka honey dressings	4.00	Clinician estimates
Proportion of patients receiving triple antibiotic dressing	0.05	[9]
Number of triple antibiotic dressings	4.00	Clinician estimates
Number of padding/soft roll bandages	4.00	Clinician estimates
Number of gauze bandage rolls	4.00	Clinician estimates
Number of compression bandages	4.00	Clinician estimates
Number of courses of antibiotic treatment	1.00	Clinician estimates
Proportion of patients undergoing an X-ray	1.00	Clinician estimates
Number of X-rays	1.00	Clinician estimates
Proportion of patients undergoing an MRI	0.63	Clinician estimates
Number of MRIs	1.00	Clinician estimates
Proportion of patients undergoing NPWT	0.05	Clinician estimates
Number of occasions of NPWT	5.00	Clinician estimates
Proportion of patients undergoing a consultation with another specialist	0.80	Clinician estimates
Number of consultations with another specialist	2.00	Clinician estimates
Proportion of patients with infected ulcers managed as inpatients inclusive of tests and standard care dressings	0.28	Clinician estimates
Proportion of inpatients undergoing NPWT	0.35	Clinician estimates
Number of occasions of NPWT for inpatients	5.00	Clinician estimates
Proportion of inpatients undergoing vascular surgery	0.55	Clinician estimates
Number of vascular surgical procedures	1.00	Clinician estimates
Length of hospital stay (days)	10.00	Clinician estimates
Management of gangrene (per episode)		
Proportion of inpatients undergoing vascular surgery	0.55	Clinician estimates
Number of vascular surgical procedures	1.00	Clinician estimates
Proportion of patients undergoing NPWT	0.15	Clinician estimates
Number of occasions of NPWT	5.00	Clinician estimates
Length of hospital stay (days)	14.00	Clinician estimates
Management of a healed ulcer		
Therapeutic shoe	1.00	Clinician estimates
Number of visits to a specialist	1.00	Clinician estimates
Amputation (per procedure)		
Proportion of patients undergoing NPWT	0.30	Clinician estimates
Number of occasions of NPWT	5.00	Clinician estimates
Number of amputation procedures	1.00	Clinician estimates
Length of hospital stay (days)	12.00	Clinician estimates

NPWT–negative pressure wound therapy; MRI–magnetic resonance imaging

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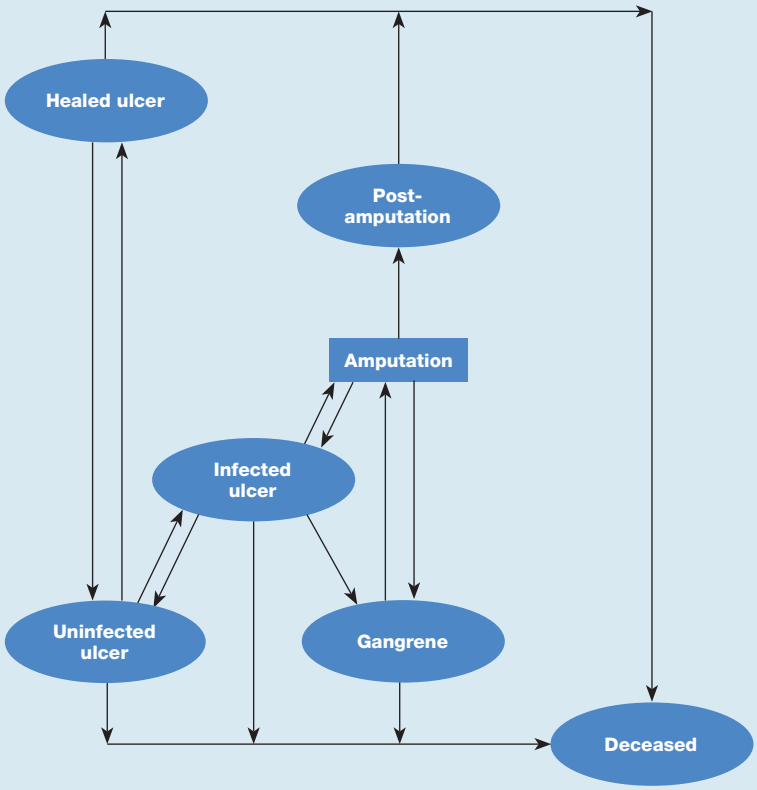
Fig 1. Depiction of the Markov model for diabetic foot ulcers



health states: uninfected ulcer, infected ulcer, gangrene, healed ulcer, post amputation and deceased. Patients enter the model at the onset of an uninfected ulcer. Patients either remain in this health state or move to one of the other health states. Patients transition in the model every month, (i.e every 4 weeks).

The clinical trial[9] only studied the effect of treatments on uninfected ulcers over a follow-up period of 12 weeks. However, the aim of this study was to model DFU management over a time horizon of 12 months, to allow sufficient time to simulate wound closure and development of complications. Hence, the patient pathways were modelled beyond the trial in order to estimate the cost-effectiveness of adjunctive SIS compared with standard care alone over a complete patient pathway encompassing 12 months after the start of treatment. To achieve this, the uninfected ulcer health states were populated with data pertaining to management and resource use obtained from the trial (Table 1)[9] and the clinical authors' management practice. The other health states were populated with information obtained from published studies and the clinical authors' management practice (Table 1). It was assumed that an infected ulcer would be treated with the same range of standard care products, debridement and offloading that were used in the trial. Additionally, according to the clinical authors, patients with gangrene would generally be hospitalised for treatment. Therefore, the model assumes that all patients with gangrene are hospitalised.

Table 2. Reimbursement values in the model

Resource	Reimbursement value	Source
Total cost of a visit to a physician when receiving standard care	$148.02	[14]
Total cost of selective debridement in the hospital outpatient department	$249.18	[14]
Total cost of an application of SIS by a physician in the hospital outpatient department	$527.13	[14]
Bacterial culture	$13.14	[14]
Antibiotics (per course of treatment)	$302.99	[14]
Total cost of inpatient care for an infected ulcer	$8,230.60	[14]
Total cost of inpatient care for gangrene	$7,954.80	[14]
Inpatient accommodation per day excluding initial day and discharge day	$116.17	[14]
Inpatient accommodation for the initial day	$158.98	[14]
Inpatient accommodation on the discharge day	$73.04	[14]
X-ray of toe, foot or heel	$76.46	[14]
Magnetic resonance imaging (MRI) scan of leg	$668.43	[14]
Magnetic resonance angiography (MRA) scan of leg blood vessels	$1,196.41	[14]
Computerised tomography (CT) scan of lower leg blood vessels	$1,026.77	[14]
Doppler ultrasound	$127.03	[14]
Bone biopsy	$223.80	[14]
Vascular surgery	$527.06	[14]
Total cost of negative pressure wound therapy for an outpatient	$276.07	[15]
Total cost of negative pressure wound therapy for an inpatient	$262.24	[15]
Hyperbaric oxygen therapy per day	$448.28	[14]
Total cost of an amputation below the ankle	$16,608.46	[14]
Total cost of a visit to a different physician	$148.02	[14]
Total cost of a follow-up visit within 90 days of the initial visit	$96.22	[14]

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Table 3. Expected outcomes at 12 months after the start of adjunctive SIS or standard care alone

Treatment	Number of ulcer-free months (over 12 months)	Probability of having a healed ulcer (at 12 months)	Probability of avoiding a complicated ulcer (at 12 months)	Probability of avoiding an amputation (over 12 months)
Standard care alone	3.11	0.31	0.79	0.91
Adjunctive SIS	4.43	0.41	0.81	0.92
Percentage improvement in effectiveness with adjunctive SIS	42.44%	32.26%	2.53%	1.10%

Table 4. Expected levels of health-care resource use over 12 months after the start of adjunctive SIS or standard care alone

	Amount of resource use per patient over 12 months after starting treatment with:		
Resource	Standard care alone	Adjunctive SIS	Percentage reduction in resource use with adjunctive SIS
Outpatient visits	11.11	9.80	12%
SIS applications	0.00	5.73	
Diagnostic tests	1.24	1.07	14%
Antibiotic prescriptions	0.47	0.41	13%
Debridement procedures	23.47	15.24	35%
Negative pressure wound therapy applications	0.77	0.67	13%
Hospital admissions	0.45	0.40	11%
Vascular surgical procedures	0.25	0.22	12%
Amputations	0.09	0.08	11%

Table 5. Expected costs (at 2016 prices) of health-care resource use over 12 months after the start of adjunctive SIS or standard care alone

	Standard care alone		Adjunctive SIS	
Resource	Cost per patient	Percentage of total cost	Cost per patient	Percentage of total cost
Outpatient visits	$1,478.08	11%	$1,217.48	9%
SIS applications	$0.00	0%	$3,019.84	22%
Diagnostic tests	$239.33	2%	$205.99	1%
Antibiotic prescriptions	$142.92	1%	$123.01	1%
Debridement procedures	$5,847.81	42%	$3,798.07	27%
Negative pressure wound therapy applications	$203.83	1%	$177.66	1%
Hospital admissions	$4,420.02	32%	$3,879.37	28%
Vascular surgical procedures	$130.95	1%	$114.90	1%
Amputations	$1,499.30	11%	$1,321.30	10%
TOTAL	$13,962.23	100%	$13,857.61	100%

The monthly transition probabilities that were used to populate the model were estimated from the trial[9] and published US-based studies (Table 1).[11–14]

In the model, amputation is viewed as a procedure, and not a separate health state, that could be performed in both the infected ulcer or gangrene health states. The model was censored at 12 months. Hence, long-term post-amputation care (home care or care at a nursing facility) was not included within the resources associated with amputation.

The measures of effectiveness in the model were: number of ulcer-free months, probability of having a healed ulcer at 12 months, probability of avoiding a complicated ulcer at 12 months and probability of avoiding an amputation over 12 months.

Reimbursement rates

The analysis was performed from the perspective of Medicare. Hence, only resources that are reimbursed by Medicare were quantified and valued in monetary terms. Where possible, the 'maximum Medicare-allowed amount' was used for a given resource. However, when it was not available the 'average supplier Medicare-allowed amount' was used.

All reimbursement rates are in US dollars at 2016 prices.[15,16] If reimbursement rates were only available for previous years, they were uprated to 2016 prices using the US Consumer Price Index.[17] The reimbursement rates (Table 2) were assigned to the estimates of health-care resource use in the model in order to estimate the reimbursable Medicare cost of

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managing a DFU over 12 months from the start of treatment with adjunctive SIS and standard care alone. A discount rate was not applied, as the model only considered a one-year time horizon.

Cost-effectiveness analyses

The model was used to estimate the cost-effectiveness of initially using adjunctive SIS compared with standard care alone to treat a DFU from the perspective of Medicare. This was calculated as the difference between the expected costs of the two treatment strategies divided by the difference between the expected effectiveness of the two strategies. Hence, the relative cost-effectiveness of adjunctive SIS was calculated as each of the following:

- The incremental cost for each additional ulcer-free month
- The incremental cost for each additional healed ulcer at 12 months
- The incremental cost for each avoided complicated ulcer at 12 months
- The incremental cost for each avoided amputation at 12 months.

If one of the treatment strategies was clinically more effective for a lower cost, it was considered to be the dominant (cost-effective) strategy.

Sensitivity analyses

Probabilistic sensitivity analyses were 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. A beta distribution was used for probabilities and a gamma distribution for resource use and costs, enabling the distribution of costs and effectiveness measures to be estimated. Using the outputs from these analyses, the probability of being cost-effective at different willingness-to-pay thresholds was estimated.

To assess whether any variable had a major impact on the cost-effectiveness results, one-way sensitivity analyses were performed on all model inputs. Base case values were decreased and increased by 25%. Various scenarios were also assessed to estimate the effect of increasing or decreasing the values of specific variables (for example, use of daily hyperbaric oxygen therapy among inpatients and number of months a patient receives reimbursable SIS).

Results

Health outcomes

At 12 months after the start of treatment, the use of adjunctive SIS instead of standard care alone is expected to lead to a:

- 42% increase in the number of ulcer-free months (from 3.11±0.7 to 4.43±0.34 per patient)

Fig 2. Scatterplot of the incremental cost for each additional ulcer-free month by 12 months with adjunctive SIS compared with standard care alone; n=10,000 iterations of the model (**a**). Scatterplot of the incremental cost for each additional ulcer healed by 12 months with adjunctive SIS compared with standard care alone; n=10,000 iterations of the model (**b**). Scatterplot of the incremental cost for each avoided complicated ulcer by 12 months with adjunctive SIS compared with standard care alone; n=10,000 iterations of the model (**c**). Scatterplot of the incremental cost for each avoided amputation by 12 months with adjunctive SIS compared with standard care alone; n=10,000 iterations of the model (**d**)

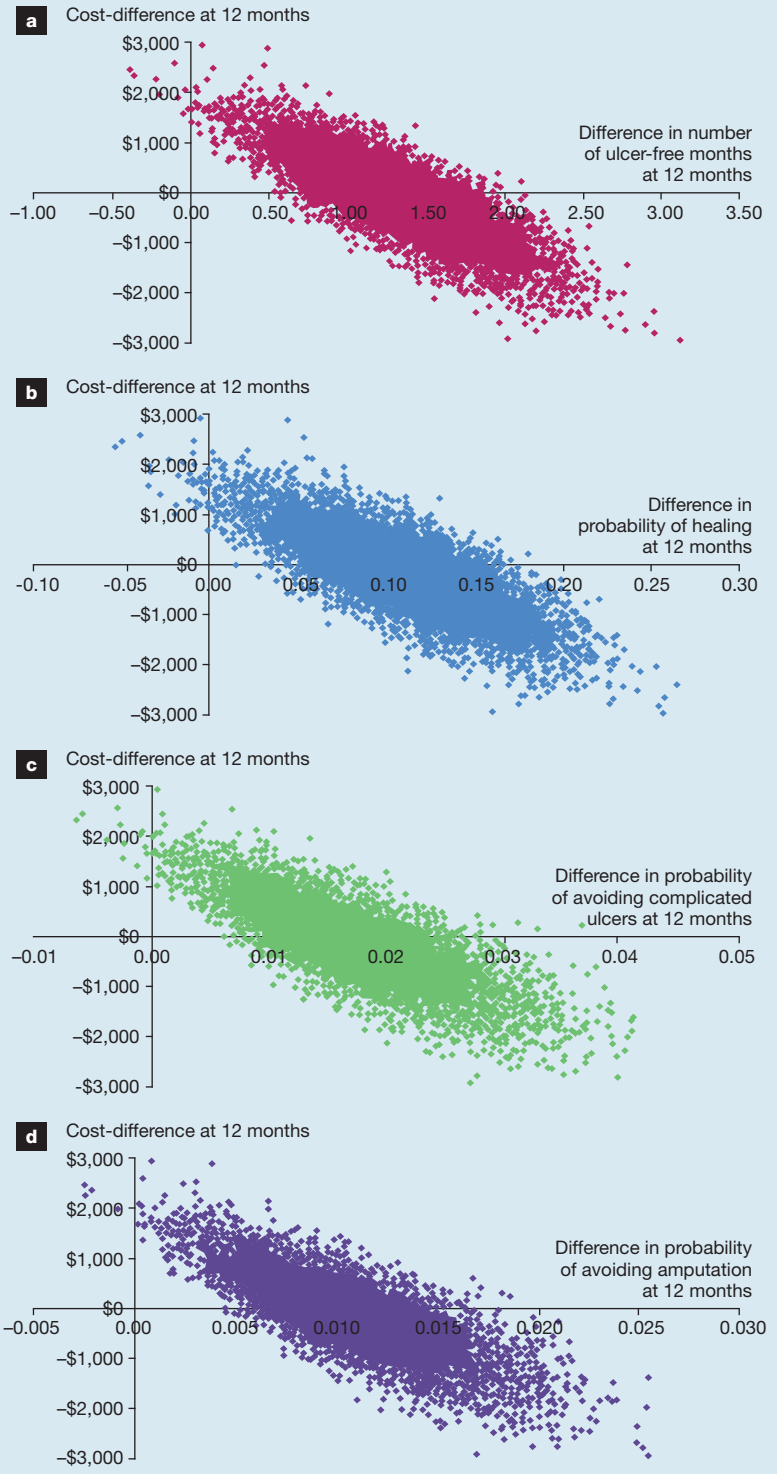

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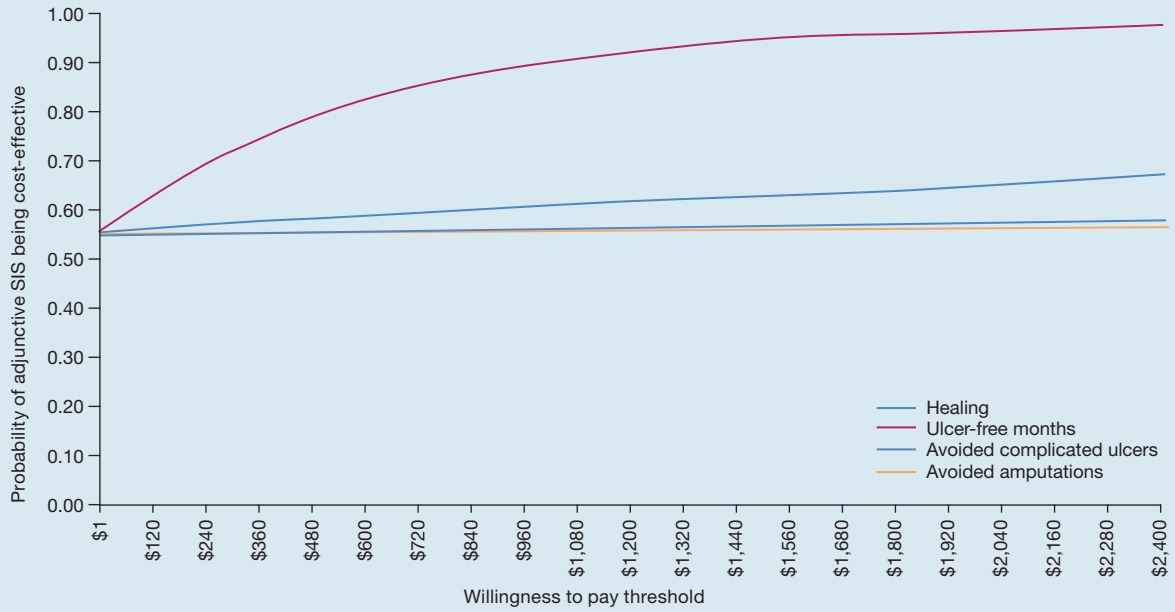
Fig 3. Cost-effectiveness acceptability curves



- 32% increase in the probability of healing (from 0.31±0.03 to 0.41±0.03)
- 3% increase in the probability of avoiding a complicated ulcer (from 0.79±0.01 to 0.81±0.01)
- 1% increase in the probability of avoiding an amputation (from 0.91±0.01 to 0.92±0.01).

Hence, initial treatment of a DFU with adjunctive SIS affords a clinically more effective strategy than starting with standard care alone (Table 3).

Health-care resource use and corresponding costs

Use of health-care resources is expected to be reduced by 11–14% among patients who are initially managed with adjunctive SIS compared with those initially managed with standard care alone, with the exception of debridement, which is expected to be reduced by 35% (Table 4). Hence, the total health-care cost of starting treatment with adjunctive SIS instead of standard care alone was estimated to reduce payer costs by $105 per patient (from $13,962±1041 to $13,858±984) over 12 months following the start of treatment (Table 5). Inpatient care and the use of debridement were the primary and secondary care cost drivers respectively in the SIS group, whereas this was reversed in the standard care group (Table 5). Amputations were found to account for 10–11% of the expected 12-month cost per patient and outpatient visits for a further 9–11%. SIS accounted for 22% of the cost of patient management in that group. The cost of outpatient visits was inclusive of the cost of standard care products.

Cost-effectiveness analyses

Use of adjunctive SIS instead of standard care alone resulted in superior clinical outcomes for less cost. Hence, initial treatment with adjunctive SIS was found to be a dominant strategy when compared with starting treatment with standard care alone. The incremental cost-reduction of using adjunctive SIS compared with standard care alone was estimated to be:

- –$79.38 for each additional ulcer-free month
- –$968.28 for each additional healed ulcer
- –$6,148.34 for each avoided complicated ulcer
- –$9,761.89 for each avoided amputation.

Sensitivity analyses

Probabilistic sensitivity analyses were performed to estimate the distribution of expected cost differences between the alternative treatment strategies over 12 months from starting treatment and expected differences in outcomes at 12 months (Fig 2). Using these distributions, it was estimated that the probability of adjunctive SIS being cost-effective compared with standard care alone (Fig 3) up to a willingness-to-pay threshold of $2,500 (that is, one month's treatment with SIS) was:

- 0.98 when the measure of effectiveness was ulcer-free months
- 0.67 when the measure of effectiveness was additional healed ulcers
- 0.58 when the measure of effectiveness was avoided complicated ulcers
- 0.57 when the measure of effectiveness was avoided amputations.

Deterministic sensitivity analyses (Table 6) demonstrated that the results were very sensitive to a 25% decrease and increase in the following model inputs, since the incremental cost-effectiveness of using adjunctive SIS compared with standard care alone varied by up to 700%:

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Table 6. Deterministic sensitivity analyses

		Range in the incremental cost of using adjunctive SIS compared with standard care alone for each:			
Transition probability (TP) or resource use decreased and increased by 25% unless otherwise stated	**Base case value**	**Additional ulcer–free month**	**Additional healed ulcer at 12 months**	**Avoided complicated ulcer at 12 months**	**Avoided amputation over 12 months**
TP: Uninfected ulcer→ healed ulcer for standard care alone and adjunctive SIS	See Table 1	$234 → –$276	$2,679 → –$3,555	$17,685 → –$21,847	$29,715 → –$32,966
TP: Uninfected ulcer → infected ulcer	0.048	$68 → –$214	$832 → –$2,614	$6,881 → –$13,749	$11,055 → –$21,592
TP: Infected ulcer → uninfected ulcer	0.425	–$163 → –$13	–$2,001 → –$160	–$10,622 → –$1,186	–$17,445 → –$1,838
TP: Infected ulcer → gangrene	0.084	–$26 → –$130	–$317 → –$1,588	–$2,144 → –$9,536	–$3,585 → –$14,511
TP: Infected ulcer → amputation → post amputation	0.018	–$80 → –$79	–$975 → –$962	–$6,277 → –$6,036	–$10,122 → –$9,460
TP: Infected ulcer → amputation → Infected ulcer	0.046	–$66 → –$92	–$805 → –$1,126	–$5,113 → –$7,152	–$8,915 → –$10,450
TP: Gangrene → amputation → post amputation	0.033	–$83 → –$76	–$1,011 → –$926	–$6,419 → –$5,877	–$10,276 → –$9,257
TP: Gangrene → amputation → gangrene	0.196	–$63 → –$96	–$763 → –$1,175	–$4,847 → –$7,462	–$8,670 → –$10,641
TP: Healed ulcer (standard care alone) → uninfected ulcer	0.158	$309 → –$284	$5,136 → –$3,102	$26,035 → –$21,222	$34,183 → –$36,917
TP: Healed ulcer (adjunctive SIS) → uninfected ulcer	0.158	–$370 → $378	–$3,903 → $5,810	–$27,256 → $31,513	–$48,871 → $42,391
TP: Healed ulcer → deceased	0.009	–$75 → –$84	–$913 → –$1,032	–$5,225 → –$7,498	–$9,350 → –$10,222
TP: Uninfected ulcer → deceased	0.009	–$92 → –$65	–$1,124 → –$793	–$7,990 → –$4,497	–$11,316 → –$8,004
TP: Infected ulcer → deceased	0.013	–$83 → –$76	–$1,012 → –$923	–$6,482 → –$5,811	–$10,170 → –$9,339
TP: Gangrene → deceased	0.013	–$82 → –$77	–$996 → –$940	–$6,326 → –$5,966	–$10,009 → –$9,507
TP: Post amputation → deceased	0.017	–$80 → –$79	–$973 → –$963	–$6,180 → –$6,117	–$9,786 → –$9,738
Number of visits to a physician in the first month by patients with an uninfected ulcer	4.00	–$247 → $88	–$3,010 → $1,073	–$19,113 → $6,816	–$30,346 → $10,823
Proportion of patients with an uninfected ulcer who receive debridement in the first month	0.77	–$30 → –$129	–$364 → –$1,572	–$2,312 → –$9,985	–$3,670 → –$15,853
Number of visits to a physician in subsequent months by patients with an uninfected ulcer	4.00	–$37 → –$122	–$450 → –$1,487	–$2,858 → –$9,439	–$4,537 → –$14,987
Proportion of patients with an uninfected ulcer who receive debridement in subsequent months	0.77	$25 → –$184	$305 → –$2,241	$1,934 → –$14,230	$3,070 → –$22,594
Proportion of patients with an infected ulcer treated as an outpatient	0.73	–$54 → –$105	–$662 → –$1,275	–$4,202 → –$8,094	–$6,672 → –$12,851
Number of outpatient visits to a physician by patients with an infected ulcer	4.00	–$68 → –$91	–$831 → –$1,105	–$5,277 → –$7,019	–$8,379 → –$11,145
Proportion of outpatients with an infected ulcer who receive debridement	0.77	–$76 → –$83	–$921 → –$1,015	–$5,849 → –$6,448	–$9,287 → –$10,237
Proportion of outpatients with an infected ulcer who receive negative pressure wound therapy	0.05	–$79 → –$80	–$958 → –$979	–$6,084 → –$6,218	–$9,660 → –$9,872
Number of occasions patients with an infected ulcer receive negative pressure wound therapy	5.00	–$79 → –$81	–$960 → –$985	–$6,095 → –$6,255	–$9,677 → –$9,931
Proportion of patients with an infected ulcer who are treated by another specialist	0.80	–$76 → –$82	–$932 → –$1,004	–$5,920 → –$6,377	–$9,399 → –$10,125
Number of outpatient visits to another specialist by patients with an infected ulcer	2.00	–$73 → –$85	–$896 → –$1,040	–$5,691 → –$6,606	–$9,036 → –$10,488
Proportion of inpatients with an infected ulcer who receive negative pressure wound therapy	0.35	–$77 → –$82	–$942 → –$995	–$5,981 → –$6,317	–$9,497 → –$10,030
Number of occasions patients with an infected ulcer receive negative pressure wound therapy	5.00	–$78 → –$83	–$947 → –$1,011	–$6,014 → –$6,417	–$9,548 → –$10,189
Proportion of inpatients with an infected ulcer who undergo vascular surgery	0.55	–$78 → –$81	–$952 → –$985	–$6,043 → –$6,255	–$9,594 → –$9,931
Number of occasions patients with an infected ulcer undergo vascular surgery	1.00	–$74 → –$85	–$901 → –$1,035	–$5,724 → –$6,573	–$9,088 → –$10,436
Proportion of inpatients with an infected ulcer who undergo daily hyperbaric oxygen therapy changes to 0.15 and 0.20	0.00	–$92 → –$96	–$1,123 → –$1,175	–$7,133 → –$7,462	–$11,326 → –$11,847
Proportion of inpatients with gangrene who undergo vascular surgery	0.55	–$78 → –$81	–$948 → –$989	–$6,019 → –$6,278	–$9,557 → –$9,968

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Table 6. Deterministic sensitivity analyses continued

Number of occasions patients with gangrene undergo vascular surgery	1.00	–$73 → –$86	–$887 → –$1,050	–$5,630 → –$6,667	–$8,939 → –$10,585
Proportion of inpatients with gangrene who receive negative pressure wound therapy	0.15	–$78 → –$81	–$955 → –$982	–$6,062 → –$6,237	–$9,624 → –$9,903
Number of occasions patients with gangrene receive negative pressure wound therapy	5.00	–$78 → –$81	–$957 → –$990	–$6,078 → –$6,289	–$9,650 → –$9,985
Proportion of inpatients with gangrene who receive daily hyperbaric oxygen therapy changes to 0.15 and 0.20	0.00	–$101 → –$108	–$1,233 → –$1,322	–$7,832 → –$8,394	–$12,435 → –$13,327
Number of visits to another specialist by patients with gangrene	1.00	–$79 → –$80	–$960 → –$977	–$6,094 → –$6,203	–$9,675 → –$9,848
Proportion of inpatients who undergo an amputation and receive negative pressure wound therapy	0.30	–$79 → –$80	–$959 → –$978	–$6,086 → –$6,210	–$9,664 → –$9,860
Number of occasions patients who undergo an amputation receive negative pressure wound therapy	5.00	–$79 → –$81	–$960 → –$984	–$6,099 → –$6,247	–$9,683 → –$9,919
Number of amputation procedures	1.00	$56 → –$214	$679 → –$2,616	$4,312 → –$16,609	$6,847 → –$26,370
Proportion of inpatients who undergo an amputation and receive hyperbaric oxygen therapy changes to 0.20 and 0.30	0.00	–$88 → –$93	–$1,075 → –$1,128	–$6,826 → –$7,165	–$10,838 → –$11,376
All the unit costs are decreased and increased by 25%		–$60 → –$99	–$726 → –$1,210	–$4,611 → –$7,685	–$7,321 → –$12,202
Frequency of SIS use ranges from 4 applications in 1 month to 12 applications over 3 months	8.00	$448 → –$677	$5,461 → –$8,261	$34,678 → –$52,454	$55,059 → –$83,282

- Probability of an uninfected ulcer becoming healed
- Probability of an uninfected ulcer becoming infected
- Probability of an infected ulcer becoming uninfected
- Probability of an infected ulcer developing gangrene
- Probability of a healed ulcer recurring
- Number of visits to a physician
- Probability of standard care-treated patients undergoing debridement
- Probability of patients with an infected ulcer being treated as outpatient rather than an inpatient
- Proportion of patients with gangrene undergoing daily hyperbaric oxygen therapy
- Number of amputation procedures
- Number of months a patient receives reimbursable SIS.

However, the results were relatively insensitive to changes in the other model inputs when they were decreased and increased by 25% (as shown in Table 6), since the relative cost-effectiveness of the alternative strategies varied by less than 25%.

Discussion

This retrospective modelling study estimated the cost-effectiveness of adjunctive SIS compared with standard care alone in the management of neuropathic foot ulcers among adult patients, at least 18 years of age, with a diagnosis of type 1 or 2 diabetes mellitus requiring medications to control blood glucose levels. The model was based on data obtained from the ITT cohort of patients who participated in a randomised, controlled study,[9] published studies and the experiences of the clinical authors. The structure of the Markov model, which was based on a comparable model for Sweden,[10] modelled the ITT cohort in the trial[9] beyond the 12-weeks follow-up period for a total time horizon of 12 months. The Swedish model structure[10] was chosen for our analysis as it appeared to be a true reflection of the main health states that a cohort of patients with a neuropathic diabetic foot ulcer can go through and it studied a patient population comparable to that in the clinical trial.[9]

The aforementioned trial[9] was the only randomised controlled study comparing adjunctive SIS with standard care alone in the management of DFUs at the time of performing this analysis. The advantage of using this data set for the economic model is that the efficacy and safety of the two treatments were measured under controlled conditions. Moreover, there were no differences in baseline parameters or ulcer characteristics between the two groups. However, the study was not blinded, patients were only followed-up for 12 weeks after the start of treatment and not all resource use was documented.[9] Hence, the model may not necessarily reflect clinical outcomes associated with managing a cohort of patients over 12 months in clinical practice. The model was informed with assumptions about treatment patterns from the clinical authors, who are based at different centres in three different towns/cities across the US; therefore the levels of healthcare resource use incorporated into the model may not be representative of the whole of the US. The inherent variability and uncertainty within the model was addressed to some extent by our extensive sensitivity analyses. Notwithstanding this, the findings from this study need to be confirmed in a randomised controlled study in which clinical outcomes and resource use are recorded over a 12-months follow-up period.

The analysis estimated the cost-effectiveness of managing a DFU up to 12 months and does not consider the potential impact of managing an unhealed wound beyond that period. Neither does the model consider home care and management at a nursing facility after

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discharge from a hospital, nor long-term rehabilitation following gangrene or an amputation. Accordingly, the model used resource estimates for the 'average patient' and does not consider the impact of other factors that may affect the results, such as comorbidities, underlying disease severity and pathology of the underlying disease. The model only analysed direct health-care costs borne by Medicare and excluded direct costs incurred by patients and indirect costs incurred by society as a result of employed patients taking time off work. Also excluded are changes in patients' health-related quality of life and improvements in general wellbeing, as well as their preferences. Consequently, this study may have underestimated the relative cost-effectiveness of adjunctive SIS.

Despite these limitations, the model showed that initial treatment with adjunctive SIS instead of standard care alone is a clinically more effective strategy and less costly from Medicare's perspective. Moreover, the model showed that the acquisition cost of SIS would be offset by its potential to increase, first, the number of ulcer-free months by 42%, second, the probability of healing by 32%, and third, the probability of not developing an ulcer complication by 3% over a 12-month time-horizon.

DFUs are complex wounds often requiring substantial time to heal. Moreover, they are associated with increased risk for infections, recurrence, hospitalisation and amputations, which can be costly.[18] Indeed, the estimated total annual treatment costs for DFUs in the US was estimated to be less than $1 billion in 2007.[19] This expenditure can be affected by a combination of poor control of diabetes, resources required for compliance with standard care (for example, offloading and infection control), complexity of some treatment regimens, high recurrence and amputation rates and post-amputation morbidity and mortality.[20] Accordingly, cost-effective management and healing of DFUs remain challenging problems. This is reflected in the financial burden that DFUs impose on Medicare and private insurers.[21] In the 12 months following the onset of a DFU, 3.8% of Medicare-covered patients and 5.0% of privately insured patients received a lower limb amputation. Additionally, increased use of health-care resources resulted in an incremental cost of $11,710 and $16,883 per patient to Medicare and a private insurer respectively, when compared with matched non-DFU controls.[21]

Despite these statistics, there have only been a limited number of economic analyses comparing alternative treatments with standard care for the management of DFUs in the US.[22–28] The findings from these analyses pertaining to standard care are concordant with the findings of the present study, which showed that use of adjunctive SIS instead of standard care alone has the potential to improve outcomes for patients and reduce the burden imposed by DFUs to third-party payers. Nevertheless, generalising the findings from this study to other health-care systems would be challenging, since resource use and the manner in which resources are reimbursed by Medicare in the US would undoubtedly be different from that in other countries. However, the model structure should be generalisable, and the clinical effectiveness of adjunctive SIS and standard care alone would be expected to be similar in comparable cohorts of patients in other countries.

In conclusion, within the study's limitations, using adjunctive SIS instead of standard care alone improves outcome for less cost and thereby affords a cost-effective use of Medicare-funded resources in the management of neuropathic foot ulcers among adults patients with type 1 or 2 diabetes mellitus in the US. **JWC**

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