Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration

Bradbury, A; EVRA Trial Investigators

DOI:
10.1002/bjs.11082

Document Version
Peer reviewed version

Citation for published version (Harvard):
Bradbury, A & EVRA Trial Investigators 2019, 'Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration', *British Journal of Surgery*, vol. 106, no. 5, pp. 555-562. https://doi.org/10.1002/bjs.11082

Cost-effectiveness analysis of a randomized clinical trial of early *versus* deferred endovenous ablation of superficial venous reflux in patients with venous ulceration

D. M. Epstein[1], M. S. Gohel[2,3], F. Heatley[3], X. Liu[4], A. Bradbury[6], R. Bulbulia[7,8,9], N. Cullum[10], I. Nyamekye[11], K. R. Poskitt[6], S. Renton[5], J. Warwick[3,12] and A. H. Davies[2], on behalf of the EVRA trial investigators*

[1]University of Granada, Granada, Spain, and [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, [3]Department of Surgery and Cancer and [4]Imperial Clinical Trials Unit, Imperial College London, and[5]North West London Hospitals NHS Trust, London, [6]College of Medical and Dental Sciences, University of Birmingham, Birmingham, [7]Gloucestershire Hospitals NHS Foundation Trust, ???, [8]Medical Research Council Population Health Research Unit and [9]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, [10]University of Manchester, Manchester, [11]Worcestershire Acute Hospitals NHS Trust, ???, and [12] Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Warwick, UK

Correspondence to: Professor A. H. Davies, Academic Section of Vascular Surgery, 4 East, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK (e-mail: a.h.davies@imperial.ac.uk)

Presented to the Charing Cross International Symposium, London, UK, April 2018

Background: Treatment of superficial venous reflux in addition to compression therapy accelerates venous leg ulcer healing and reduces ulcer recurrence. The aim of this study was to evaluate the costs and cost-effectiveness of early *versus* delayed endovenous treatment of patients with venous leg ulcers.

Methods: This was a within-trial cost-utility analysis with a 1-year time horizon using data from the EVRA (Early Venous Reflux Ablation) trial. The study compared early *versus* deferred endovenous ablation for superficial venous truncal reflux in patients with a venous leg ulcer. The outcome measure was the cost per quality-adjusted life-year (QALY) over 1 year. Sensitivity analyses were conducted with alternative methods of handling missing data, alternative preference weights for health-related quality of life, and per protocol.

Comment [A1]: Au: Does this asterisk relate to anything? Or should it be deleted?

Comment [MJM2]: This refers to the full list of EVRA investigators, which can be found in the Collaborators section, page 11

Comment [A3]: Au: For **all affiliations**, BJS style is to have a department/unit name. Please add where missing.

Comment [MJM4]: Affiliations appear to have been altered during the proofing process, please see attached document 'Affiliations' (Department/unit have been added where applicable):

Comment [A5]: Au: As well as department(s) please add location (town/city) (?Gloucester).

Comment [MJM6]: This has been added- see attached document 'Affiliations'

Comment [A7]: Au: As well as department(s) please add location (town/city) (?Worcester).

Comment [MJM8]: This has been added- see attached document 'Affiliations'

Comment [A9]: Au: Has any abstract been published in a medical/surgical journal?

Comment [MJM10]: No

Results: After early intervention, the mean(SE) cost was higher (difference in cost per patient £163(SE 318; €184, SE 358)) and early intervention was associated with more QALYs at 1 year (mean(SE) difference 0.041(0.017). The incremental cost-effectiveness ratio (ICER) was £3976 (€4482) per QALY. There was an 89 per cent probability that early venous intervention is cost-effective at a threshold of £20 000 (€22 546)/QALY. Sensitivity analyses produced similar results, confirming that early treatment of superficial reflux is highly likely to be cost-effective.

Conclusion: Early treatment of superficial reflux is highly likely to be cost-effective in patients with venous leg ulcers over 1 year. Further studies are required to assess the impact in the long term. Registration number: ISRCTN02335796 (http://www.isrctn.com).

Comment [A11]: Au: Is this s.e.m. (standard error of the mean)?

Comment [JM12]: Yes this refers to the S.E.M

Deleted: s.e.

Comment [A13]: Au: BJS style is to use euro values throughout papers. Please make currency conversions throughout the paper where highlighted.

Comment [JM14]: This has been amended in the text, and the date of conversion is cited in the methods and the footnote of Table 2

Deleted: s.e.

Comment [A15]: Au: In an instance such as this, where the euro value may not be such a round figure, it is acceptable to give the sterling value in brackets after the euro value for clarification.

+A: Introduction

Leg ulcers are a major burden to healthcare providers and represent a source of discomfort and social isolation to patients. In 70 per cent of cases, the underlying cause of leg ulceration is venous disease, sometimes evident as varicose veins but often undetectable by visual examination alone. One UK study[1] found a point prevalence of 1.5 cases of complex wounds per 1000 population, of which 28 per cent were leg ulcers. It should also be noted that, with an ageing and increasingly obese population, the incidence and prevalence of venous ulceration are both likely to increase. Treatment of venous leg ulcers has been estimated to cost £941 (€1061) million per annum in the UK[2].

Venous leg ulcers are characterized by protracted healing. Some patients may never heal, and those who do are at high risk of recurrence[3]. The mainstay of therapy for venous ulceration is compression therapy using bandages or stockings[3]. Current guidelines[4] recommend treatment of superficial venous reflux using endovenous ablation techniques (ultrasound-guided foam sclerotherapy (UGFS), endovenous laser or radiofrequency ablation), but many practitioners delay intervention until the ulcer has healed. More recently,

the EVRA trial[5] found that early endovenous ablation significantly reduced time to ulcer healing. This study presents an analysis of the cost-effectiveness of early *versus* delayed endovenous treatment, based on the EVRA trial data to 1 year. The protocol is available at http://www.imperial.ac.uk/media/imperial-college/medicine/surgery-cancer/clinical-trials/EVRA-Protocol-06.04.2017.pdf.

+A: Methods

This study was a within-trial cost-utility analysis comparing early *versus* deferred endovenous ablation for truncal superficial venous reflux in patients with venous ulceration, within a 1-year time horizon. The primary difference between the two strategies was the timing of endovenous ablation: patients in the early intervention arm were treated within 2 weeks of randomization, whereas those randomized to deferred intervention arm underwent endovenous ablation once the ulcer had healed, or after 6 months. All patients were treated with compression therapy in accordance with local standard practice.

Patients in the EVRA trial were aged at least 18 years, presented with a venous leg ulcer of between 6 weeks' and 6 months' duration, ankle : brachial pressure index 0.8 or above, able to tolerate compression therapy, and had superficial venous reflux requiring endovenous ablation. Patients were recruited from 20 vascular centres in the UK, and endovenous interventions were performed in outpatient clinic, operating room or treatment room settings (as per local practice). Most leg ulcer management takes place in a community care setting (community clinics or patient's home) or in primary care clinics.

+B: Outcome assessment

The cost analyses were performed from the perspective of the UK National Health Service and Personal Social Services in accordance with UK methods guidance[6]. The price year was 2015–2016, and currency conversion was calculated at 2016 purchasing power parity[7]. No

discounting was applied as the follow-up was 1 year. The study was reported according to guidelines for economic evaluation[8].

The primary health outcome in the cost-effectiveness analysis was QALYs at 1 year. Participants in the EVRA study were asked to complete the EQ-5D-5L™ (EuroQol Group, Rotterdam, the Netherlands) questionnaire at baseline, 6 weeks, 6 months and 1 year after randomization. EQ-5D™ is an instrument to measure generic health-related quality of life and has been validated in this population[9]. To convert patient responses into a health utility scale (where 1 represents perfect health and 0 a state equivalent to death), the base-case economic analysis used the crosswalk tariff, as recommended by the UK National Institute for Health and Care Excellence (NICE) in August 2017[10]. This algorithm maps the EQ-5D™ five-level responses to three-level responses, and then values those health states using the original EQ-5D™ three-level tariff developed by Dolan[11]. As a sensitivity analysis, an alternative health utility tariff developed by Devlin and colleagues[12] for the EQ-5D-5L™ was used. Quality-adjusted life-years (QALYs) were estimated for each participant to 1 year as the area under the curve of EQ-5D-5L™ index values.

Comment [A16]: Au: Please clarify to which population you are referring.

Comment [MJM17]: This refers to the EVRA Trial participants i.e. leg ulcer patients. The inclusion criteria is summarised on page 3, paragraph 3

Comment [A18]: Au: Current reference 10 is not a NICE reference. Please advise.

Comment [JM19]: This reference should be moved to the line above, after "crosstalk tariff"

Resource use items were recorded for each participant at monthly follow-up telephone calls. The total cost per patient included the following resource items for vein or ulcer-related reasons: trial endovenous ablation procedures, dressings and bandaging consumables for wound healing, compression therapy to prevent recurrence after wound healing, visits to or from a district nurse, visits to or from a general practitioner, visits to a primary care practice nurse, inpatient and day-case hospital admissions, outpatient visits, use of antiplatelet and anticoagulant medicines, physiotherapy and occupational therapy, auxiliary nursing (home care) and personal care (home help).

To obtain a precise estimate of the effect of the intervention on healthcare use, and avoid statistical noise, the study aimed to include only resource use related to the ulcer. Researchers recorded the reason for the use of each item of healthcare as free text. Ulcer-related activity was considered to include: ulcer care, skin care, leg care, venous procedures, angiography, infection, rehabilitation, deep vein thrombosis and related keywords. Non-ulcer-related healthcare, as well as out-of-pocket expenses and time lost from usual activities, were tabulated but not included in total cost per patient. Costs were estimated by multiplying resource use by unit costs obtained from published literature[13], national unit cost databases for the UK[14–18], and manufacturers' list prices for catheters and other disposable items (*Table S1*, supporting information). Currency conversions (£GBP/€EURO) were calculated to the rate applicable at the time of conversion (£1 = €1.1273; 20 September 2018).

+B: Handling of missing data

There was a small amount of missing data in the trial owing to patient withdrawal and other reasons. Costs and EQ-5D-5L™ index were set to zero after the date of death. The base-case cost-effectiveness analysis used complete cases in an intention-to-treat analysis. A participant was considered a complete case if they completed all the EQ-5D™ questions at baseline, 6 weeks, 6 months and 1 year, and did not withdraw from the study before 12 months.

As a sensitivity analysis, multiple imputation using chained equations was employed to impute the remaining missing data by regression under the assumption of 'missingness at random' (*Appendix S1*, supporting information)[19]. Missing costs in each treatment group were considered predictable from observed data, plus or minus a random error. For those lost to follow-up, costs for each participant were imputed at each month after the time of withdrawal, and the EQ-5D-5L™ index was imputed at 6 weeks, 6 months and 1 year if these data were missing. Ten imputed data sets were created and analysed using Rubin's rules (this was sufficient to give stable results allowing for Monte Carlo error)[19].

+B: Handling of protocol deviations

In the clinical study, protocol deviations were seen in 117 patients (59 and 58 in early and deferred groups respectively), the majority of which were late or missed follow-up appointments (40 of 59 patients in the early intervention group and 34 of 58 in the deferred intervention group)[5]. A sensitivity analysis was carried out excluding these patients.

+B: Cost-effectiveness analysis

The difference in mean total cost and mean total QALY per participant between the treatment groups was estimated using regression methods, including baseline EQ-5D-5L™ in the QALY regression Monte Carlo resamples[20].

The incremental cost-effectiveness ratio (ICER) was calculated. An intervention may be considered cost-effective when its ICER is less than the threshold set by health policy decision-makers[21]. In the UK, the cost-effectiveness threshold is in the range £20 000 - £30 000 (€22 546 - €33819)/per QALY[6].

Deleted: £20 000

The probability that early ablation was more cost-effective than deferred ablation was estimated at different cost-effectiveness thresholds. The base-case analysis used bootstrapping, with 1000 Monte Carlo resamples with replacement. The bootstrap was used only for the analysis of complete cases, as bootstrap combined with multiple imputation can be very complex[22]. As an alternative method in sensitivity analyses, standard errors and correlation between total costs and QALYs were estimated assuming bivariable normality (*Appendix S1*, supporting information).

+B: Sensitivity analyses

Five models were estimated: model 1, the base case – complete cases with bootstrap standard errors and crosswalk EQ-5D-5L™ tariff; model 2, complete case with bivariable normal standard errors and crosswalk EQ-5D-5L™ tariff; model 3, multiple imputation with

bivariable normal standard errors and crosswalk EQ-5D-5L™ tariff; model 4, complete case with bootstrap standard errors and EQ-5D-5L™ tariff estimated according to Devlin *et al.*[12]; model 5, per-protocol analysis (this was the same as model 1, but excluded patients with a protocol deviation).

+A: Results

Baseline characteristics for the study groups, described in full elsewhere[5], were evenly matched across the arms of the EVRA trial (*Table 1*).

+B: Resource use and total cost analysis

The total mean cost per patient over 1 year, excluding patients who did not complete follow-up to 12 months are shown in *Table S2* (supporting information). Participants who died during the year were included in these data, with costs set to zero after the date of death. For the purposes of this analysis, 419 patients completed 12 months of the study or died, 211 in the deferred ablation group (226 randomized, less 15 withdrawals or lost to follow-up) *versus* 208 in the early group (224 randomized, less 16 withdrawals or lost to follow-up).

The total mean (SD) cost per patient over 1 year was similar in the two study groups: £2514 (SD 2770; €2834, SD 3123) for 208 patients randomized to early ablation *versus* £2516 (SD 3242; €2836, SD 3655) for 211 patients in the deferred group *(Fig.1)*.

Deleted: s.d.

The early ablation group incurred a greater initial cost due to the allocated endovenous ablation procedure. Although the study protocol recommended that participants in the deferred group should have an ablation procedure once the ulcer had healed, many did not receive this treatment. At 1 year, 55 of the 226 patients in the deferred arm had received no intervention, compared with seven of 224 in the early arm (*Table S2*, supporting information). Of the 55 with no intervention in the deferred arm, 35 subjects completed the study, of whom 26 had a healed ulcer after 1 year. Reasons for not performing ablation

procedures in participants randomized to deferred ablation were unclear, but both participant and clinician preferences are likely to have played a role. The greater initial costs in the early ablation group were compensated by lower costs of district nurse home visits due to quicker wound healing (*Table S2*, supporting information). Other resource use was similar in the two groups.

+B: Cost-effectiveness analysis

Table 2 shows the results of the cost and QALY regressions for the cost-effectiveness analyses. In the complete case analysis (model 1 or base case), 106 of 450 patients (23.6 per cent) had incomplete EQ-5D™ or cost data over the year, and thus 344 (76.4 per cent) were included in this analysis. The proportion of missing data was similar in early (22.8 per cent) and deferred (24.3 per cent) intervention arms. Greater costs and QALYs were recorded for patients in the early intervention group, with a mean (SE) difference in cost per patient of £163(SE 318; €184, SE 358), a difference in QALYs at 1 year of 0.041(0.017). The ICER was £3976(€4482)/QALY. There was an 89 per cent probability that early endovenous intervention is cost-effective at a threshold of £20 000(€22 546)/QALY (*Fig. 2*). When bivariable normality was assumed to estimate standard errors, the results were similar (model 2). There was a significant negative correlation between costs and QALYs, indicating that participants with a worse quality of life were also those who tended to incur greater healthcare costs (correlation –0.294, $P < 0.001$).

In model 3, missing data were imputed. All 450 randomized patients were included in this model. The mean(SE) difference in total cost was −£72(SE 290; -€81, SE 327) (early intervention was cost-saving) and the mean difference in QALYs over 1 year was 0.058(0.018) (greater in the early intervention group), with a greater than 99 per cent probability of being cost-effective at a threshold of £20 000(€22 546)/QALY. The use of alternative tariff values for the EQ-5D-5L™ (model 4) resulted in a slightly smaller

Deleted: 23

Comment [A20]: Au: BJS style is to give percentage values derived from samples ≥100 to one decimal place. Please amend accordingly.

Comment [JM21]: This should read… in early (22.8 per cent) and deferred (24.3 per cent) intervention arms. Text has been amended

Deleted: 24

Deleted: s.e.

Deleted: £163(318)

Comment [A22]: Au: Note that Fig. 1 has not been cited in the text.

Comment [JM23]: This has now been cited on page 7

Deleted: s.e.

difference in QALYs between the treatment groups than for the base case, but the ICER was similar.

The per-protocol analysis was carried out using the same approach as model 1, but excluding patients with protocol deviations. Protocol deviations were seen in 117 patients (59 and 58 in early and deferred groups respectively), of whom 71 had complete data. This left 273 patients for analysis (344 with complete data at 12 months, less 71 protocol deviations). The ICER was £8679 (€9784)/QALY (model 5).

+A: Discussion

This study has demonstrated that early endovenous intervention for superficial venous reflux is highly likely to be a cost-effective treatment for patients with a venous leg ulcer. The complete case analysis showed little difference in total mean cost per patient over 1 year between the early and deferred ablation strategies (mean(SE) difference £163(SE 318; €184, SE 358), $P = 0.607$). The greater initial mean cost of the early intervention strategy was mostly offset by the reduced cost of treating unhealed leg ulcers. There was, however, a substantial and statistically significant gain in QALYs over 1 year, with a mean difference of 0.041(0.017) in favour of early intervention ($P = 0.017$). The ICER for early intervention at one year is therefore £3976 (€4482)/ QALY.

From the complete case analysis, the probability of cost-effectiveness was 89 per cent using UK thresholds. Therefore, there is little chance that delayed ablation would offer greater net benefit at conventional thresholds of willingness-to-pay. Sensitivity analyses using alternative statistical models gave qualitatively similar results.

This economic analysis compared early *versus* delayed endovenous ablation for venous leg ulcers. Tricco and colleagues[23] reviewed studies that evaluated the costs and benefits of alternative medical therapeutic strategies. [1][2] It was notable that the difference in QALYs

Deleted: s.e.

Deleted: £163(318)

Comment [A24]: Au: What do these numbers denote? Should they simply be deleted?

Comment [JM25]: Yes please delete

between the strategies reported by these studies was generally small. For example, the largest QALY gain observed in any previous study was in VenUS I (difference of 0.02 QALYs for four-layer bandages *versus* short stretch bandages)[24]. The difference in QALYs between early and delayed ablation found in the present study was much larger: 0.041 over 1 year. This study did not consider whether cost-effectiveness might vary across subgroups. The EVRA trial[5] assessed the clinical benefit across several predefined subgroups and detected some interesting trends for potentially greater benefits for early intervention, such as in patients with longer ulcer duration. However, the clinical study was not powered to detect differences across subgroups, and furthermore patients with ulcer duration more than 6 months were excluded. Thus, further studies are required to confirm these findings and assess whether there may be greater cost-effectiveness in these populations, or with specific endovenous interventions such as UGFS.

The benefits of early endovenous ablation in the present study arose because of faster ulcer healing in the first 12 months after randomization. The long-term benefits and costs will also depend on whether the treatments can reduce ulcer recurrence rates. Evidence from other randomized trials suggests that surgical intervention for superficial reflux reduces recurrence, compared with compression therapy alone[25]. If early endovenous ablation can impact on both healing and recurrence, it could be even more cost-effective over the patient's lifetime[26]. In the EVRA study, there were insufficient recurrences over 1 year to permit meaningful comparison. Evaluation of ulcer recurrence in the EVRA population is ongoing.

This study showed that early endovenous ablation had a significant and substantial impact on a patient's quality of life, with no material increase in the burden of cost on payers. Hence this strategy is very likely to be cost-effective. The resources needed for implementation of an early intervention strategy will depend on the individual setting[3], but any effective wound management strategy would require close multidisciplinary teamwork

between primary care and specialist vascular centres, in order to conduct prompt assessment of promptly assess patients with a venous leg ulcer, referral and treatment of superficial venous reflux.

+A: Collaborators

Comment [A26]: TYPESETTER: PLEASE SET COLLABORATORS TEXT IN SMALLER TYPESIZE.

The EVRA team thanks the National Health Service trusts and participating principal investigators and their colleagues for recruiting and monitoring trial participants. These include (in alphabetical order of participating hospitals followed by the local principal investigators and their colleagues): Addenbrooke's Hospital, Cambridge – M. S. Gohel, D. Read, S. Hargreaves, K. Dhillon, M. Anwar, A. Liddle, H. Brown; Bradford Royal Infirmary, Bradford – K. Mercer, F. Gill, A. Liu, W. Jepson, A. Wormwell, H. Rafferty; Charing Cross and St Mary's Hospitals, London – A. H. Davies, K. Dhillon, R. Kaur, E. Solomon, K. Sritharan, R. Velineni, C. S. Lim, A. Busuttil, R. Bootun, C. Bicknell, M. Jenkins, T. Lane, E. Serjeant; Cheltenham General Hospital – K. Poskitt, R. Bulbulia, J. Waldron, G. Wolfrey, F. Slim, C. Davies, L. Emerson, M. Grasty, M. Whyman, C. Wakeley, A. Cooper, J. Clapp, N. Hogg, J. Howard, J. Dyer, S. Lyes, D. Teemul, K. Harvey, M. Pride, A. Kindon, H. Price, L. Flemming, G. Birch, H. Holmes, J. Weston; Cumberland Infirmary, Carlisle – T. Joseph, R. Eiffel, T. Ojimba, T. Wilson, A. Hodgson, L. Robinson, J. Todhunter, D. Heagarty, A. Mckeane, R. McCarthy; Derriford Hospital, Plymouth – J. Barwell, C. Northcott, A. Elstone, C. West; Frimley Park Hospital, Frimley – P. Chong, D. Gerrard, A. Croucher, S. Levy, C. Martin, T. Craig; Hull Royal Infirmary, Hull – D. Carradice, A. Firth, E. Clarke, A. Oswald, J. Sinclair, I. Chetter, J. El-Sheikha, S. Nandhra, C. Leung; Leeds General Infirmary, Leeds – J. Scott, N. Dewhirst, J. Woods, D. Russell, R. Darwood, M. Troxler, J. Thackeray, D. Bell, D. Watson, L. Williamson; Musgrove Park Hospital, Taunton – J. Coulston, P. Eyers, K. Darvall, I. Hunter, A. Stewart, A. Moss, J. Rewbury, C. Adams, L. Vickery, L. Foote, H. Durman, F. Venn, P. Hill, K. James, F.Luxton, D. Greenwell, K. Roberts, S. Mitchell, M. Tate, H. Mills; New Cross Hospital, Wolverhampton – A. Garnham, S. Hobbs, D. McIntosh, M. Green, K. Collins, J. Rankin, P. Poulton, V. Isgar; Northwick Park Hospital, Harrow – S. Renton, K. Dhillon, M. Trivedi, M. Kafeza, S. Parsapour, H. Moore, M. Najem, S. Connarty, H. Albon, C. Lloyd, J. Trant; Queen Elizabeth Hospital, Birmingham – R. Vohra, J. McCormack, J. Marshall, V. Hardy, R. Rogoveanu, W. Goff; Russell's Hall Hospital, Dudley – A. Garnham, R. Gidda, S.Merotra, S. Shiralkar, A. Jayatunga, R. Pathak, A. Rehman, K. Randhawa, J. Lewis, S. Fullwood, S. Jennings, S. Cole, M. Wall; Salisbury District Hospital, Salisbury – C. Ranaboldo, S. Hulin, C. Clarke, R. Fennelly, R. Cooper, R. Boyes, C. Draper, L. Harris, D. Mead; Solihull Hospital, Solihull – A. Bradbury, L. Kelly, G. Bate, H. Davies, M. Popplewell, M. Claridge, M. Gannon, H. Khaira, M. Scriven, T. Wilmink, D. Adam, H. Nasr; Northern General Hospital, Sheffield – D. Dodd, S. Nawaz, J. Humphreys, M. Barnes, J. Sorrell, D. Swift, P. Phillips, H. Trender, N. Fenwick; Royal Bournemouth General Hospital, Bournemouth – D. Rittoo, S. Baker, R. Mitchell, S. Andrews, S. Williams, J. Stephenson; Worcester Royal Hospital – I. Nyamekye, S. Holloway, W. Hayes, J. Day, C. Clayton, D. Harding; York Hospital, York – A. Thompson, A. Gibson, Z. Murphy, T. Smith.

+A: Acknowledgements

This paper reports the results of a preregistered study, which can be accessed at the ISRCTN registry (http://www.isrctn.com/ISRCTN02335796).

All data requests should be submitted to the corresponding author for consideration. Access to available anonymized data may be granted following review and appropriate agreements being in place.

This project is funded by the National Institute for Health Research Health Technology Assessment programme (project number 11/129/197).

The authors also thank members of the two oversight committees for their support and guidance: Trial Steering Committee – J. Brittenden (Chair); R. J. Winterborn (Consultant Vascular Surgeon), A. Nelson (Head of School and Professor of Wound Healing), R. Haynes (Research Fellow and Honorary Consultant Nephrologist) and B. Ley-Greaves, who provided invaluable input and advice as the independent lay member over the course of the study; Data Monitoring Committee – G. Stansby (Chair, Professor of Vascular Surgery), F. Smith (Professor of Vascular Surgery and Surgical Education), M. Flather (Professor of Medicine – Clinical Trials) and I. Nunney (Medical Statistician).

Disclosure: The authors declare no conflict of interest.

Comment [A27]: Au: Please confirm that this statement is correct.

Comment [JM28]: NIHR HTA Funding only, declared above

+A: References

1 <EPATH>Cullum N, Buckley H, Dumville J, Hall J, Lamb K, Madden M *et al. Wounds Research for Patient Benefit: a 5-Year Programme of Research*. NIHR Journals Library No. 413. Programme Grants for Applied Research; 2016. https://www.ncbi.nlm.nih.gov/books/NBK379923/ [accessed ???].

2 Guest JF, Ayoub N, McIlwraith T, Uchegbu I, Gerrish A, Weidlich D *et al.* Health economic burden that wounds impose on the National Health Service in the UK. *BMJ Open* 2015; **5**: e009283.

3 Franks PJ, Barker J, Collier M, Gethin G, Haesler E, Jawien A *et al.* Management of patients with venous leg ulcers: challenges and current best practice. *J Wound Care* 2016; **25**(Suppl 6): S1–S67.

4 <EPATH>National Institute for Health and Care Excellence (NICE). *Varicose Veins: Diagnosis and Management.* Clinical Guideline CG168; 2013. https://www.nice.org.uk/guidance/cg168 [accessed ???].

Comment [A29]: Au: Please provide date on which this site was last accessed.

Comment [JM30]: 01 September 2018

Comment [A31]: Au: Please provide date on which this site was last accessed.

Comment [JM32]: 01 September 2018

5 Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N *et al.*; EVRA Trial Investigators. A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med* 2018; **378**: 2105–2114.

6 <B>National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal 2013. NICE Process and Methods Guides*. NICE: London, 2013.

7 <EPATH>Organisation for Economic Co-operation and Development (OECD). *EUROSTAT-OECD. Methodological Manual on Purchasing Power Parities (PPPs)*; 2012. http://www.oecd.org/sdd/prices-ppp/eurostat-oecdmethodologicalmanualonpurchasingpowerparitiesppps.htm [accessed ???].

8 Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D *et al.*; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Int J Technol Assess Health Care* 2013; **29**: 117–122.

9 Iglesias CP, Birks Y, Nelson EA, Scanlon E, Cullum NA. Quality of life of people with venous leg ulcers: a comparison of the discriminative and responsive characteristics of two generic and a disease specific instruments. *Qual Life Res* 2005; **14**: 1705–1718.

10 van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D *et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**: 708–715.

11 Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; **35**: 1095–1108.

12 Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018; **27**: 7–22.

13 Brittenden J, Cotton SC, Elders A, Tassie E, Scotland G, Ramsay CR *et al.* Clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation and surgery for varicose veins: results from the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) randomised controlled trial. *Health Technol Assess* 2015; **19**: 1–342.

14 <B>Joint Formulary Committee, British National Formulary. *BNF 73*. BNF Publications: London, 2017.

15 <EPATH>Curtis L, Burns A. *Unit Costs of Health and Social Care 2015*. https://www.pssru.ac.uk/pub/uc/uc2015/full.pdf [accessed 5 December 2018].

16 <EPATH>Curtis L, Burns A. *Unit Costs of Health and Social Care 2016*. https://www.pssru.ac.uk/pub/uc/uc2016/full.pdf?uc=2016-full [accessed 5 December 2018].

17 <EPATH>NHS Supply Chain. *Advanced Wound Care*. *Dressings Price List*; 2017. https://www.supplychain.nhs.uk/product-news/contract-launch-briefs/contract-information/advanced-wound-care [accessed ???].

Comment [A33]: Au: Please provide date on which this site was last accessed.

Comment [JM34]: 01 September 2018

Comment [A35]: Au: OK to use this URL (found by copy-editor)?

Comment [JM36]: Yes this is ok

Comment [A37]: Au: Query as above.

Comment [JM38]: Yes this is ok

Comment [A39]: Au: Please provide date on which this site was last accessed.

Comment [JM40]: This website is restricted access to authorised personnel only (Accessed 11/04/2017)

18 <EPATH>Department of Health and Social Care. *NHS Reference Costs 2015 to 2016*; 2016. https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [accessed ???].

19 Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014; **32**: 1157–1170.

20 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005; **14**: 487–496.

21 Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness – the curious resilience of the $50 000-per-QALY threshold. *N Engl J Med* 2014; **371**: 796–797.

22 Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Stat Med* 2018; **37**: 2252–2266.

23 Tricco AC, Cogo E, Isaranuwatchai W, Khan PA, Sanmugalingham G, Antony J *et al.* A systematic review of cost-effectiveness analyses of complex wound interventions reveals optimal treatments for specific wound types. *BMC Med* 2015; **13**: 90.

24 Iglesias CP, Nelson EA, Cullum N, Torgerson DJ; VenUS I collaborators. Economic analysis of VenUS I, a randomized trial of two bandages for treating venous leg ulcers. *Br J Surg* 2004; **91**: 1300–1306.

25 Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ *et al.* Long term results of compression therapy alone *versus* compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. *BMJ* 2007; **335**: 83.

26 Epstein D, Gohel M, Heatley F, Davies AH. Cost-effectiveness of treatments for superficial venous reflux in patients with chronic venous ulceration. *BJS Open* 2018; **2**: 203–212.

Comment [A41]: Au: Please provide date on which this site was last accessed.

Comment [JM42]: 01 September 2018

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article

<TYPESETTER: PLEASE FOLLOW MARK-UPS OF FIGS 1 & 2>

Fig. 1 Costs of early and deferred strategies for treatment of venous leg ulcers over 1 year

Mean National Health Service and personal social services costs for early *versus* deferred strategies for patients with complete data on costs.

Fig. 2 Cost-effectiveness acceptability curves for models 1–5

Model 1, complete case; model 2, complete case using bivariable normal model; model 3, multiple imputation; model 4, alternative EQ-5D-5L™ tariff; model 5, per-protocol. QALY, quality-adjusted life-year,

Comment [A43]: Au: Please provide new Fig. 1 with costs in euros.
NB: This figure is currently not cited in the text. Please indicate clearly where it should go.

Comment [JM44]: This has now been cited on page 7.
New Figure 1 attached as separate document

Comment [A45]: Au: Please provide new Fig. 2 with euros (€)/QALY (not GBP).

Comment [JM46]: Figure 2 has been amended (attached as separate document)

Table 1 Baseline characteristics of trial participants			
	Early intervention (*n* = 224)	**Deferred intervention (*n* = 226)**	**Total (*n* = 450)**
Age (years)*	67.0(15.5)	68.9(14.0)	68.0(14.8)
Height (cm)*	171.9(11.1)	170.5(10.8)	171.2(11.0)
Weight (kg)*	89.5(25.6)	88.8(24.1)	89.1(24.9)
BMI (kg/m^2)*	30.1(7.8)	30.4(7.4)	30.3(7.6)
Sex			
F	97 (43.3)	106 (46.9)	203 (45.1)
M	127 (56.7)	120 (53.1)	247 (54.9)
Smoking			
Current	23 (10.3)	19 (8.4)	42 (9.3)
Former	86 (38.4)	101 (44.7)	187 (41.6)
Never	115 (51.3)	106 (46.9)	221 (49.1)
Ethnicity			
White	206 (92.0)	208 (92.0)	414 (92.0)
Mixed	1 (0.4)	0 (0)	1 (0.2)
Asian	11 (4.9)	12 (5.3)	23 (5.1)
Black	3 (1.3)	5 (2.2)	8 (1.8)
Other	3 (1.3)	1 (0.4)	4 (0.9)
EQ-5D™			
Health state score	70.2(17.7)	70.1(17.1)	70.2(17.4)
Index value	0.7(0.2)	0.7(0.2)	0.7(0.2)
SF-36*			
Physical function	37.3(12.0)	37.5(12.5)	37.4(12.2)
Role physical	39.0(12.2)	39.7(12.1)	39.4(12.2)
Body pain	41.3(11.1)	41.6(11.9)	41.4(11.5)
General health	45.8(9.2)	46.0(9.8)	45.8(9.5)
Vitality	48.2(10.2)	47.8(10.6)	48.0(10.4)
Social functioning	42.6(12.4)	42.4(13.5)	42.5(13.0)
Role emotional	42.7(13.8)	43.7(13.6)	43.2(13.7)
Mental health	49.2(10.3)	49.3(10.7)	49.2(10.5)
Physical component summary	38.5(9.9)	38.8(10.8)	38.6(10.4)
Mental component summary	49.2(10.9)	49.4(11.6)	49.3(11.2)
Total AVVQ*	44.1(9.0)	44.3(8.7)	44.2(8.8)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Data for up to seven patients were missing for some continuous variables. SF-36, Short Form 36; AVVQ, ???. Adapted from Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N *et al.*; EVRA Trial Investigators. A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med* 2018; **378**: 2015–2114. Copyright © (2018) Massachusetts Medical Society.

Comment [A47]: Au: Do you know which version of the Short Form 36 was used (Rand Corporation or other)?

Comment [JM48]: 36-Item Short Form Health Survey (SF-36®) (Short Form questionnaire-36 items, Standard U.K. Version 1.0) , QualityMetric, Lincoln, RI, USA

Comment [A49]: Au: Please define AVVQ [?Aberdeen Varicose Vein Questionnaire].

Comment [JM50]: Aberdeen Varicose Vein Questionnaire

Table 2 Results of regression for cost-effectiveness analysis

	Model 1*	Model 2†	Model 3†	Model 4	Model 5
Coefficient	Complete case (n = 344), with bootstrap standard errors (1000 samples) and crosswalk EQ-5D™ tariff	Complete case (n = 344), with bivariable normal standard errors and crosswalk EQ-5D™ tariff	10 multiple imputations (n = 450), with bivariable normal standard errors and crosswalk EQ-5D™ tariff	Complete case (n = 344) with bootstrap standard errors and Devlin EQ-5D-5L™ tariff	Per-protocol compliers (n = 273) with bootstrap standard errors
Difference in cost					
Mean(s.e.)	£163(318) (€184(358))	£163(322) (€184(363))	−£72(290) (-€81(327))	£163(322) (€184(363))	£486(326) (€548(367))
P	0.607	0.612	0.803	0.612	0.137
Difference in QALYs					
Mean(s.e.)	0.041(0.017)	0.041(0.018)	0.058(0.018)	0.033(0.016)	0.056(0.019)
P	0.017	0.024	0.002	0.039	0.003
ICER (£/QALY)	3976 (€4482)	3976 (€4482)	n.c.	4939 (€5568)	8679 (€9784)

*Base-case or primary analysis. †Estimated correlation of residuals between cost and quality-adjusted life-years (QALYs) in the bivariable normal model: −0.294 (P < 0.001). n.c., Incremental cost-effectiveness ratio (ICER) not calculable because early ablation dominates (both cost-saving and more effective). Currency conversions (£GBP/€EURO) are correct at the date of conversion (£1 = €1.1273; 20 September 2018).

Comment [A51]: Au: Please convert to euro (€) values where highlighted [perhaps add date of conversion in table footnote].

Comment [JM52]: Amended as requested

Deleted: (£)