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ORIGINAL ARTICLE

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Potential cost-effectiveness of using adjunctive dehydrated human amnion/chorion membrane allograft in the management of non-healing diabetic foot ulcers in the United Kingdom

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Abstract

The aim of this study was to estimate the cost-effectiveness of using dehydrated human amnion/chorion membrane (dHACM) allografts (Epifix) as an adjunct to standard care, compared with standard care alone, to manage non-healing diabetic foot ulcers (DFUs) in secondary care in the United Kingdom, from the perspective of the National Health Service (NHS). A Markov model was constructed to simulate the management of diabetic lower extremity ulcers over a period of 1 year. The model was used to estimate the cost-effectiveness of using adjunctive dHACM, compared with standard care alone, to treat non-healing DFUs in the United Kingdom, in terms of the incremental cost per quality-adjusted life year (QALY) gained at 2019/2020 prices. The study estimated that at 12 months after the start of treatment, use of adjunctive dHACM instead of standard care alone is expected to lead to a 90% increase in the probability of healing, a 34% reduction in the probability of wound infection, a 57% reduction in the probability of wound recurrence, a 6% increase in the probability of avoiding an amputation, and 8% improvement in the number of QALYs. Additionally, if £4062 is spent on dHACM allografts per ulcer, then adjunctive use of dHACM instead of standard care alone is expected to lead to an incremental cost per QALY gain of £20 000. However, if the amount spent on dHACM allografts was ≤£3250 per ulcer, the 12-month cost of managing an ulcer treated with adjunctive dHACM would break-even with that of DFUs treated with standard care, and it would have a 0.95 probability of being cost-effective at the £20 000 per QALY threshold. In conclusion, within the study's limitations, and within a certain price range, adjunctive dHACM allografts afford the NHS a

cost-effective intervention for the treatment of non-healing DFUs within secondary care among adult patients with type 1 or 2 diabetes mellitus in the United Kingdom.

KEYWORDS

cost-effectiveness, dehydrated human amnion/chorion membrane (dHACM) allograft, diabetic foot ulcer, Epifix, United Kingdom

1 | INTRODUCTION

Diabetic foot ulcers (DFUs) are a frequent and serious complication of diabetes mellitus with up to 34% of people with diabetes possibly developing lower extremity ulcers over their lifetime.[1,2] DFUs are often difficult to heal and may become chronic, substantially increasing the risk of becoming infected leading to hospital admissions and a possible lower limb amputation.[3,4] Indeed, an estimated 12% of patients with a DFU will ultimately require a lower extremity amputation.[1,2] Moreover, the 5-year mortality for people with diabetic foot complications is comparable to that of cancer.[5]

Patients with a DFU should be managed holistically by a multidisciplinary care team.[6] 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 (HRQoL) 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.[7] However, many DFUs can take many months to heal.[4] Guidelines suggest that advanced wound therapies should be incorporated into the treatment plan if a DFU does not reduce in size by at least 40% after 4 weeks of standard care.[8]

Advanced therapies for DFUs include collagen, biological dressings and skin equivalents, platelet-derived growth factors, platelet-rich plasma, silver products, negative pressure wound therapy, and hyperbaric oxygen therapy.[2] However, there is little consensus as to which advanced therapy provides the greatest benefit in rates of complete healing and time to wound closure.[2]

One such advanced therapy with supportive evidence for efficacy and safety in the treatment of DFUs is dehydrated human amnion/chorion membrane (dHACM) allografts (Epifix) when used adjunctively to standard care and offloading.[9-12] One of these studies was a multicentre, randomised controlled trial (RCT) conducted at 14 wound care centres across the United States.[12] Adult patients with a mean age of 57.2 years, of whom 73% were male, who had a diagnosis of type 1 or 2 diabetes mellitus and a foot ulcer of at least 4-week duration were entered into a 2-week run-in phase and treated with alginate wound dressings and appropriate offloading. Those with ≤25% wound closure after the run-in period were randomly assigned to receive a weekly application of dHACM

Key Messages

- Markov modelling estimated the cost-effectiveness of using dehydrated human amnion/chorion membrane (dHACM) allografts as an adjunct to standard care, compared with standard care alone, to manage non-healing diabetic foot ulcers (DFUs) in secondary care in the United Kingdom, from the perspective of the National Health Service (NHS)
- treating a non-healing DFU with adjunctive dHACM allografts affords a clinically more effective strategy than standard care alone because it is expected to lead to a 90% increase in the probability of healing and 8% improvement in the number of quality-adjusted life years (QALYs) at 12 months after the start of treatment
- if £4062 is spent on dHACM allografts per ulcer, then adjunctive use of dHACM instead of standard care alone is expected to lead to an incremental cost per QALY gain of £20 000
- use of adjunctive dHACM allografts by a multidisciplinary team in secondary care who are managing non-healing DFUs would lead to a reduction in resource use for no additional cost if the amount spent on the allografts was ≤£3250 per ulcer
- adjunctive dHACM allografts can potentially afford the NHS a cost-effective intervention for the treatment of non-healing DFUs within secondary care among adult patients with type 1 or 2 diabetes mellitus in the United Kingdom and free-up hospital resources for alternative use

allograft in addition to standard care (n = 54) or standard care alone (n = 56) for 12 weeks. Standard care comprised a weekly alginate dressing (optional in the adjunctive dHACM group), a foam secondary dressing, rolled gauze, as well as an offloading device where indicated. During the RCT, patients could receive one of eight different sizes of dHACM allograft, depending on the size of their wound. Over the course of the RCT, patients in the modified intention-to-treat (ITT) cohort received a mean of 7.24 dHACM allografts. At baseline, patients' wound size was a mean of 3.6 cm^2 per DFU, and wound duration was a mean of 21.1 weeks per DFU. The study found that significantly more ulcers in the adjunctive dHACM group healed by 12 weeks compared with those in the standard care group (70% versus 50% in the modified ITT cohort: $P = .0338$). At 16 weeks, 70% of ulcers in the adjunctive dHACM group and 46% in the standard care group were actually healed because 10% and 27% of ulcers in each group, respectively, had recurred. Additionally, 28% and 34% of ulcers in the adjunctive dHACM group and standard care group, respectively, developed a putative infection over the period of the RCT. A total of 84% of infected ulcers in the adjunctive dHACM group were resolved after a mean of 2 weeks compared with 79% of infected ulcers in the standard care group, which resolved after a mean of 4 weeks.[12]

The comparative health economic impact of adjunctive dHACM and standard care is unknown, and therefore, treatment choices are based largely on their perceived clinical value, safety, and purchase cost. Hence, the objective of this study was to use the aforementioned RCT[12] to estimate the cost-effectiveness of using adjunctive dHACM (Epifix) compared with standard care alone in managing DFUs in secondary care in the United Kingdom, from the perspective of the public-funded National Health Service (NHS).

2 | METHODS

2.1 | Study design

This was a decision-modelling study based on the aforementioned RCT,[12] supplemented with information pertaining to patient management obtained from the published literature.

2.2 | Markov model

A Markov model (Figure 1) was constructed to simulate the management of non-healing DFUs over a period of 1 year in the United Kingdom, based on the aforementioned study.[12] The model comprised the following seven health states: unchanged (if the ulcer size remained unchanged), worsened (if the ulcer size increased), improved (if the ulcer size decreased), healed (if the ulcer healed), infected (if the ulcer became infected), post-amputation (rehabilitation following an amputation), and recurrence (if the ulcer recurred). Amputation was considered to be a procedure rather than a health state.

Patients enter the model with an uninfected ulcer and receive treatment with either adjunctive dHACM or standard care. Patients then transition to one of three health states (ie, unchanged ulcer, worsened ulcer, or improved ulcer). They can then remain in their current health state or move to one of the other states or undergo an amputation. Patients' transition in the model at monthly intervals was up to 12 months. The model's health states were mutually exclusive and so each patient represented in the model can be in only one of these states at any given time during the time horizon of the model.

The RCT only studied the effect of adjunctive dHACM or standard care over a follow-up period of 16 weeks. Hence, the patient pathways were modelled beyond the

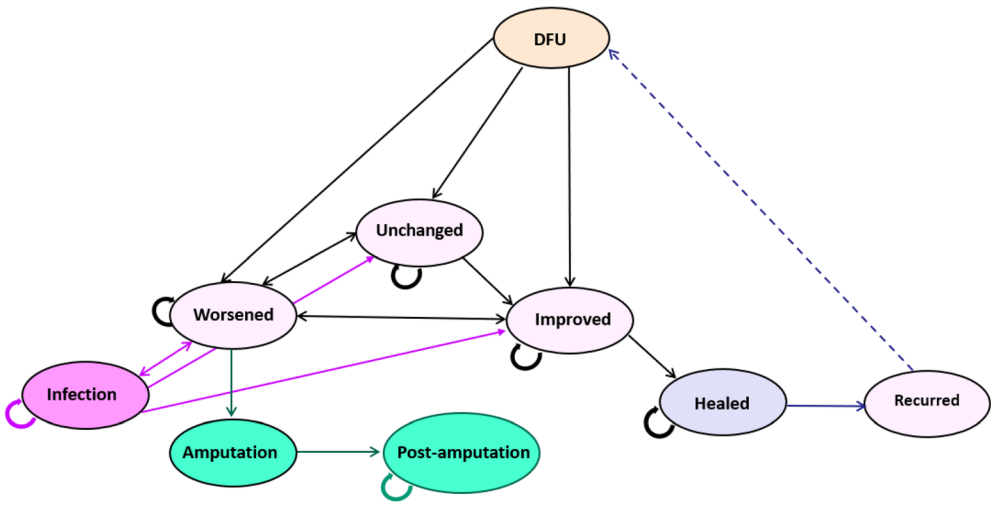

FIGURE 1 Markov model

trial in order to estimate the cost-effectiveness of adjunctive dHACM compared with standard care alone over a complete patient pathway encompassing 12 months after the start of treatment. To achieve this, time series forecasting was used to interpolate a patient's wound size at 13, 14, and 15 weeks after the start of treatment and to project a patient's wound size from 16 weeks up to 52 weeks. This was supported with a Kaplan-Meier analysis (Figures 2 and 3), which predicted that 78% of ulcers treated with adjunctive dHACM would be healed by 12 months compared with 59% of ulcers treated with standard care.

In the United Kingdom, the annual healing rate of non-healing DFUs was estimated to be 30% in clinical practice in 2012/2013.[4,13] However, in 2017/2018, this healing rate was found to have increased to 41%.[14,15] Therefore, the 12-month healing rate in the standard care arm of the Markov model was adjusted to 41%, in order to reflect the healing rates observed in clinical practice in the United Kingdom. The model incorporated a relative risk of developing a putative infection in accordance with the mean estimates from the RCT.[12] Additionally, the model incorporated a relative risk of having an amputation in accordance with estimates from the RCT in combination with those expected from clinical practice in the United Kingdom.[4,16-18] The resulting transition probabilities over a time horizon of 12 months are shown in Table 1.

The model assumed that patients in both groups would be managed by a multidisciplinary team (MDT) in secondary care, in accordance with clinical practice.[6] The model assumed that the frequency of clinician visits would be comparable to that seen in clinical practice in the United Kingdom[4,13,15] and not the protocol-driven frequency of visits that took place during the RCT.[12] The model also assumed that standard care would comprise the combination of dressings, bandages, and offloading devices patients receive in routine clinical practice in the United Kingdom,[4,13,15] and not the combination of foam, silicone, and hydropolymer dressings and offloading devices administered to patients in the RCT.[12] If a patient's ulcer became worse, the model assumed there was a 0.02 probability of attending Accident and Emergency, based on our estimates of patient management in clinical practice.[4]

2.3 | Utilities

Utility scores express patient preferences for specific health states on a scale ranging from 0, representing death, to 1, representing perfect health. These scores provide the weights to estimate HRQoL in terms of the number of quality-adjusted life years (QALYs) gained by an intervention or service. Published utility scores for DFUs

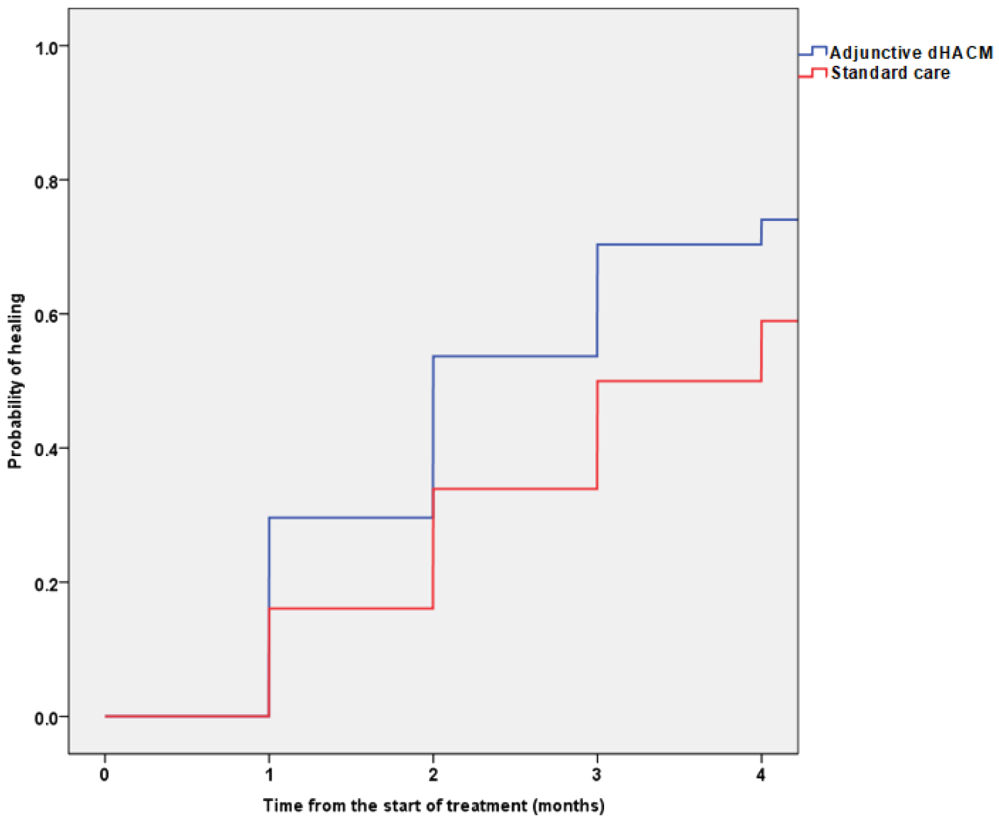

FIGURE 2 Kaplan-Meier probability of healing analysis

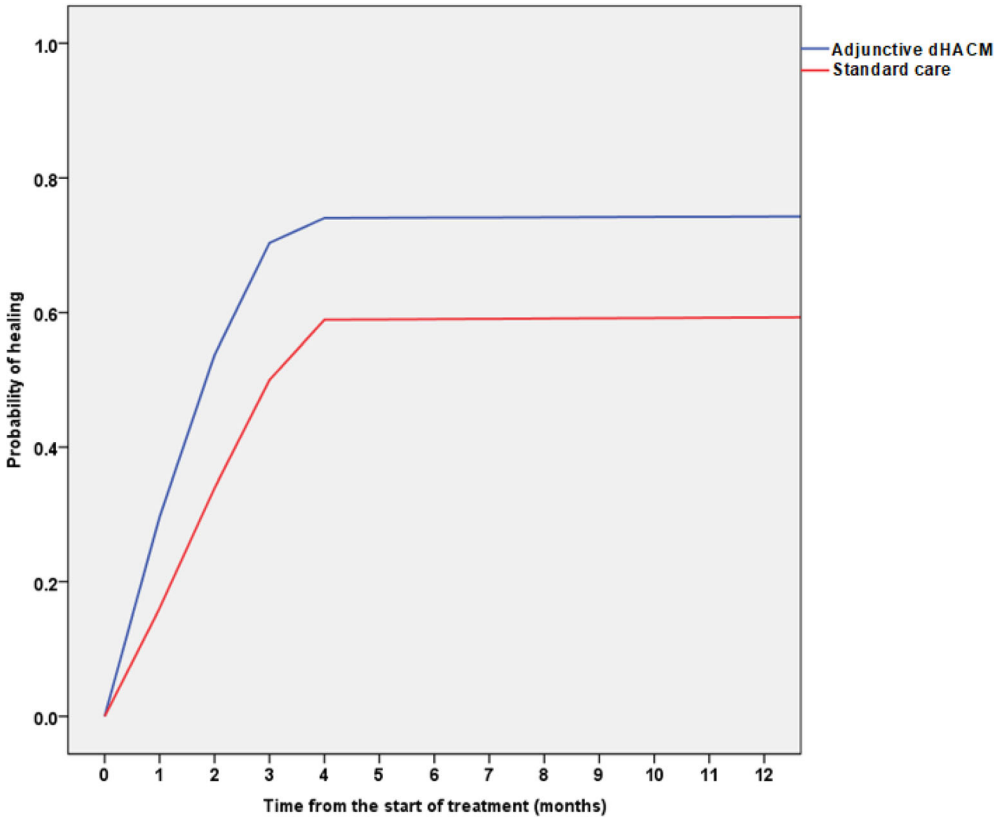

FIGURE 3 Kaplan-Meier time to healing projection

(0.465 for an unhealed ulcer, 0.465 for an infected ulcer, 0.60 for a healed ulcer, 0.45 for an amputation, 0.45 for post-amputation, and 0.465 for a recurred ulcer)[19] were assigned to each health state in the model. This enabled patients' expected HRQoL in terms of the number of QALYs at 12 months from the start of treatment to be estimated.

2.4 | Unit costs

NHS secondary care costs of DFU management[4,13,15,17] were uprated to 2019/2020 prices using NHS Improvement's latest assumptions for NHS provider inflation[20] (Table 2). These costs were applied to the health states in the model to estimate the total NHS secondary care cost of managing a DFU with adjunctive dHACM or standard care alone over 12 months. A discount rate was not applied as the time horizon of the model was limited to 1 year.

2.5 | 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 secondary care cost of wound management over 12 months from the time patients entered the model was estimated at 2019/2020 prices.

2.5.1 | Cost-effectiveness analysis

The potential cost-effectiveness of adjunctive dHACM compared with standard care 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'. The resulting incremental cost-effectiveness ratio (ICER) was expressed as the incremental cost per QALY gained from the perspective of secondary care. If one of the strategies generated more QALYs for less cost, it was considered to be the dominant intervention.

The cost of individual dHACM allografts was unknown at the time of performing the study, and the size of the allografts administered would be dependent on wound size. Therefore, the analysis estimated the amount of expenditure that could be incurred to purchase dHACM allografts over an episode of care to reach three cost per QALY thresholds, namely, an ICER of £20 000 per QALY, £25 000 per QALY, and £30 000 per QALY. The analysis assumed that adjunctive dHACM would not be used for longer than 12 weeks and any unhealed wounds would continue to be managed with standard care alone.

TABLE 1 Monthly transition probabilities in the Markov model

Month	Treatment group	Unhealed	Improved	Healed	Recurrence	Amputation	Post-amputation	Infection
Start	Adjunctive dHACM	1.000	0.000	0.000	0.000	0.000	0.000	0.000
Month 1	Adjunctive dHACM	0.037	0.889	0.056	0.000	0.000	0.000	0.019
Month 2	Adjunctive dHACM	0.056	0.556	0.352	0.000	0.000	0.000	0.037
Month 3	Adjunctive dHACM	0.130	0.222	0.519	0.000	0.019	0.000	0.111
Month 4	Adjunctive dHACM	0.037	0.167	0.685	0.000	0.019	0.019	0.074
Month 5	Adjunctive dHACM	0.019	0.074	0.741	0.000	0.019	0.056	0.093
Month 6	Adjunctive dHACM	0.056	0.056	0.741	0.019	0.000	0.056	0.074
Month 7	Adjunctive dHACM	0.074	0.037	0.759	0.000	0.000	0.056	0.074
Month 8	Adjunctive dHACM	0.093	0.037	0.741	0.019	0.000	0.056	0.056
Month 9	Adjunctive dHACM	0.093	0.019	0.778	0.000	0.000	0.056	0.056
Month 10	Adjunctive dHACM	0.093	0.019	0.759	0.019	0.000	0.056	0.056
Month 11	Adjunctive dHACM	0.093	0.000	0.796	0.000	0.000	0.056	0.056
Month 12	Adjunctive dHACM	0.111	0.000	0.778	0.000	0.000	0.056	0.056
Start	Standard care	1.000	0.000	0.000	0.000	0.000	0.000	0.000
Month 1	Standard care	0.393	0.536	0.018	0.000	0.000	0.000	0.054
Month 2	Standard care	0.339	0.482	0.107	0.000	0.000	0.000	0.071
Month 3	Standard care	0.339	0.321	0.232	0.000	0.000	0.000	0.107
Month 4	Standard care	0.321	0.214	0.321	0.000	0.000	0.000	0.143
Month 5	Standard care	0.375	0.125	0.321	0.018	0.018	0.000	0.143
Month 6	Standard care	0.393	0.107	0.339	0.018	0.018	0.018	0.107
Month 7	Standard care	0.375	0.089	0.375	0.018	0.018	0.018	0.107
Month 8	Standard care	0.357	0.071	0.393	0.018	0.018	0.036	0.107
Month 9	Standard care	0.339	0.054	0.411	0.018	0.018	0.054	0.107
Month 10	Standard care	0.304	0.036	0.411	0.018	0.018	0.071	0.143
Month 11	Standard care	0.268	0.018	0.429	0.018	0.018	0.089	0.161
Month 12	Standard care	0.286	0.000	0.411	0.018	0.000	0.107	0.179

Abbreviation: dHACM, dehydrated human amnion/chorion membrane.

2.5.2 | 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 15% 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. Outputs from this analysis enabled the construction of a cost-effectiveness acceptability curve showing the probability of adjunctive dHACM being cost-effective at different cost per QALY thresholds.

Deterministic sensitivity analysis was also performed to assess the impact of independently varying the values of individual parameters within the model. The parameter estimates were individually varied over plausible ranges within the model.

2.6 | Resource implications and budget impact

A mean of 511 people with a DFU were seen by a NHS secondary care provider/service in 2018.[21] The analysis assumed that 250 of these patients (49%) had a non-healing DFU. The budget impact analysis assumed that these 250 non-healing DFUs would be eligible to be managed with adjunctive dHACM. Hence, the annual resource implications and budget impact to an average NHS secondary care provider/service was estimated by treating varying percentages of 250 non-healing DFUs with adjunctive dHACM and standard care alone.

TABLE 2 Secondary care costs of DFU management uprated to 2019/2020 prices

	NHS cost	Source
Weekly cost of managing a healed DFU by an MDT in secondary care	£92.14	4,13
Monthly cost of managing an improving DFU by an MDT in secondary care	£399.25	4,13
Monthly cost of managing a non-improving DFU by an MDT in secondary care	£696.20	4,13
Monthly cost of managing an infected DFU by an MDT in secondary care	£733.31	4,13
Monthly cost of managing a DFU post-infection by an MDT in secondary care	£422.84	4,13
Mean cost per amputation	£6648.10	17
Mean cost of post-amputation rehabilitation	£1268.36	17

Abbreviations: DFU, diabetic foot ulcer; MDT, multidisciplinary team.

3 | RESULTS

3.1 | Health outcomes and costs

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

- 90% increase in the probability of healing (from 0.41 to 0.78).
- 34% reduction in the probability of wound infection (from 0.62 to 0.41).
- 57% reduction in the probability of wound recurrence (from 0.30 to 0.13).
- 6% increase in the probability of avoiding an amputation (from 0.89 to 0.94).
- 8% improvement in HRQoL (from a mean of 0.51 to 0.55 QALYs per patient).

Hence, treating a non-healing DFU with adjunctive dHACM allografts affords a clinically more effective strategy than with standard care alone (Table 3).

The total 12-month secondary care cost of wound management in the adjunctive dHACM group was estimated to be £2502 (excluding the cost of dHACM allografts) per DFU. The corresponding cost in the standard care group was £5764 per ulcer. Amputations were found to account for 17–18% of the expected 12-month cost.

TABLE 3 Health outcomes and costs over the time horizon of the model

	Adjunctive dHACM	Standard care
Probability of the wound being healed by 12 months	0.78	0.41
Probability of the wound remaining unchanged at 12 months (ie, not healed or improved)	0.11	0.29
Probability of the wound being infected at 12 months	0.06	0.18
Probability of wound infection over 12 months	0.41	0.62
Probability of recurrence of a healed wound over 12 months	0.13	0.30
Probability of having an amputation over 12 months	0.06	0.11
Mean number of QALY's per patient at 12 months	0.55	0.51
Mean cost of wound management per DFU at 12 months (excluding the cost of dHACM allografts)	£2502	£5764

Abbreviations: DFU, diabetic foot ulcer; dHACM, dehydrated human amnion/chorion membrane; QALY, quality-adjusted life year.

3.2 | Cost-effectiveness analysis

Outputs from the model showed that if £4062 is spent on allografts, then adjunctive use of dHACM instead of standard care alone is expected to lead to an incremental cost per QALY gain of £20 000 (Table 4). Hence, including dHACM into a standard care protocol could potentially afford the NHS a cost-effective treatment. Table 4 also shows how the incremental cost per QALY gained with adjunctive dHACM increases in parallel with increasing expenditure on the allografts.

3.3 | Sensitivity analyses

3.3.1 | Probabilistic sensitivity analyses

Probabilistic sensitivity analyses highlighted the distribution in the incremental costs and QALYs at 12 months between each treatment strategy (Figure 4). The graphs indicate that a greater proportion of samples are located

TABLE 4 Cost-effectiveness analysis

Intervention	Mean secondary care cost of wound management per patient over 12 months	Mean number of QALYs per patient at 12 months	NHS cost difference	QALY difference	Incremental cost per QALY gained
Standard care	£5764	0.51			
Adjunctive dHACM with £4062 being spent on allografts	£6564	0.55	£800	0.04	£20 000
Adjunctive dHACM with £4262 being spent on allografts	£6764	0.55	£1000	0.04	£25 000
Adjunctive dHACM with £4462 being spent on allografts	£6964	0.55	£1200	0.04	£30 000

Abbreviations: DFU, diabetic foot ulcer; dHACM, dehydrated human amnion/chorion membrane; QALY, quality-adjusted life year.

FIGURE 4 Scatterplot of the incremental cost-effectiveness of adjunctive dehydrated human amnion/chorion membrane compared with standard care alone following 10 000 iterations of the model

in the bottom right-hand (dominant) quadrant in parallel with decreasing expenditure on dHACM allografts. Outputs from the analysis showed that at a cost-effectiveness threshold of £20 000 per QALY, up to 94%, 88%, 80%, 62%, and 42% of a cohort is expected to be treated cost-effectively with adjunctive dHACM, compared with standard care alone, if expenditure on the allografts amounts to £3300, £3500, £3700, £4000, and £4300 per DFU, respectively (Figure 5).

3.3.2 | Deterministic sensitivity analysis

Deterministic sensitivity analyses (Figure 6) showed that adjunctive dHACM's cost-effectiveness is potentially sensitive to changes in

- healing rates.
- probability of recurrence, especially in the adjunctive dHACM group.

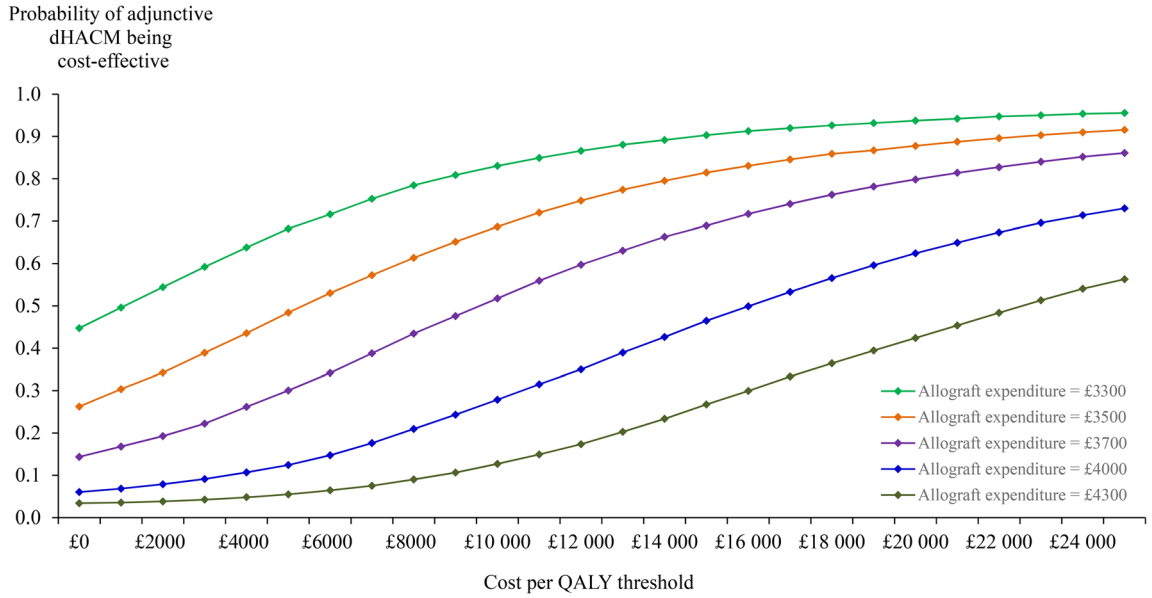

FIGURE 5 Probability of adjunctive dehydrated human amnion/chorion membrane being cost-effective compared with standard care alone

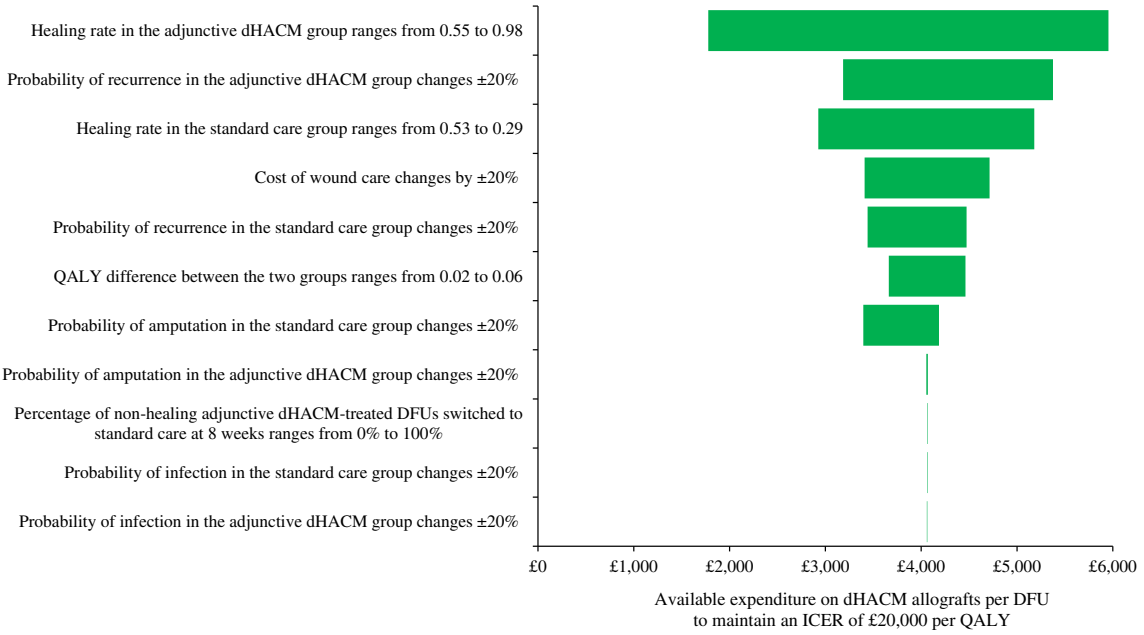

FIGURE 6 Tornado diagram showing the influence of increasing or decreasing key variables on dehydrated human amnion/chorion membrane expenditure in order to maintain an incremental cost-effectiveness ratio of £20 000 per quality-adjusted life year

- cost of wound care.
- difference in HRQoL between the two groups.

Adjunctive dHACM's relative cost-effectiveness was insensitive to plausible changes in the probability of amputation and probability of wound infection over the time horizon of the model.

Additionally, sensitivity analyses showed that if the healing rates in both groups were as observed in the RCT and Kaplan-Meier projections (ie, 78% and 59% in the adjunctive dHACM and standard care group, respectively) and the relative risk of infection, amputation, and recurrence were adjusted accordingly, with no other changes being made, then the available expenditure on dHACM allografts to maintain a cost per QALY of £20 000 would be £2280 per DFU. Furthermore, if the healing rates were 78% and 59% in the adjunctive dHACM and standard care group, respectively

(as observed in the RCT and Kaplan-Meier projections) and the relative risk of infection, amputation, and recurrence were adjusted accordingly, and patients were managed according to the RCT protocol in terms of dressings and frequency of clinician visits, then the available expenditure on dHACM allografts to maintain a cost per QALY of £20 000 would be reduced to £1520 per DFU.

Sensitivity analysis also found that if the amount spent on dHACM allografts was ≤£3250 per DFU, the 12-month cost of wound management per ulcer in the adjunctive dHACM group breaks-even with the per ulcer cost in the standard care group. Furthermore, probabilistic sensitivity analyses found that if the expenditure on dHACM allografts was ≤£3250 per ulcer, then treating non-healing DFUs with adjunctive dHACM instead of standard care had a 0.95 probability of being cost-effective at the £20 000 per QALY threshold.

3.4 | Resource implications and budget impact of adjunctive dHACM

The model indicated that over 12 months from the start of treatment with adjunctive dHACM, an average patient with one DFU would have a mean 25 visits to the MDT, a mean 0.15 visits to an accident and emergency department, and a mean of 0.06 amputations. In comparison, a standard care-treated patient with one DFU would have a mean 57 visits to the MDT, a mean 0.41 visits to an accident and emergency department, and a mean of 0.11 amputations. Hence, in the first 12 months, use of adjunctive dHACM has the potential to significantly heal more DFUs and release ~30 visits per patient to the MDT, reduce the probability of attending an accident and emergency department by ~60%, and reduce the probability of requiring an amputation by 45%.

The annual resource implications and budget impact to an average secondary care provider/service managing 250 non-healing DFUs with adjunctive dHACM allografts and standard care alone are shown in Table 5. The analysis showed that use of adjunctive dHACM allografts by a MDT in secondary care who was managing non-healing DFUs would lead to a reduction in resource use for no additional cost if the amount spent on the allografts was ≤£3250 per ulcer.

4 | DISCUSSION

This modelling study estimated the cost-effectiveness of adjunctive dHACM compared with standard care alone in the management of DFUs among adult patients, at least 18 years of age, who had a diagnosis of type 1 or 2 diabetes mellitus. The model was based on the modified ITT cohort of patients who participated in a randomised, controlled study.[12] The structure of the Markov model simulated the pathways of the modified ITT cohort in the trial[12] beyond the 16-week follow-up period for a total period of 12 months. It was decided to model DFU management over a time horizon of 12 months rather than the RCT follow-up period of 16 weeks, in order to allow sufficient time to better reflect a patient's journey in the

TABLE 5 Annual resource implications and budget impact to a NHS secondary care provider/service managing 250 non-healing DFUs with adjunctive dHACM and standard care alone

	Ratio of patients (n = 250) treated with standard care and adjunctive dHACM				
	100%:0%	75%:25%	50%:50%	25%:75%	0%:100%
Number of healed ulcers	103	126	149	172	195
Annual amount of resource use associated with managing 250 patients (with one DFU)					
Multidisciplinary team visits	14 225	12 244	10 263	8281	6300
Accident and emergency attendances	102	86	70	54	38
Amputations	28	24	21	18	15
Annual cost of resource use associated with managing 250 patients (with one DFU):					
Secondary care associated with managing DFUs	£1 441 087	£1 237 212	£1 033 337	£829 462	£625 587
dHACM allografts @ £3250 per ulcer	£0	£203 125	£406 250	£609 375	£812 500
Total NHS secondary care cost of wound management	£1 441 087	£1 440 337	£1 439 587	£1 438 837	£1 438 087

Abbreviations: DFU, diabetic foot ulcer; dHACM, dehydrated human amnion/chorion membrane.

real world. The beyond-trial modelling was principally predicated on the Kaplan-Meier projected wound healing rates as well as projected rates of wound infections and lower limb amputations. The impact of changing these values was shown in the sensitivity analyses.

The aforementioned RCT[12] was the only phase III study comparing the efficacy and safety of adjunctive dHACM with standard care alone in the management of DFUs at the time of performing this analysis. The advantage of using this RCT for the economic model is that there were no differences in baseline parameters or ulcer characteristics between the two groups, and the efficacy and safety of the two treatments were measured under controlled conditions. The healing rate with adjunctive dHACM observed in the RCT was comparable to that seen in clinical practice in the United Kingdom by the clinical authors of this study. However, the healing rates with standard care observed in the RCT were not comparable to those seen in clinical practice in the United Kingdom[4,15] and were adjusted in our model accordingly. Furthermore, in one earlier exploratory RCT that compared the use of adjunctive dHACM (n = 15) with standard care alone (n = 14) over 6 weeks, 33% of non-healing DFUs in the adjunctive dHACM group had healed by week 6, compared with 0% in the standard care group.[22]

The aforementioned RCT was not blinded, patients were only followed up for 16 weeks after the start of treatment, HRQoL was not measured, and only protocol-driven resource use was documented.[12] Consequently, the Markov model was informed with assumptions about treatment patterns from the clinical authors and published estimates seen in clinical practice in the United Kingdom.[4,13-18] The inherent variability and uncertainty within the model was addressed to some extent by our extensive sensitivity analyses. Notwithstanding this, patients in clinical practice are managed with different dressings and seen at different frequencies to those in the RCT (which were protocol-driven). Sensitivity analyses showed the impact of replacing the model's base case values with the healing rates observed in the RCT and of adopting protocol-driven dressings and frequencies of clinician visits. Nevertheless, the findings from this economic analysis need to be validated in a randomised controlled study in the United Kingdom.

The study is subject to some other limitations. The model was unable to stratify the impact of adjunctive dHACM between ulcers of neuropathic and neuroischaemic origin. Nevertheless, it could be implied that the patients who participated in the RCT[12] were largely neuropathic because the inclusion criteria required patients to have had 'adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test (TcPO2) ≥30 mm Hg, ankle-brachial pressure index (ABPI) between 0.7 and 1.2, or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg'.[12] The study simulated wound management in the hospital outpatient setting because it is unknown if dHACM can or would be used more widely in primary care in the United Kingdom. Hence, the relative cost-effectiveness of using dHACM outside of secondary care is unknown at this time and it is not possible to predict with any certainty what its cost-effectiveness might be in primary care. Because the economic analysis was based on the results of a single RCT in non-healing DFUs, it precludes generalisation of our findings to patients with other wound types, although adjunctive dHACM has been shown to be efficacious in treating non-healing venous leg ulcers[23,24] and difficult-to-heal fistulas.[25] Predicting whether the use of dHACM would be cost-effective in treating these wound types is beyond the remit of this study because the patient pathways and treatment algorithms for non-healing venous leg ulcers and difficult-to-heal fistulas differ from those of non-healing DFUs. Despite this limitation, the model structure should be generalisable to other countries that encompass similar patient pathways. Additionally, the clinical effectiveness of adjunctive dHACM 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. Nevertheless, it cannot be implied that this study's estimate of cost-effectiveness of adjunctive dHACM would be transferable to other countries if those countries used different treatment pathways or reimbursement mechanisms to those in the United Kingdom or if they had a private-funded health care system, such as in the United States. The provision of wound care is heterogeneous between different settings and different management systems, and this variation can impact on the level of cost-effectiveness of adjunctive dHACM.

The model does not incorporate the probability of a patient developing a second DFU at a different location to the ulcer being evaluated in this analysis. Such an ulcer would be considered a new wound and would enter the model at the start and receive treatment with either adjunctive dHACM or standard care. However, the model does incorporate the probability (as well as costs and outcomes) of a healed ulcer recurring in the same location as the original wound.

The analysis does not consider the potential impact of managing an unhealed wound beyond a time horizon of 12 months. However, if the time horizon of the model was extended beyond 12 months, dHACM would become more cost-effective because there were more unhealed wounds in the standard care group at 12 months. 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 and underlying disease severity. The model excluded direct costs incurred by patients and indirect costs incurred by society as a result of employed patients taking time off work. Consequently, this study may have underestimated the relative cost-effectiveness of adjunctive dHACM allografts.

Despite these limitations, the model showed that initial treatment with adjunctive dHACM instead of standard care alone is a clinically more effective strategy because the probability of wound healing was estimated to increase by 90% and there was an 8% improvement in patients' HRQoL. A range of geometric configurations of dHACM allografts will be made available in the United Kingdom, which could be matched to the size of a wound at each dressing change. In the meantime, adopting a 'one-size-fits-all' approach to costing the use of the allografts in the model would potentially lead to the wrong result because allograft sizes would inevitably be determined by the wound size at baseline and the healing trajectory adopted by each individual wound. Hence, the analysis estimated the amount of expenditure that could be incurred to purchase the dHACM allografts over an episode of care to reach three cost per QALY thresholds (ie, £20 000, £25 000, and £30 000 per QALY). While technologies that afford a cost-effectiveness ratio of £20 000 per QALY are considered being cost-effective in the United Kingdom,[26] it must be recognised that the benchmarks for cost-effectiveness are largely arbitrary and need reviewing periodically. Sensitivity analyses showed that the expenditure that could be incurred to purchase dHACM allografts over an episode of care to maintain a £20 000 per QALY level of cost-effectiveness is sensitive to changes in healing rates, recurrence rates, QALY differences, and cost of wound care. However, the study also suggested that if expenditure on dHACM allografts was ≤£3250 per ulcer, then treating non-healing DFUs with adjunctive dHACM instead of standard care would break-even and have a 0.95 probability of being cost-effective at the £20 000 per QALY threshold. There will always be considerable heterogeneity in the delivery of wound care both between centres, clinicians, and patients. Nevertheless, it should be possible to treat non-healing DFUs with adjunctive dHACM allografts, instead of standard care, cost-effectively in most scenarios.

DFUs are complex wounds often requiring substantial time to heal.[27] Moreover, they are associated with an increased risk for infection, recurrence, hospitalisation, and amputation, which can be costly.[1,3,27] Indeed, the estimated total annual NHS cost of managing DFUs in the United Kingdom was estimated to be £1.28 billion in 2017/2018.[15] This expenditure can be affected by a combination of poor control of diabetes, compliance with treatment (eg, offloading and infection control), complexity of some treatment regimens, recurrence and amputation rates, and post-amputation morbidity and mortality[4,13] Accordingly, cost-effective management and healing of DFUs remain challenging. Despite these statistics, a recent systematic literature review of economic analyses on the management of DFUs[28] only found 19 cost-effectiveness studies and only one UK-based study (which we published in 2018[29]). One study published since this review found dHACM to be cost-effective in the United States when used adjunctively with standard care in a defined trial population, compared with standard care alone.[30] No attempt was made to generalise the findings from this study.

In conclusion, within the study's limitations, and within a certain price range, adjunctive dHACM affords the NHS a cost-effective intervention for the treatment of non-healing DFUs within secondary care and has the potential to free-up hospital resources for alternative use in the management of foot ulcers among adult patients with type 1 or 2 diabetes mellitus in the United Kingdom.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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