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A Critical Review of Economic Evaluations for Diabetic Foot Ulcer (DFU) treatments in the UK

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Introduction

- Convincing and positive economic evaluation of DFU treatments is essential for wide-scale adoption in the UK via the National Institute of Clinical and Health Excellence (NICE) or within local formularies.
- Many such evaluations are routinely described as poor-quality, methodologically weak and failing on consistent grounds. Thus, many effective and cost-effective treatments are dismissed, leading to sub-optimal outcomes for both patients and the NHS.
- We conducted a targeted literature review of cost-effectiveness (CE) studies of interventions for DFU management in the UK to identify lessons for improving methodology and increasing the availability and use of economic evidence.

Methods

- Searches were conducted in MEDLINE, EMBASE, CINAHL, EconLit, Scopus and Cochrane Library and grey literature for studies from inception to April 2023. Available UK-based CE studies were included from a broad strategy including 'diabetic foot', and 'cost-effective' or 'economic evaluation' as search terms.

Results

- UK was in the top three of countries covered in the publications (Figure 1). A summary of features of the UK-based studies are shown on Table 1.
- Dressings were the most evaluated interventions (Figure 2). Majority of evaluations were industry-funded (Figure 3), took healthcare payer perspective and included mixed DFU populations.
- There were two within-trial analyses (24-26 weeks duration) (6,7), six Markov models (mostly 1 year) (1-2,4-5,9-10) and two decision trees (4 month- and 3-year durations) (3,8) (Figure 4). Utility data sources for cost-utility analyses (CUAs) are shown on Figure 5. Details of utility estimation were unclear for one model (11).
- Effectiveness outcomes were derived either directly from randomised, controlled trials (RCTs) (n=8) (2,4-9,11), meta-analysis (n=1) (10), retrospective cohort data (n=1) (3) or published literature (n=1) (2) (see Figure 6). RCTs had 54-240 participants with follow-up 12-20 weeks. Uncertainty was addressed in most evaluations via probabilistic and deterministic sensitivity analyses, mostly in favour of the interventions.
- Ulcer progression was modelled in terms of wound closure (healed/closed vs. unhealed/open), often based on a core model from non-UK sources (12). Only two other studies (1,5) modelled in terms of healing progress – ulcer size and response to treatment (improved/increased, worsened/decreased or unchanged). Although resource use vs. treatment response data was available for the latter study (5), no utility data was reported. The second UK study did not report clinical basis for the ulcer size-based health states (1).

Figure 1

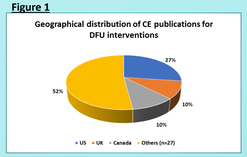

Figure 2

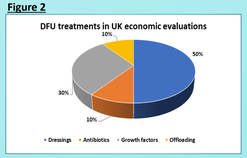

Figure 3

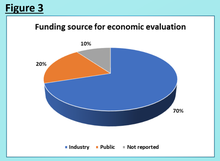

Figure 4

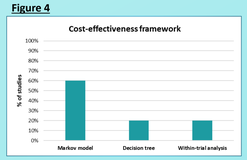

Figure 5

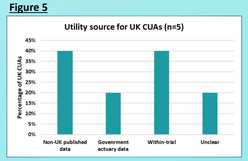

Figure 6

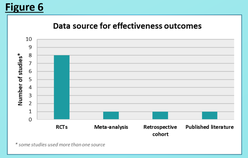

Table 1: Characteristics of UK cost-effectiveness studies for DFU management

Author10	DFU population	Comparators	Analysis type/evaluation tool/time horizon	Outcome	Utility source/values	Model health states (#; list)	Effectiveness data source	Results (base case and uncertainty	Funding
1. Guest 2021	Non-healing DFUs in secondary care	dHACM vs. SC	CUA/Markov model/ 1 year	Incremental cost per QALY	Flack 2008 data (US), derived from mixed sources (US and Swedish data) 0.465 -unhealed ulcer, 0.465 - infected ulcer, 0.60 - healed ulcer, 0.45 - amputation, 0.45 - post-amputation, and 0.465 for a recurred ulcer)	Unchanged (by ulcer size), worsened (ulcer size increased), improved (ulcer size decreased), healed (ulcer healed), infected, post-amputation, death	US RCT, 110 patients across 14 wound centres, 16-week follow-up in trial;	Adjunctive dHACM allografts afford the NHS a cost-effective intervention. DSA and PSA outputs: At a CE 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 SC alone, if expenditure on the allografts amounts to £3300, £3500, £3700, £4000, and £4300 per DFU, respectively	Industry, MAMediXGroup Inc.
2. Guest 2018	DFU > 6 months duration	Collagen dressing vs SC	CUA/Decision tree/ 4 months	Incremental cost per QALY	Flack 2008 data (US), derived from mixed sources (US and Swedish data)	NA	Retrospective cohort for SC; systematic literature review for collagen	Collagen-containing dressing plus standard care instead of standard care alone potentially affords the NHS a cost-effective (dominant) treatment for both non-healing and new DFUs, since it improves outcomes for less cost. DSA and PSA outputs: At a CE threshold of £20 000 per QALY, up to 99% of a cohort is expected to be treated cost-effectively with a collagen-containing dressing plus standard care compared to standard care alone.	Industry
3. Betts 2018 (abstract)*	All DFU	sucrose octasulfate (Urgostart) dressing vs. neutral dressing	CEA and CUA/Markov model/ 1 year	Incremental cost per QALY Incremental cost per healed wound	Based on EXPLORER RCT, values not available in abstract.	open, closed, and complicated (pre and post amputation), and deceased	Double-blind EXPLORER RCT, 240 participants (126 sucrose octasulfate vs. 114 control) in 43 hospitals across ELA and UK	UrgoStart was the dominant treatment strategy, a cost saving of £666.51 and a 0.022 QALY per patient. Using UrgoStart leads to more wounds healed at 52 weeks than a neutral dressing, 653 and 473 respectively at a cost of £4073.84 per healed wound for UrgoStart compared with £8136.19 for a neutral dressing. The use of UrgoStart also avoided 19 amputations over a year.	Not reported, may be related to a PhD thesis
4. Industry (sponsor) submission (Chris 2020/NICE EAC report)*	All DFU	Urgostart dressing vs. neutral dressing (UrgoTul)	CUA/Markov model/1 year	Incremental cost per QALY	NICE EAC report: Trial-based EXPLORER, data not available, EAC is unclear on how the sponsor estimated separate utilities for the 8 health states in the model, as this is not reported in Edmonds 2018 (EXPLORER).	From NICE EAC report: Open (pre-amputation) Complicated (pre-amputation) Closed (pre-amputation) Open (post-amputation) deceased complicated (postamputation) closed (post-amputation)	Double-blind EXPLORER RCT, as above	The EAC agreed with sponsor found UrgoStart to be cost saving for diabetic foot ulcers. UrgoUlcer was cost saving in all sensitivity analyses except for the analysis in which healing rates with UrgoStart estimated from the Explorer trial were reduced by 50%. In this scenario UrgoStart generated a modest cost increase compared to UrgoTul.	NICE assessment in response to industry sponsor (UrgoMedical) submission
5. Cutting 2017	DFU for at least 4 weeks but < 2years	Soluble Beta -Glucan (SBG) gel	CEA/Markov/12 weeks and 1 year	Percent healed, Mean weeks in a healed state Mean cost per patient Incremental cost-effectiveness ratio (ICER) = incremental cost per additional week healed	NA, CEA	Based on treatment response: no response (static), partial response (improving), complete response (healed), progressive disease (deteriorating)	Double blind RCT two-centre, placebo-controlled phase II, 54 patients, 12 weeks follow-up	The shorter healing time associated with the SBG gel treatment leads to a cost saving because fewer weeks of treatment are required to heal the wound.	Industry, Biotech Beta Glucan
6. Jeffcoate 2017	DFU on the heel	Offloading (lightweight fibreglass casts) vs. usual care	CUA/Within-trial analysis/26 weeks	Incremental cost per QALY	EQ-5D 3L trial-based. Usual care vs Intervention Baseline: 0.43 vs 0.45 12 weeks: 0.49 vs. 0.50 24 weeks: 0.54 vs. 0.52 Adjust difference 0.02(-0.03 to 0.07)	NA	Within-trial, parallel group design RCT, 309 participants in the UK, 26 weeks	Usual care dominated the intervention, that is, had lower costs and more QALY gains under the base case. The probability of the intervention being cost-effective at a societal willingness-to-pay threshold of £20,000 was estimated at 5%.	NIHR HTA programme
7. Jeffcoate 2009	DFU present for at least 6 weeks	Dressings: non-adherent preparation (N-A) vs. hvadine vs. Aquacel	CEA/Within-trial analysis/24 weeks	Cost per healed ulcer, cost per ulcer-free day	NA	NA	Within-trial, observer blind, multicentre RCT, 229 evaluable patients, 24 weeks	Statistically significant difference in the cost associated with the provision of dressings (mean cost per patient: N-A £14.85, hvadine £427.48, Aquacel £403.60). The higher cost of Aquacel was not offset by the fewer dressings required. There was no difference in measures of either generic or condition-specific measures of quality of life	NIHR HTA programme
8. Jansen 2009	Patients with DFU infections	Antibiotics: ertapenem vs. piperacillin/tazobactam	CUA/decision tree/3 years	Cost per QALY saved	Government actuary data for an average patient	NA	Double -blind RCT SIDESTEP, 586 patients	Ertapenem cost-saving and possibly dominant over piperacillin/tazobactam	Industry - Merck and Co
9. Ghatnekar 2002	non-superficial (neuropathic)DFUs	Promogran dressing + GWC vs. GWC alone	CEA/Markov/1 year	Cost per ulcer-free day	NA, CEA	Healed ulcer (Wagner grade 0), Uninfected ulcer (Wagner grade II), Infected ulcer (Wagner grade III), Gangrene (Wagner grade IV), healed ulcer with history of amputation (grade 0), deceased	RCT 276 patients from 11 centres in the USA, 12 weeks.	Promogran +GWC may be cost-effective, perhaps even cost-saving under a wide variety of assumptions via DSA	Industry - Johnson and Johnson
10. Ghatnekar 2001	non-superficial DFUs	Becaplermin gel + GWC vs. GWC alone	CEA/Markov/1 year	Cost per ulcer-free month gained	NA	Healed ulcer (Wagner grade 0), Uninfected ulcer (Wagner grade II), Infected ulcer (Wagner grade III), Gangrene (Wagner grade IV), healed ulcer with history of amputation (grade 0), deceased	Meta-analysis of clinical trials involving 440 patients	Becaplermin may be cost-effective, perhaps even cost-saving; deterministic and scenario analysis	Johnson Pharmaceutical Research Institute

*Some details of model inputs and assumptions reported in Betts 2018 abstract and sponsor submission (via EAC report) are similar.

CEA: cost-effectiveness analysis; CUA: cost-utility analysis; dHACM: adjunctive dehydrated human amnion/chorion membrane allograft; DSA: Deterministic sensitivity analysis; GWC: Good wound care; SC, standard care; HTA: Health Technology Assessment; NICE: National Institute for Health and Care Excellence; NIHR: National Institute of Health and Care Research

Discussion

- Few UK-based economic evaluations exist covering only a small set of recommended interventions. Formal economic models are not always used but where they exist, are based on seemingly appropriate Markov modelling and generally meet most economic evaluation principles.
- Like non-UK literature, most UK-based models ignore the trajectory between 'not healed' and 'healed' – which is especially important when trials are short, as this may systematically undervalue benefit of treatments. Representative utility data was lacking and where available, not always consistent across health states.
- Although good clinical data is emerging, the evidence base to support modelling is still challenging, with short trials, mainly sponsored by industry, leading to doubts from decision-makers about impartiality and, paucity of network comparisons.

Conclusions

Lack of CE data, inconsistency and intrinsic weaknesses of models used, mean that economic evaluation methods can be improved, to effectively incorporate costs and benefits of any DFU wound care intervention, thereby enhancing optimal decision-making for affected patients.

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