A cost analysis of a living skin equivalent in the treatment of diabetic foot ulcers
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of living skin equivalent (LSE) to treat diabetic foot ulcers (DFUs). LSE is a bioengineered tissue consisting of dermal and epidermal layers containing human keratocytes and fibroblasts.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with Type 1 or 2 diabetes, who were aged from 18 to 80 years, and had HbAlc levels of between 6 and 12% and full-thickness neuropathic ulcers (excluding the dorsum of the foot and the calcaneus). The ulcer was required to have persisted for at least 2 weeks and the postdebridement ulcer size had to be between 1 and 16 cm². All the patients were also required to have dorsalis pedis and posterior tibial pulses audible by Doppler. The exclusion criteria were clinical infection at the studied ulcer site, clinically significant lower-extremity ischaemia (as defined by an ankle/brachial index of less than 0.65), and active Charcot's disease (as determined by clinical and radiographic examination). Patients with an ulcer that was of a nondiabetic pathophysiology (e.g. rheumatoid, radiation-related, and vasculitis-related ulcers) were excluded, as were patients with significant medical conditions that would impair wound healing (liver disease, aplastic anaemia, scleroderma, malignancy, and treatment with immunosuppressive agents or steroids).

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The dates to which the effectiveness and resource use data related were not reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the Apligraf Diabetic Foot Ulcer Study, which was published in 2001 (see Other Publications of Related Interest). The authors also made some assumptions.

Link between effectiveness and cost data
The costing was performed retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations to determine the sample size were not reported. The patients were enrolled in 24 medical centres, but the method of sample selection was unclear. Of an initial sample of 227 patients allocated to the study groups, 69 were excluded as they were not eligible. Reasons for exclusion were characteristics of wound closure, abnormal blood test, and ulcer characteristics. Thus, the final sample comprised 208 patients. There were 112 patients in the intervention group and 96 in the control group. The mean age in the intervention group was 57.8 (+/- 10) years and 78.6% were men. The mean age in the control group was 55.7 (+/- 10) years and 77.1% were men.

Study design
This was a prospective, multicentre, randomised clinical trial that was conducted in 24 centres. The patients were randomised according to a computer-generated schedule, and were evaluated every month for an overall follow-up period of 6 months. Of the patients included in the initial study sample, 20% withdrew from the intervention group and 22% from the control group. Reasons for withdrawal included adverse events (AEs), loss to follow-up and withdrawal of informed consent. The assessment of the outcome was not blind.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. Several outcome measures were estimated in the primary studies. However, those relevant in the present economic evaluation were the mean number of ulcer-free months and the mean number of amputations or resections. The occurrence of AEs was recorded to calculate the use of additional resources. The two study groups were comparable at baseline in terms of their demographics, type and duration of diabetes, and ulcer size and duration. The only statistically significant difference between the two groups was related to the mean body mass index, which was 31.9 for the LSE group and 33.1 for the control group, (p=0.026). Those patients who were disqualified were not statistically different from those who remained into the study.

Effectiveness results
The mean number of LSE applications per patient was 3.9.

The mean number of ulcer-free months was 2.3 in the intervention group and 1.5 in the control group, (p=0.010).

The mean number of amputations or resections was 5.4% in the intervention group and 12.5% in the control group, (p=0.085).

The rate of AEs was 19.8% in the control group and 10.7% in the intervention group, (p=0.08).

Statistically significant differences were found with respect to severe abscess, mild/moderate diarrhoea, severe osteoemyelitis, and mild/moderate peripheral oedema.

Clinical conclusions
The effectiveness analysis showed that, compared with the standard treatment, LSE significantly increased the number of ulcer-free months among patients with DFUs. There was also a trend towards fewer AEs and amputations or resections.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used to define the benefit measures.

Estimates of effectiveness and key assumptions
It was assumed that:
if the ulcer were open at the patient's last protocol visits, then it remained open from this date to 6 months' follow-up;
if the ulcer were closed at the patient's last protocol visits, then it remained closed from this date to 6 months’ follow-up, unless an ulcer-related AE occurred during this time;

if an ulcer-related AE occurred after the patient's last visit date, the ulcer was considered open from the last visit date to 6 months’ follow-up.

**Measure of benefits used in the economic analysis**

The benefit measures used in the economic analysis were the incremental number of amputations or resections avoided, and the ulcer-free months gained with LSE relative to standard treatment. Both were derived from the effectiveness study.

**Direct costs**

Discounting was not relevant because the costs per patient were incurred during a short time. The unit costs were not analysed separately from the quantities of resources used. The health services included in the economic evaluation were study intervention (LSE and saline-moistened gauze) and economically important events such as the treatment of AEs, nonprotocol-scheduled office visits, and debridement procedures performed during office visits. Nonulcer-related AEs were included only if they were statistically significant. The cost/resource boundary adopted in the study was that of the third-party payer. Resource use was estimated from actual data evaluated alongside the clinical trial used to provide the effectiveness evidence. The costs were estimated from Medicare reimbursement rates. Average wholesale prices were used for medications and LSE treatment, and these were discounted by 20% to reflect a more accurate estimate of the actual drug and product costs. The price year was 2000.

**Statistical analysis of costs**

Standard statistical tests were conducted to compare the estimated costs. A linear regression analysis was conducted to control for the influence of factors that were statistically significant different between the study groups, such as body mass index.

**Indirect Costs**

The indirect costs were not included in the economic analysis.

**Currency**

US dollars ($).

**Sensitivity analysis**

One-way sensitivity analyses were conducted to investigate uncertainty in some baseline estimates used in the analysis. The mean number of LSE applications per patient was changed from 3.9 (reported in the trial) to 1.5 (which reflected routine practice). The authors also considered the sub-groups of patients with no evidence of Charcot's disease, and those whose ulcer lasted more or less than 2 months (considering all patients included in the study).

**Estimated benefits used in the economic analysis**

The incremental benefit of LSE relative to standard care was 0.062 in terms of amputations or resections avoided, and 0.8 in terms of ulcer-free months.

**Cost results**

The mean cost per patient was $7,366 in the intervention group and $2,020 in the control group, (p<0.001). Thus, the incremental cost associated with LSE relative to standard care was $5,346.
The regression analysis revealed that body mass index did not represent a confounding factor.

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio (ICER) was calculated to combine the costs and benefits of the study interventions.

The ICER of LSE over standard care was $86,226 when the benefit measure was the amputations or resections avoided, and $6,683 when ulcer-free months were considered. These estimates decreased by about 50% in patients with no evidence of Charcot's disease. Also, when 1.5 LSE applications (instead of 3.9) were assumed to reflect routine practice, the incremental cost of LSE per amputations or resections avoided fell to $30,403, while the incremental costs per ulcer-free month fell to $2,356.

The basic results were sensitive to ulcer duration and the number of LSE applications.

The use of median rather than mean values also had a strong impact on the estimated ICERs.

**Authors' conclusions**
The treatment of diabetic foot ulcers (DFUs) with living skin equivalent (LSE) may be cost-effective from the perspective of the third-party payer, especially among patients with no evidence of Charcot's disease.

**CRD COMMENTARY - Selection of comparators**
The authors justified their choice of the comparator. Saline-moistened gauze was selected as the basic comparator because it was considered by the American Diabetes Association to represent standard care. You should decide whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of effectiveness used the results of a published clinical trial. This trial was multicentred and randomised, thus the internal validity of the study was ensured. In addition, the basis of the analysis was intention to treat and baseline comparability was demonstrated. However, there were two potential limitations to the internal validity. First, the lack of a blind assessment of the outcome. Second, power calculations were not conducted. In addition, there was no evidence that the sample size was appropriate. The authors noted that the time horizon of the study was limited to that used in the primary study.

**Validity of estimate of measure of benefit**
The benefit measures were derived from the effectiveness analysis and were disease-specific. Thus, it could be difficult to make comparisons with the benefits of other interventions relevant to the third-party payer. The authors noted that it would have been interesting to have evaluated quality of life issues.

**Validity of estimate of costs**
The perspective adopted in the study was explicitly reported, but a detailed breakdown of the costs was not provided. Overall, there were few details of the cost categories. The unit costs and resource use were not analysed separately. However, the price year was reported, thus simplifying reflation exercises. Statistical tests were conducted on the costs and quantities, and sensitivity analyses were performed. The source of the cost data was reported. The costs were reflated to reflect the perspective adopted in the study.

**Other issues**
The authors compared their findings with those from other studies and found consistent results. In terms of the generalisability of the study results to other settings, sensitivity analyses were conducted to address such issues, and
alternative scenarios and sub-group analyses were conducted. Thus, the external validity of the analysis is high. The study referred to patients with DFUs and this was reflected in the conclusions of the analysis. The authors noted some limitations of their study.

**Implications of the study**
The study results suggested that some categories of patients may benefit more than other categories from using LSE to treat DFUs. Future research should explore a longer time horizon and routine clinical practice outcomes associated with LSE.

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**Bibliographic details**

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by CRD

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