Cost-effectiveness of an electroceutical device in treating non-healing venous leg ulcers: results of an RCT

Objective: To estimate the cost-effectiveness of an externally applied electroceutical (EAE) device, Accel-Heal, in treating non-healing venous leg ulcers (VLUs) in the UK.

Method: This was a prospective, randomised, double-blind, placebo-controlled, multi-centre study of patients aged ≥18 years with a non-healing VLU. Patients were randomised in the ratio of 1:1 to receive six units of the EAE (consisting of a self-contained, programmed electric microcurrent generator and two skin contact pads) or an identical-looking placebo device over 12 consecutive days. Patients were followed-up for 24 weeks from randomisation, during which time patients received wound care according to the local standard care pathway, completed health-related quality of life (HRQoL) instruments, and health-care resource use was measured. The cost-effectiveness of the EAE device was estimated at 2015/16 prices in those patients who fulfilled the study's inclusion and exclusion criteria (economic analysis population).

Results: At 24 weeks after randomisation, 34% and 30% of VLUs in the EAE and placebo groups in the economic analysis population, respectively, had healed. The time-to-healing was a mean of 2.6 and 3.5 months in the EAE and placebo groups, respectively. The area of the wounds that healed in the EAE group was nearly twice that of those in the placebo group (mean: 13.3 versus 7.7cm^2 per VLU). Additionally, the pre-randomised duration of the wounds that healed in the EAE group was double that of those in the placebo group (mean: 2.6 versus 1.2 years per VLU). By the end of the study, EAE-treated patients reported less pain, more social functioning and greater overall wellbeing/satisfaction than placebo-treated patients. None of these differences reached statistical significance, but they may be important to patients. There were no significant differences in health-care resource use between the two groups. The incremental cost per quality-adjusted life year (QALY) gained with the EAE device was £4480 at eight weeks, decreasing to £2265 at 16 weeks and –£2388 (dominant) at 24 weeks. The study was confounded by unwarranted variation in patient management between centres and between individual clinicians within each centre.

Conclusion: Despite the unwarranted variation in the provision of wound care observed in this study, the use of the EAE device resulted in some improved clinical outcomes and patient-reported outcomes, for the same or less cost as standard care, by 24 weeks. Clinicians managing VLUs may wish to consider the findings from this study when making treatment decisions.

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Accel-Heal • cost-effectiveness • randomised controlled trial • venous leg ulcers • externally applied electroceutical device

Use of an external electric current to promote healing of chronic wounds was first introduced more than 40 years ago.[1] A systematic review and meta-analysis of 21 randomised controlled trials (RCTs) concluded that electrical stimulation appears to increase the rate of chronic ulcer healing and may be superior to standard care for these wounds.[2] However, a more recent systematic review of three RCTs concluded that it was unclear whether electromagnetic therapy influences the rate of healing of venous leg ulcers (VLUs).[3]

Accel-Heal (Synapse Electroceutical Ltd, UK) is an externally applied electroceutical (EAE) device with a mode of action that delivers a proprietary sequence of electrical currents at a microcurrent level in order to augment soft-tissue healing, particularly in dermal tissue, via two skin surface electrodes. The net effect is a flow of ions through the wound tissue. The device is key-fob sized and comprises a programmed electric microcurrent generator which is connected to self-adhering skin contact pads. These pads are placed on normal skin adjacent to the wound for the duration of treatment, and the device can be replaced without disturbing the skin contacts, or wound dressings and bandages. The EAE delivers microcurrent for a continuous period of 48 hours and is a certified Class IIA medical device which has been approved under the Medical Devices Directive 93/42/EEC.

The EAE has been evaluated in several single-arm, non-blinded evaluations in patients with VLUs.[4–6] It was found to improve granulation and healing rates, reduce exudate levels and lead to a reduction in patient-reported pain scores.[4–6] Additionally, it was estimated to improve patients' health-related quality of life

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(HRQoL) and to afford the UK's National Health Service (NHS) a cost-effective intervention for the treatment of VLUs.[4,5]

The aim of this study was to conduct a randomised, placebo-controlled trial to evaluate whether application of the EAE device (i.e. Accel-Heal) improves healing in non-healing VLUs compared with standard care. However, the study was designed to allow each centre to maintain its normal care pathways, in order to reflect the introduction of the device into 'real world' clinical practice. The secondary objectives were to evaluate patients' HRQoL, and estimate the cost-effectiveness of using the EAE in combination with compression therapy compared with the locally specified pathway for standard care. Within the intention-to-treat (ITT) population, 31% of patients treated with the EAE and 34% of those treated with placebo had healed by 24 weeks after the start of the study.[7] Additionally, there were no significant differences in the incidence of adverse events (29% versus 20% in the EAE and placebo groups, respectively). The investigators confirmed, post-hoc, that no serious adverse events or infections were wound- or device-related.[7] The ITT population comprised 99 patients, of whom nine did not fulfil the study's inclusion/exclusion criteria. Therefore, these were excluded from the economic analysis since they would not be eligible to receive the EAE in clinical practice. The aim of this analysis was to estimate the cost-effectiveness of the EAE in a sub-group of the ITT population (economic analysis population) that would be eligible to receive the device in clinical practice.

Methods

Study design

This was a prospective, randomised, double-blind, placebo-controlled, multi-centre (five centres participated) study, which recruited patients aged ≥18 years with a non-healing VLU.

Ethics approval

Ethics approval to perform this study was obtained from the National Research Ethics Service (NRES) Committee Yorkshire and The Humber—Leeds Bradford (reference no: 13/YH/0264), and local Research and Development approval was subsequently obtained from the centres.

Study population

To be eligible for inclusion patients had to:

- Be ≥18 years of age with a confirmed VLU
- Receive good standard care for four weeks from a member of the clinical study team
- Have an ulcer that had not reduced in size by >20% from the screening visit
- Have an ankle brachial pressure index (ABPI) between ≥0.8 and ≤1.3
- Provide signed and dated informed consent
- Be available for the full duration of the study.

Patients were excluded from the study if they:

- Were of child-bearing potential and not using a reliable birth control method
- Were pregnant or lactating
- Had an existing condition, or evidence of a clinically significant medical condition that would impair wound healing, as determined by the investigator
- Had a diagnosis of a suspected collagen disease, such as vasculitis or rheumatoid arthritis, or active osteomyelitis
- Had chronic renal insufficiency requiring haemodialysis
- Were known to abuse alcohol or drugs, or to have psychological disorders that could affect follow-up care or treatment outcomes
- Had received a short course of corticosteroids within 60 days, or oral or parenteral chronic immunosuppressants within 120 days before screening
- Had a malignancy, apart from non-melanoma skin cancer, within the last five years
- Had participated in a clinical study of an investigational product within one month before the start of this study.

Sample size and randomisation

The primary aim of the study was to detect a difference in healing rate between the EAE and placebo. In our previous observational study, 38% of VLUs of >6 months' duration treated with the EAE healed within five months from the start of treatment.[4] Additionally, in our study assessing the management of VLUs in clinical practice, we estimated that 11% of VLUs of >6 months' duration healed within six months.[8] In performing the power calculation for this study, the healing rates for the active and placebo treatments were assumed to be below the 38% and 11% rates, respectively, since these healing rates were obtained from open, uncontrolled studies.

The study was powered to detect a difference in healing rate between the EAE and placebo by assuming a healing rate of 5% and 30% for placebo and the EAE, respectively. By assuming these healing rates, it was calculated that a sample of 50 patients in each treatment arm would be sufficient to detect a difference of approximately 25% (absolute values) between the two treatments with 90% power. The calculation assumed a two-sided 5% significance level and followed standard methods of calculation for binary data.

The EAE and placebo devices were packed in boxes labelled with the study randomisation numbers, preceded by a two-digit study code. These supplies were sent out to each site by the study's sponsor. A randomisation list, with treatments balanced in random block sizes, was computer-generated and whole blocks were allocated to each centre. When a patient was identified as being suitable for randomisation, the research staff at each site took the next consecutively numbered box at their site. Patients were randomised in the ratio of 1:1 to receive the EAE or the placebo

device, and to receive six units of the EAE (consisting of a self-contained programmed electric microcurrent generator and two skin contact pads) or placebo device over 12 consecutive days.

The EAE and placebo devices were outwardly identical in appearance, but the placebo device did not deliver an electric microcurrent.

Study procedures

Eligible patients attending the investigators' clinics were invited by a member of the study team to participate in the study and to provide informed consent. Patients then underwent a four-week run-in period with locally defined standard care during which their ulcer size was measured. Patients whose ulcer was still not healing, defined as a reduction in wound area of no more than 20%, were eligible to be randomised. Baseline assessments were performed and patients were randomised to receive treatment with either the EAE or placebo device for 12 consecutive days, with the device being changed every two days (i.e. six applications of the device in total). Patients were evaluated every two days during the 12 treatment days. However, patients were not seen on day 12. Instead, the device was removed after 14 days (i.e. two weeks after starting the EAE or placebo treatment). Follow-up assessments were performed at this visit and at eight, 16 and 24 weeks after starting treatment. Hence, there were 10 scheduled visits. Additionally, patients had unscheduled appointments for regular dressing changes, as deemed clinically necessary, in between the scheduled visits. Once a patient's wound had healed their participation in the study ended, although they were asked to return to complete pain scores and HRQoL instruments at the scheduled visits. Hence, each patient was evaluated over a period of 24 weeks after randomisation. For the duration of the study, patients were managed with standard care in accordance with the investigators' ongoing clinical protocols for VLUs at their respective centres.

This study was conducted under double-blind conditions. Participants, the investigators and study site clinical personnel were blinded to the treatment group assignment unless unblinding was indicated for medical reasons. The study was conducted by the clinical investigators and monitored by the study's sponsor's clinical research team. Completed case report forms (CRFs) were returned to the sponsor and entered onto a database. After completion of the study, the complete clinical trial data set was exported from the locked database and provided to the authors for health economics analysis.

Study measurements and assessments

At the time of randomisation, the patients' general clinical history and concomitant medications were documented. At all the scheduled visits, wound area (measured using rulers by the research staff) and exudate levels (recorded as none, light, medium or heavy)[9] were measured and patients were asked to complete a 10cm visual analogue pain score (VAS) (0=no pain, 10=worst possible pain). At randomisation, and at weeks two and 24 after randomisation, patients were also asked to complete the McGill pain questionnaire (MPQ).[10] At randomisation, and at weeks two, eight, 16 and 24 after randomisation, patients were asked to complete the following HRQoL instruments: Cardiff Wound Impact Schedule (CWIS),[11] the Short Form-36 (SF-36)[12] and EuroQol (EQ-5D-5L).[13] Health-care resource use was recorded at all the visits. Any adverse events that occurred at any time were also documented.

Analysis population

The economic analysis population was comprised of all the patients who were randomised to the EAE or placebo and who fulfilled the study's inclusion and exclusion criteria.

Study variables and statistical analysis

Analysis of covariance (ANCOVA) was performed to enable differences in patients' outcomes and resource use between the two groups to be adjusted for any heterogeneity in the following: age; gender; smoking status; wound size at baseline; wound duration; centre; relevant comorbidities (i.e. cardiovascular disease, endocrinological disease, musculoskeletal disease, pain), and percentage change in wound area between screening and randomisation.

Kaplan-Meier analysis was undertaken to determine whether the healing distribution of each group was significantly different from one another.

All statistical analyses were performed using IBM SPSS Statistics (IBM Corporation).

Efficacy variables

This analysis focused exclusively on the economic analysis population. The incidence of wound healing in each group at eight, 16 and 24 weeks after randomisation was estimated and tested for significant difference using a Chi-squared test. Differences between the groups in the rate of change of ulcer size from baseline and degree of exudate levels were quantified. Completed MPQ, CWIS, SF-36 and EQ-5D-5L instruments were analysed in accordance with the manufacturers' instructions. Use of all health-care resources was quantified individually for each treatment group at eight, 16 and 24 weeks after randomisation. Differences between the groups were tested for statistical significance using an independent samples T-test or Chi-squared test.

Safety analysis

The overall incidence of all adverse events experienced during the study by the economic analysis population was quantified according to treatment group, and the cost of managing these adverse events was included in the analysis.

Table 1. Baseline characteristics of the patients in the economic analysis population

	EAE	Placebo
Number of patients	43	47
Age (mean±SD per patient, years)	71.0±15.0	68.3±15.1
Male (%)	60	50
Patients who never smoked (%)	44	43
Patients who were ex-smokers (%)	40	40
Patients who were current smokers (%)	16	15
Patients who drank alcohol (%)	61	70
Body mass index (mean±SD per patient, kg/m^2)	32.5±6.9	34.7±9.8
Wound duration (mean±SD per patient, years)	5.7±10.9	2.7±3.4
Wound area (mean±SD per patient, cm^2)	20.2±22.8	18.9±20.3
Exudate levels		
Light exudate (%)	28	44
Medium exudate (%)	62	47
Heavy exudate (%)	11	9
Number of comorbidities (mean±SD per patient)	3.4±1.9	3.1±2.0

EAE—externally applied electroceutical device; SD—standard deviation

Table 2. Comorbidities of the patients in the economic analysis population

	EAE	Placebo
Cardiovascular	77%	60%
Pain	70%	64%
Endocrinological	35%	23%
Gastrointestinal	33%	36%
Musculoskeletal	28%	26%
Infection	23%	23%
Nutritional deficiency	14%	17%
Psychiatric	14%	6%
Respiratory disease	14%	17%
Neurological	9%	9%
Peripheral vascular disease	9%	11%
Genitourinary	7%	9%
Opthalmological	5%	0%
Substance abuse	5%	2%
Audiological	2%	0%
Oncology	2%	6%
Gynaecological	0%	2%
Haematological	0%	2%

Cost-effectiveness analysis

National unit costs were obtained from relevant NHS tariffs, at 2015/16 prices,[14–16] and applied to the amounts of health-care resource use to estimate the cost per patient in each group. Patients' utility values were calculated from the scores of the five states in the completed EQ-5D-5L questionnaires, based on the weights in Devlin et al.[17] and used to estimate the number of quality-adjusted life years (QALYs) at eight, 16 and 24 weeks after randomisation. Completed SF-36 questionnaires were not used to estimate utilities or QALYs. The primary measure of effectiveness was patients' health status in terms of the number of QALYs. The secondary measure of effectiveness was the probability of healing.

The relative cost-effectiveness of the EAE (from the perspective of the NHS) was determined by dividing the estimated cost-difference between the two groups at a given time point by the estimated effect difference between the two groups at the same time point. When the QALY difference was selected as the effect, the cost-effectiveness of the EAE was expressed as the incremental cost per QALY gained. When the probability of being healed was selected as the effect, the cost-effectiveness of the EAE was expressed as the incremental cost for each additional healed patient.

Bootstrapping was performed to estimate the distribution of expected costs and QALYs. This involved generating 10,000 subsets of the data from each group, on the basis of random sampling, and replacing the data once sampled. Use of these subsets enabled the construction of cost-effectiveness acceptability curves showing the probability of the EAE being cost-effective at different cost per QALY thresholds. Additionally, deterministic sensitivity analyses were performed to test the robustness of the results to changes in different parameters.

Results

Baseline characteristics

The first patient was screened for eligibility in January 2014 and the last patients completed their final study visit in September 2015. A total of 140 patients were screened for eligibility, of whom 99 were randomised; 49 to the EAE and 50 to placebo. The primary reason for screen failure was wound healing or reduction in wound area during the run-in (n=36 patients). A total of five patients failed to return to the clinic and one did not wish to participate in the trial. Hence, the ITT population comprised 99 patients.

The ecomomic population comprised 90 patients (43 on the EAE, 47 on placebo). The reasons for exclusion from the ecomonic analysis population was an ABPI outside the permitted range (n=3 patients), had a wound area reduction of >20% during the run-in (n=4 patients), and a run-in period <4 weeks (n=2 patients). There was enormous variation in sample size across all five centres, ranging from 35 patients at one centre to eight patients at another centre. Patients' baseline characteristics are summarised in Table 1. There were no significant differences in baseline characteristics between the patients in the two groups. However, the pre-randomised mean wound duration of patients in the EAE group was twice that of the placebo group (p=0.08). Furthermore, there was unwarranted variation in mean wound duration across the five centres (ranging from a mean of 2.1 to 7.6 years per centre in the EAE group and from a mean of 0.5 to 7.4 years per centre in the placebo group) and between groups at

Table 3. Clinical outcomes of patients in the economic analysis population

	8 weeks		16 weeks		24 weeks	
	EAE	Placebo	EAE	Placebo	EAE	Placebo
Healed wounds (%)	18	6	28	22	34	30
Area of all VLUs (mean±SD cm^2)	12.7±24.6	15.1±36.3	12.5±27.8	14.8±40.6	11.4±26.1	17.4±62.2
Area of VLUs that healed by 24 weeks (mean±SD cm^2)	6.7±2.7	12.1±5.1	6.0±4.0	10.0±2.8	0.0	0.0
Area of VLUs that remain unhealed (mean±SD cm^2)	15.7±20.1	16.4±23.2	15.8±24.5	16.9±27.4	13.7±23.4	19.7±38.5
Reduction in wound size from randomisation (%)	37	20	38	22	44	8
Patients with no exudate (%)	12	21	34	35	41	41
Patients with light exudate (%)	38	26	34	28	30	30
Patients with medium exudate (%)	45	44	30	28	20	22
Patients with heavy exudate (%)	5	10	2	9	9	8

EAE—externally applied electroceutical device; SD—standard deviation; VLU—venous leg ulcer

each centre (e.g. a mean of 7.6 years per patient versus 2.1 years per patient in the EAE and placebo groups, respectively, at one of the centres). Similarly, there was unwarranted variation in the pre-randomised mean wound area across the five centres (ranging from a mean of 4.7 to 27.8cm^2 per centre in the EAE group, and from a mean of 9.9 to 31.4cm^2 per centre in the placebo group), and between groups at each centre (e.g. a mean of 27.8cm^2 per patient versus 12.9cm^2 per patient in the EAE and placebo groups, respectively, at one of the centres). There were no significant differences in the comorbidities profile between the two groups (Table 2). However, more patients in the EAE group had pre-existing cardiovascular and endocrinological symptoms and pain.

Clinical outcomes

More wounds in the EAE group had healed at eight, 16 and 24 weeks after randomisation compared with placebo. However, none of these differences reached statistical significance (Fig 1 and Table 3). At 24 weeks after randomisation 34% and 30% of wounds in the EAE and placebo groups, respectively, had healed (Table 3). The percentage of wounds healed at each centre ranged from 0% to 50% in the EAE group, and 0% to 56% in the placebo group. The mean time to healing was 2.6±0.5 months per patient, and 3.5±0.5 months per patient in the EAE and placebo groups, respectively. However, these values varied by as much as 27% in the EAE group and 30% in the placebo group across the different centres.

The mean area of the wounds that healed in the EAE group was nearly twice as large as those that healed in the placebo group (13.3 versus 7.7cm^2). Additionally, the mean duration of the wounds that healed in the EAE group was twice as long as those that healed in the placebo group (2.6 versus 1.2 years). However, these differences did not reach statistical significance.

Exudate levels decreased in both groups over the study period (Table 3). Nevertheless, there were no significant differences between the groups.

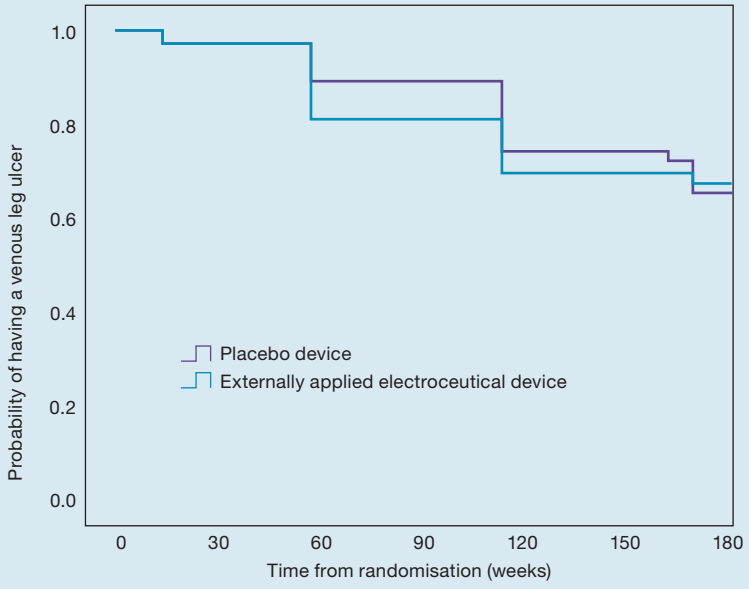
There was an inconsistency between investigators in the way adverse events were reported, since a VLU increasing in size was reported as wound deterioration by some but not by others. Accordingly, 23% and 15% of patients in the EAE and placebo groups, respectively, were reported as having an adverse event. In the EAE group, 40% of the adverse events were an infection, 20% a skin rash, 10% pain and 30% wound deterioration. In the placebo group, 71% of the adverse events were an infection, 14% a skin rash and 14% pain.

Patient reported outcomes

There were no significant differences in patient reported outcomes between the two groups at any time point (Table 4).

Based on the completed VAS and MPQ, patients in both groups reported a reduction in pain over the study

Fig 1. Kaplan-Meier time-to-healing analysis



The healing distribution between the two groups was not significantly different (Log Rank (Mantel-Cox): p>0.90)

Table 4. Patients' reported outcomes among the economic analysis population

	Randomisation		8 weeks		16 weeks		24 weeks	
	EAE	Placebo	EAE	Placebo	EAE	Placebo	EAE	Placebo
Visual analogue scale (VAS)								
Pain score per patient (mean±SD)	4.1±3.2	3.5±3.0	3.4±3.2	2.9±3.0	2.6±2.6	2.8±3.0	2.2±2.9	2.8±3.1
McGill pain questionnaire (MPQ)								
Pain score per patient (mean±SD)	9.4±8.2	10.5±9.5					2.8±3.7	4.2±7.8
Patients with 1–2 categories of pain (%)	43	37					33	28
Patients with >2 categories of pain (%)	50	54					14	17
Patients with no pain (%)	7	9					52	50
Cardiff Wound Impact Schedule								
Global HRQoL score per patient (mean±SD)	7.2±2.8	6.1±3.8	6.8±2.6	6.1±3.4	6.9±2.8	6.4±3.3	6.9±3.2	6.2±3.6
Wellbeing score per patient (mean±SD)	41.3±30.4	47.6±25.5	42.4±30.6	49.2±28.9	41.9±31.4	54.6±31.9	50.0±26.7	53.1±35.6
Physical functioning and everyday living score per patient (mean±SD)	63.6±33.0	63.2±34.1	64.9±32.5	66.6±33.0	67.5±29.9	69.3±30.3	77.2±22.0	71.9±28.5
Social functioning score per patient (mean±SD)	71.3±28.3	69.7±30.7	71.6±28.4	76.3±23.6	73.7±26.2	74.4±25.4	79.6±20.7	71.5±28.1
Satisfaction with HRQoL score per patient (mean±SD)	6.6±4.5	5.7±4.4	6.2±4.2	5.9±4.1	6.5±4.4	6.0±4.1	7.1±3.5	5.6±4.8
Short Form-36 (SF36)								
Physical function score per patient (mean±SD)	44.2±30.5	39.5±30.5	44.2±29.2	42.4±30.6	43.2±27.8	39.4±31.5	40.8±26.8	30.7±30.2
Role physical score per patient (mean±SD)	61.5±31.5	54.5±32.1	63.8±30.4	54.5±32.8	59.0±33.7	51.0±32.3	62.7±32.0	54.6±30.3
Bodily pain score per patient (mean±SD)	36.1±25.3	43.1±25.8	36.9±24.3	33.5±24.9	36.6±21.9	32.2±25.4	32.8±23.9	29.4±28.6
General health score per patient (mean±SD)	59.8±19.5	57.7±21.7	61.4±21.9	53.9±22.9	60.2±19.9	53.1±22.6	57.2±19.2	48.6±21.8
Vitality score per patient (mean±SD)	52.3±24.8	50.3±23.0	49.5±23.2	48.7±21.1	48.8±24.1	47.4±22.4	51.2±23.0	45.8±20.7
Social function score per patient (mean±SD)	79.2±28.7	71.9±30.9	76.3±25.9	71.0±26.5	74.2±32.1	74.7±26.1	76.5±29.6	71.4±29.1
Role emotional score per patient (mean±SD)	79.6±31.2	83.3±26.6	82.5±26.8	82.7±28.8	80.7±31.8	82.9±31.4	88.0±18.8	79.6±28.4
Mental health score per patient (mean±SD)	73.3±23.6	75.3±18.4	75.1±23.5	76.0±17.4	69.7±26.5	78.5±18.7	74.4±19.8	79.1±15.3
Physical component score per patient (mean±SD)	35.3±7.7	33.5±7.5	35.2±7.2	32.4±8.8	35.2±7.8	31.5±10.1	33.1±7.4	30.1±9.0
Mental component score per patient (mean±SD)	52.6±15.3	53.4±10.8	52.9±13.5	53.1±11.4	51.6±15.3	54.5±12.3	54.6±10.6	54.3±10.8
EuroQol (EQ-5D-5L)								
Patients who had no problems with mobility (%)	16	21	18	21	9	23	20	12
Patients who had no problems with self-care (%)	74	60	73	60	63	58	68	48
Patients who had no problems with usual activities (%)	37	30	38	28	41	35	36	24
Patients who had no pain and discomfort (%)	23	15	28	21	16	30	32	30
Patients who were not anxious or depressed (%)	60	66	70	74	63	68	60	58
Utility per patient (mean±SD)	0.72±0.23	0.67±0.23	0.75±0.32	0.70±0.38	0.75±0.29	0.70±0.39	0.76±0.31	0.68±0.37

EAE—externally applied electroceutical device; SD—standard deviation; HRQoL—health-related quality of life

period. However, the mean pain scores were smaller in the EAE group at 24 weeks. There was no correlation between the pain scores derived from the two instruments. Based on the completed CWIS, patients in the EAE group reported an increase in social functioning and satisfaction with their HRQoL over the study period. However, patients in both groups reported an increase in wellbeing and physical functioning over the study period.

At the study start, 28% of patients (n=12) in the EAE group and 38% (n=18) in the placebo group completed an old version of the SF36. Mid-way through the study, the SF-36 questionnaires in their respective CRFs were changed to the new version by the study's sponsor. Consequently, some of their data is not analysable. Only 72% of patients (n=31) in the EAE group and 62% of patients (n=29) in the placebo group completed the same version of the SF36 throughout the study (Table 4). However, no inferences have been drawn from these values since they are only derived from a proportion of the patients.

Based on the completed EQ-5D-5L forms, patients in both groups reported an increase in mobility problems over the study period. Fewer patients in the placebo group reported being able to self-care or perform usual activities at the start of the study. Nevertheless, the proportion of patients who reported being able to self-care and perform usual activities

Table 5. Health-care resource use in each group over eight, 16 and 24 weeks among the economic analysis population

	8 weeks		16 weeks		24 weeks	
	EAE	Placebo	EAE	Placebo	EAE	Placebo
Number of dressings per patient (mean±SD)	13.5±8.4	14.3±12.2	23.6±17.8	25.5±24.5	29.9±26.2	36.0±39.5
Patients who had a gauze (%)	55	62	55	59	56	54
Patients who had a composite (%)	18	14	14	14	12	13
Patients who had a film (%)	10	0	11	1	12	4
Patients who had an alginate (%)	9	14	8	16	8	16
Patients who had a foam (%)	2	1	3	2	2	6
Patients who had a hydrocolloid (%)	3	6	7	7	9	8
Patients who had an antimicrobial (%)	1	1	1	1	1	1
Patients who had a protease modulating matrix (%)	1	1	0	0	0	0
Patients who had a silicone (%)	1	1	0	0	0	0
Number of compression bandages per patient (mean±SD)	14.7±12.7	17.2±13.9	22.0±24.0	26.0±26.4	34.7±29.2	39.9±39.0
Patients who had multilayer (%)	65	67	66	66	52	57
Patients who had short stretch (%)	33	33	33	33	28	29
Patients who had hosiery (%)	2	1	1	2	20	14
Number of debridements per patient (mean±SD)	1.7±3.7	1.2±3.7	3.7±3.8	2.7±4.3	3.9±4.0	3.0±4.5
Patients who had autolytic (%)	82	75	41	41	44	47
Patients who had larval therapy (%)	0	0	46	41	44	37
Patients who had enzymatic (%)	6	17	8	15	8	13
Patients who had mechanical (%)	12	8	5	4	5	3
Number of district nurse visits per patient (mean±SD)	0.6±2.6	0.8±3.4	0.6±2.6	0.8±3.4	0.6±2.6	0.8±3.4
Number of practice nurse visits per patient (mean±SD)	2.2±7.9	2.0±8.4	4.8±18.5	6.4±22.9	5.8±22.6	10.5±37.5
Number of tissue viability nurse visits per patient (mean±SD)	16.4±11.9	18.0±12.6	30.1±25.6	30.2±25.1	37.2±35.8	37.9±37.2
Number of GP visits per patient (mean±SD)	0.1±0.5	0.1±0.3	0.2±1.9	0.1±1.8	0.2±2.0	0.2±1.9
Number of specialist visits per patient (mean±SD)	0.0±0.3	0.0±0.3	0.1±0.6	0.1±0.4	0.2±0.8	0.1±0.4
Number of diagnostic tests per patient (mean±SD)	0.1±0.5	0.0±0.0	0.1±0.5	0.0±0.2	0.1±0.6	0.0±0.4
Number of laboratory tests per patient (mean±SD)	0.2±0.8	0.1±0.4	0.2±0.8	0.1±0.5	0.2±0.8	0.1±0.6
Number of prescribed drugs per patient (mean±SD)	1.9±3.0	1.7±2.8	3.2±5.8	3.1±5.6	4.2±8.4	4.3±8.3
Patients prescribed analgesics (%)	47	59	47	55	48	53
Patients prescribed non-steroidal anti-inflammatories (%)	5	18	9	16	10	14
Patients prescribed antiplatelets (%)	5	12	6	13	5	12
Patients prescribed antidepressants (%)	5	6	9	6	7	7
Patients prescribed antiepileptics (%)	5	3	3	6	5	7
Patients prescribed antibiotics (%)	21	3	22	3	21	5
Patients prescribed anticoagulants (%)	5	0	2	0	2	2

EAE—externally applied electroceutical device; SD—standard deviation

decreased over the study period in both groups. More patients in the placebo group reported experiencing pain and discomfort at the start of the study. However, there was a decrease in the proportion of patients in both groups who reported experiencing pain and discomfort over the study period. Fewer patients in the placebo group reported experiencing anxiety and depression at the start of the study, after which the proportion of patients who reported experiencing anxiety and depression decreased by month two, but increased thereafter in both groups and there was minimal difference between the two groups by the end of the study. None of the changes reached statistical significance, but may be of importance to patients.

Health-care resource use

There were no significant differences in health-care resource use between the two groups (Table 5). Patients were predominantly managed by tissue viability nurses in outpatient clinics and, to a lesser extent, by practice nurses in a general practice clinic and by district nurses in a patient's home. It appears that 7% and 13% of patients in the EAE and placebo groups, respectively, received at least one device in the community by either a practice or district nurse, who was not part of the

Table 6. Mean cost of health-care resource use per patient in each group over eight, 16 and 24 weeks among the economic analysis population

	8 weeks		16 weeks		24 weeks	
	EAE	Placebo	EAE	Placebo	EAE	Placebo
Nurse visits	£1038.64	£1102.64	£1803.07	£1942.50	£2215.79	£2524.79
Compression	£75.82	£66.76	£270.86	£347.72	£326.40	£447.46
Hospitalisation	£32.19	£0.00	£139.72	£75.13	£139.18	£178.49
Dressings	£28.16	£31.31	£95.31	£103.02	£122.49	£142.30
Drugs	£17.65	£19.64	£33.62	£38.23	£51.93	£56.55
Physician visits	£14.89	£13.41	£50.51	£16.47	£87.93	£22.30
Debridement	£15.45	£15.90	£16.45	£18.26	£18.15	£19.54
Tests	£7.30	£0.34	£8.54	£2.68	£10.11	£7.58
EAE	£243.90	£0.00	£236.92	£0.00	£236.01	£0.00
TOTAL	£1474.00	£1250.00	£2655.00	£2544.00	£3208.00	£3399.00

EAE—externally applied electroceutical device

Table 7. Cost-effectiveness analysis among the economic analysis population at eight, 16 and 24 weeks after randomisation

	Mean NHS cost per patient	NHS cost-difference	Mean number of QALYs per patient	QALY difference	Probability of healing	Difference in probability of healing	Incremental cost per QALY gained	Incremental cost for each additional healed ulcer
8 weeks								
EAE	£1474	£224	0.748	0.050	0.18	0.12	£4480	£1867
Placebo	£1250		0.698		0.06			
16 weeks								
EAE	£2655	£111	0.746	0.049	0.28	0.06	£2265	£1850
Placebo	£2544		0.697		0.22			
24 weeks								
EAE	£3208	–£191	0.757	0.080	0.34	0.04	–£2388 (dominant)	–£4775 (dominant)
Placebo	£3399		0.677		0.30			

EAE—externally applied electroceutical device; QALY—quality adjusted life years

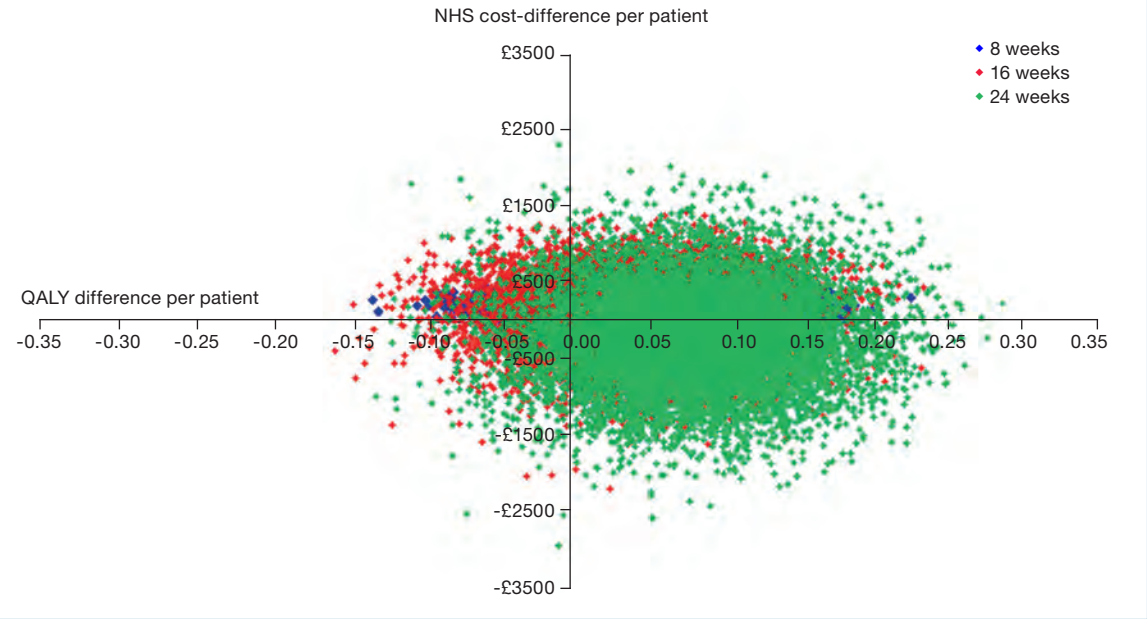
Table 8. Cost-effectiveness analysis among the economic analysis population at eight, 16 and 24 weeks after randomisation without any analysis of covariance (ANCOVA) adjustments

	Mean NHS cost per patient	NHS cost-difference	Mean number of QALYs per patient	QALY difference	Incremental cost per QALY gained
8 weeks					
EAE	£1450	£200	0.748	0.037	£5405
Placebo	£1250		0.711		
16 weeks					
EAE	£2690	£143	0.721	0.008	£17,875
Placebo	£2547		0.713		
24 weeks					
EAE	£3262	-£143	0.746	0.069	–£2072 (dominant)
Placebo	£3405		0.677		

EAE—externally applied electroceutical device; QALY—quality adjusted life years

clinical investigator's team. Once the 12 days of treatment with the EAE or placebo had finished, 7% and 21% of patients in the EAE and placebo groups, respectively, were at times managed in the community by practice or district nurses, who were also not part of the clinical investigator's team. Overall, patients' dressings were changed, on average, every four days throughout the course of the study for those wounds

Fig 2. Scatterplot of the incremental cost-effectiveness of the externally applied electroceutical device compared with placebo at eight, 16 and 24 weeks. (n=10,000 bootstrapped samples per comparison)



that remained unhealed. The frequency of dressing changed decreased from every four days to once every 7–10 days among wounds that were healing.

All patients in both groups received compression during the first month of the study. However, the study protocol enabled clinicians to manage patients according to their local standard care pathway. Accordingly, the use of a recognised compression system in 7% of the EAE treated patients and 2% of placebo-treated patients had ceased by the third month of the study.

Health-care cost of patient management

The total NHS cost of managing patients in each group is summarised in Table 6. The mean NHS cost of patient management at eight, 16 and 24 weeks in the EAE group was £1474 (95% confidence interval (CI): £1462 to £1486), £2655 (95%CI: £2624 to £2686) and £3399 (95%CI: £3165 to £3251), respectively. The mean NHS cost of patient management at eight, 16 and 24 weeks in the placebo group was £1250 (95%CI: £1234 to £1266), £2544 (95%CI: £2507 to £2581) and £3208

Fig 3. Probability of the externally applied electroceutical device being cost-effective at different cost per QALY thresholds

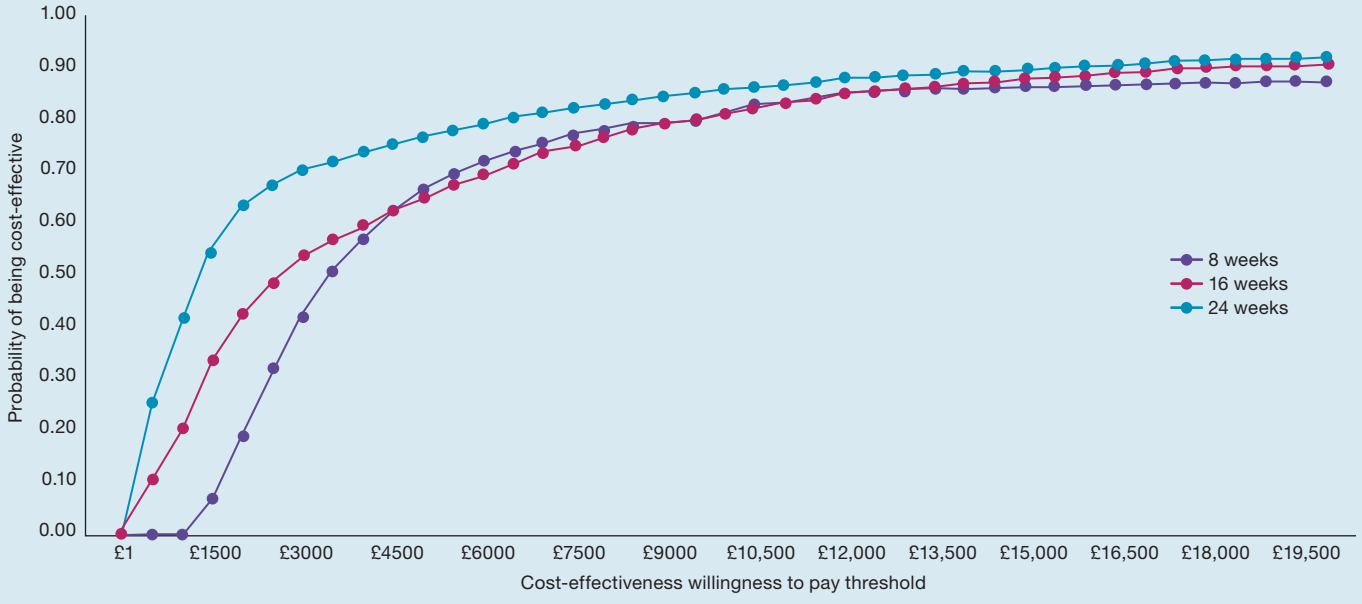


Table 9. Cost-effectiveness analysis among the ITT population at eight, 16 and 24 weeks after randomisation

	Mean NHS cost per patient	NHS cost-difference	Mean number of QALYs per patient	QALY difference	Incremental cost per QALY gained
8 weeks					
EAE	£1470	£217	0.754	0.077	£2818
Placebo	£1253		0.677		
16 weeks					
EAE	£3125	£632	0.714	0.051	£12,392
Placebo	£2493		0.663		
24 weeks					
EAE	£3678	£319	0.728	0.077	£4143
Placebo	£3359		0.651		

ITT—intension to treat; EAE—externally applied electroceutical device; QALY—quality adjusted life years

(95%CI: £3340 to £3458), respectively. The acquisition cost of the EAE was offset by a reduction in resource use by the end of the study, but resulted in an additional cost of £224 and £110 at eight and 16 weeks after the start of randomisation.

Nurse visits were the primary cost driver in all groups, accounting for >68% of the total management costs. Dressings and compression bandages accounted for up to 18% of the costs. The EAE accounted for 17% of the two-monthly cost of patient management in this group, decreasing to 7% of the six-monthly cost.

Cost-effectiveness analyses

The mean number of QALYs per patient in the EAE group was higher than that in the placebo group at eight, 16 and 24 weeks after the start of treatment. Hence, the incremental cost per QALY gained with the EAE was £4480 (95%CI: –£2129 to £11,089) at eight weeks, decreasing to £2265 (95%CI: −£3761 to £8291) at 16 weeks, and –£2388 (95%CI: −£4766 to –£10) at 24 weeks. Additionally, the incremental cost for each additional healed ulcer was £1867 (95%CI: –£601 to £3113), £1850 (95%: CI: −£1155 to £2545) and –£4775 (95%CI: −£9570 to –£20) at eight, 16 and 24 weeks, respectively (Table 7).

Sensitivity analyses

Bootstrapping was performed to identify the distribution in the incremental costs and QALYs at eight, 16 and 24 weeks after the start of treatment (Fig 2), with samples from the more cost-effective state at 24 weeks being located in the bottom right-hand (dominant) quadrant. Cost-effectiveness acceptability curves were generated from the bootstrapped subsets (Fig 3), showing the probability of the EAE being cost-effective for different incremental cost per QALY thresholds. Fig 3 showed that at a cost-effectiveness threshold of £20,000 per QALY, up to 88%, 91% and 92% of a cohort is expected to be treated cost-effectively with the EAE by eight weeks, 16 weeks and 24 weeks, respectively.

Deterministic sensitivity analysis showed that ANCOVA had minimal impact on the results (Table 8). However, when the econmic cohort is replaced with the ITT cohort, the EAE becomes less cost-effective, reflecting the fact that not all the patients in the ITT cohort had either a VLU or a non-healing VLU (Table 9).

Discussion

This was a placebo-controlled study in which patients were randomised in a 1:1 ratio to receive the EAE or an identical-looking placebo device. Nevertheless, in many respects this was an observational study, conducted as an adjunct to each centre's normal clinical practice, and designed to evaluate the effect of introducing the EAE into the local standard care pathway of a group of hard-to-heal VLUs. Accordingly, apart from receiving six units of the EAE or placebo over a period of 12 days, and patients being asked to complete HRQoL instruments at the scheduled appointments, the clinicians were allowed to manage their patients according to their usual practice. Moreover, patients were managed by non-wound specialist practice nurses, district nurses and, on rare occasions, by health-care assistants who were not part of the clinical investigator's team, in addition to tissue viability nurses. This resulted in considerable variation in patient management and corresponding resource use, both between centres and between individual patients within the centres. Furthermore, the sample sizes varied from eight patients at one centre to 35 at another. Consequently, the vagaries of patient management at one centre potentially dominated the results of the study. This possibly confounded the study's findings because management practices varied between the centres and wound care was often variable between patients, creating a degree of bias. This was further compounded by the wound population not having been properly controlled by the randomisation design leading to an imbalance of patients between centres in terms of sample sizes, wound area and wound duration.

Notwithstanding the above, there was some unexplained variability in the use of compression and dressings which did not correlate directly with exudate levels. Large amounts of gauze were used and relatively

little superabsorbents and alginates, which is difficult to explain in relation to patients' exudate levels. Additionally, there was a lack of clinical correlation between signs and symptoms and dressing/compression frequency. This may reflect the fact that patients were, at times, managed in the community by practice nurses or district nurses. This may be coincidental, but we have previously highlighted inconsistencies in wound care and dressing choice by practice and district nurses, and their apparent lack of a patient-specific treatment plan in many instances.[8,18–20] The use of rulers to measure wound area may have increased the variability of measurements between individual clinicians. The Eykona camera system was planned to be used for wound area measurements, but due to external problems with the camera's manufacturer, the data could not be automatically downloaded from the cameras.

Proportionally more wounds healed with the EAE and the mean time to healing was one month shorter with the EAE than with placebo. Nevertheless, the healing rate was lower than expected in the EAE group and higher than expected in the placebo group. An explanation for these findings may be that two skin surface metallic electrodes on either side of a wound can create a potential gradient causing a flow of ions through wound tissue resulting in a microcurrent without the need for an electric microcurrent generator. Another explanation may be that the EAE is only able to exert a therapeutic effect on those wounds where the 'natural' electric current is absent or deficient,[21] as may be the case in large wounds or wounds of long duration. So, in this study, many of the wounds in both groups may have had an effective 'natural' electric current, and that would explain why the device was more effective in larger wounds and those of longer duration. Such an explanation may also explain why the EAE performed better in the previous clinical evaluations than in this study, where the wound duration before the start of treatment was a mean ≥2.0 years per patient.[4,5] In comparison, 50% of the wounds in this study had a pre-randomised mean duration of 0.8 and 0.6 years in the EAE and placebo groups, respectively. The presence of bacteria and the impact of dressings and bandages with different surface charge characteristics may also affect the 'natural' current. The interaction and surface charge characteristics of different dressings and bandages could potentially neutralise some or all of the electrical cycle when an alternating current is being employed. This clearly warrants further investigation.

Reflective questions

- How should excessive variations in standard care be addressed in clinical practice?
- Is a better understanding of 'natural' electrical current activity necessary to plan effective studies?
- Do electroceutical devices have a role in wound care?

The clinical differences were reflected in the patient reported outcomes. By the end of the study, EAE-treated patients appeared to have a better HRQoL than placebo-treated patients as they reported less pain, more social functioning and greater overall wellbeing/satisfaction. Even though these differences did not reach statistical significance they may be of importance to the patients.

The clinical and HRQoL differences translate into the EAE possibly affording the NHS a cost-effective intervention for the treatment of non-healing VLUs, since the incremental cost per QALY gained was less than the National Institute for Health and Care Excellence's (NICE) recommended threshold of £20,000 for affording value for money within the NHS. When the analyses were performed in the ITT population, which included other wound types and non-hard-to-heal VLUs, the incremental cost per QALY gained with the EAE was not as favourable as that seen in the EA population, but it remained <£20,000.

Conducting controlled studies in wound care are known to be notoriously difficult, partially because of unacceptable levels of inter-rater reliability,[22] and this study was no exception. Consistent monitoring of the study became challenging. Hence, there was poor or inaccurate completion of the CRFs on some occasions, and inaccurate administration of SF36. Additionally, the clinicians at the different centres interpreted the meaning of an adverse event differently and patients were managed by clinicians in the community who were not part of the clinical investigator's team at the centres. Furthermore, different centres documented resource use between the scheduled visits in different ways resulting in inconsistencies in documentation associated with unscheduled visits.

Limitations

Other limitations, in particular, should be considered when interpreting this study's findings. The study results were truncated at 24 weeks, and excluded the costs and consequences of managing patients with an unhealed ulcer beyond this period. There was, inevitably, an under-recording of the use of some health-care resources in the community, and patient fatigue at completing multiple questionnaires cannot be excluded. The analysis only considered NHS resource use and associated costs for the 'average patient' and was not stratified according to gender, comorbidities, other disease-related factors and level of clinician's skills. Patients' costs and indirect societal costs as a result of patients being absent from work were also excluded from the analysis. However, patients' mean age was >65 years, so it is unlikely that many were in employment.

Conclusion

In conclusion, the study was confounded by unwarranted variation in the provision of wound care both within and between centres. Nevertheless, the use of the EAE resulted in some improved clinical outcomes

and patient-reported outcomes for the same or less cost as standard care by 24 weeks (but not by 16 weeks). Clinicians managing VLUs may wish to consider the findings from this study when making treatment decisions. **JWC**

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