Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration

Gohel, Manjit S; Heatley, Francine; Liu, Xinxue; Bradbury, Andrew; Bulbulia, Richard; Cullum, Nicky; Epstein, David M; Nyamekye, Isaac; Poskitt, Keith R; Renton, Sophie; Warwick, Jane; Davies, Alun H

DOI:
10.3310/hta23240

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 23 ISSUE 24 MAY 2019
ISSN 1366-5278

Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT

Manjit S Gohel, Francine Heatley, Xinxue Liu, Andrew Bradbury, Richard Bulbulia, Nicky Cullum, David M Epstein, Isaac Nyamekye, Keith R Poskitt, Sophie Renton, Jane Warwick and Alun H Davies on behalf of the EVRA trial investigators

NHS
National Institute for Health Research

DOI 10.3310/hta23240

Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT

Manjit S Gohel,[1,2] Francine Heatley,[2] Xinxue Liu,[3] Andrew Bradbury,[4] Richard Bulbulia,[5,6,7] Nicky Cullum,[8] David M Epstein,[9] Isaac Nyamekye,[10] Keith R Poskitt,[5] Sophie Renton,[11] Jane Warwick[3,12] and Alun H Davies[2]* on behalf of the EVRA trial investigators

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

*Corresponding author

Declared competing interests of authors: Manjit S Gohel has received personal fees from Medtronic pLc (Minneapolis, MN, USA) and Cook Medical LLC (Bloomington, IN, USA), plus a grant from Laboratoires Urgo S.A. (Chenôve, France). Andrew Bradbury had committee membership for the National Institute for Health Research Health Technology Assessment (HTA) Prioritisation Group and HTA Surgery Themed Call Board 2012–13, HTA Efficient Study Designs Board 2014–16, HTA Interventional Procedures Methods Group 2015–19 and HTA IP Panel 2015–19. In addition, Andrew Bradbury has received funding from STD Pharmaceutical Products Ltd (Hereford, UK) to travel to a foam sclerotherapy workshop in Tehran, Iran, in October 2016 and a grant to cover costs of undertaking a post-authorisation safety study in the UK and Europe. He also sat on the National Institute for Health and Care Excellence (NICE) committee for a clinical guideline (CG168) for the diagnosis and management of varicose veins. Nicky Cullum had committee membership on the HTA Commissioning Board from 2003 to 2008. David M Epstein has received grant funding from Vascular Insights LLC (Quincy, MA, USA) which was administered by the University of Granada. Alun H Davies has received grant funding from Medtronic, Vascular Insights, Laboratoires Urgo, Vascutek (Inchinnan, UK) and Actegy Health Ltd (Bracknell, UK), which are administered by Imperial College London. In addition, Alun H Davies has chaired the NICE clinical guideline (CG168) for the diagnosis and management of varicose veins.

Published May 2019
DOI: 10.3310/hta23240

This report should be referenced as follows:

Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, *et al*. Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT. *Health Technol Assess* 2019;**23**(24).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/129/197. The contractual start date was in November 2016. The draft report began editorial review in May 2018 and was accepted for publication in September 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

Early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration: the EVRA RCT

Manjit S Gohel,[1,2] Francine Heatley,[2] Xinxue Liu,[3] Andrew Bradbury,[4] Richard Bulbulia,[5,6,7] Nicky Cullum,[8] David M Epstein,[9] Isaac Nyamekye,[10] Keith R Poskitt,[5] Sophie Renton,[11] Jane Warwick[3,12] and Alun H Davies[2]* on behalf of the EVRA trial investigators

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

*Corresponding author a.h.davies@imperial.ac.uk

Background: Venous ulceration is a common and costly health-care issue worldwide, with poor healing rates greatly affecting patient quality of life. Compression bandaging has been shown to improve healing rates and reduce recurrence, but does not address the underlying cause, which is often superficial venous reflux. Surgical correction of the reflux reduces ulcer recurrence; however, the effect of early endovenous ablation of superficial venous reflux on ulcer healing is unclear.

Objectives: To determine the clinical effectiveness and cost-effectiveness of compression therapy with early endovenous ablation of superficial venous reflux compared with compression therapy with deferred endovenous ablation in patients with venous ulceration.

Design: A pragmatic, two-arm, multicentre, parallel-group, open randomised controlled trial with a health economic evaluation.

Setting: Secondary care vascular centres in England.

Participants: Patients aged ≥ 18 years with a venous leg ulcer of between 6 weeks' and 6 months' duration and an ankle–brachial pressure index of ≥ 0.8 who could tolerate compression and were deemed suitable for endovenous ablation of superficial venous reflux.

Interventions: Participants were randomised 1 : 1 to either early ablation (compression therapy and superficial endovenous ablation within 2 weeks of randomisation) or deferred ablation (compression therapy followed by endovenous ablation once the ulcer had healed).

Main outcome measures: The primary outcome measure was time from randomisation to ulcer healing, confirmed by blinded assessment. Secondary outcomes included 24-week ulcer healing rates, ulcer-free time, clinical success (in addition to quality of life), costs and quality-adjusted life-years (QALYs). All analyses were performed on an intention-to-treat basis.

Results: A total of 450 participants were recruited (224 to early and 226 to deferred superficial endovenous ablation). Baseline characteristics were similar between the two groups. Time to ulcer healing was shorter in participants randomised to early superficial endovenous ablation than in those randomised to deferred ablation [hazard ratio 1.38, 95% confidence interval (CI) 1.13 to 1.68; $p = 0.001$]. Median time to ulcer healing was 56 (95% CI 49 to 66) days in the early ablation group and 82 (95% CI 69 to 92) days in the deferred ablation group. The ulcer healing rate at 24 weeks was 85.6% in the early ablation group, compared with 76.3% in the deferred ablation group. Median ulcer-free time was 306 [interquartile range (IQR) 240–328] days in the early ablation group and 278 (IQR 175–324) days in the deferred endovenous ablation group ($p = 0.002$). The most common complications of superficial endovenous ablation were pain and deep-vein thrombosis. Differences in repeated measures of Aberdeen Varicose Vein Questionnaire scores ($p < 0.001$), EuroQol-5 Dimensions index values ($p = 0.03$) and Short Form questionnaire-36 items body pain ($p = 0.05$) over the follow-up period were observed, in favour of early ablation. The mean difference in total costs between the early ablation and deferred ablation groups was £163 [standard error (SE) £318; $p = 0.607$]; however, there was a substantial and statistically significant gain in QALY over 1 year [mean difference between groups 0.041 (SE 0.017) QALYs; $p = 0.017$]. The incremental cost-effectiveness ratio of early ablation at 1 year was £3976 per QALY, with a high probability (89%) of being more cost-effective than deferred ablation at conventional UK decision-making thresholds (currently £20,000 per QALY). Sensitivity analyses using alternative statistical models give qualitatively similar results.

Limitations: Only 7% of screened patients were recruited, treatment regimens varied significantly and technical success was assessed only in the early ablation group.

Conclusions: Early endovenous ablation of superficial venous reflux, in addition to compression therapy and wound dressings, reduces the time to healing of venous leg ulcers, increases ulcer-free time and is highly likely to be cost-effective.

Future work: Longer-term follow-up is ongoing and will determine if early ablation will affect recurrence rates in the medium and long term.

Trial registration: Current Controlled Trials ISRCTN02335796.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 23, No. 24. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 Ethics approval

Report Supplementary Material 2 Patient information sheet and informed consent form (PISIC)

Report Supplementary Material 3 GP letter V1.0

Report Supplementary Material 4 Case report forms (CRFs)

Supplementary material can be found on the NIHR Journals Library report project page (www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/documentation).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ABPI	ankle–brachial pressure index
AE	adverse event
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	body mass index
CCG	Clinical Commissioning Group
CEAP	clinical, aetiological, anatomical and pathophysiological
CI	confidence interval
CRF	case report form
DMC	Data Monitoring Committee
DVT	deep-vein thrombosis
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
ESCHAR	Effect of Surgery and Compression on Healing And Recurrence
EVLA	endovenous laser ablation
EVRA	Early Venous Reflux Ablation
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICTU	Imperial Clinical Trials Unit
IQR	interquartile range
ITT	intention to treat
KM	Kaplan–Meier
MOCA	mechanochemical endovenous ablation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OR	odds ratio
PCT	primary care trust
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFA	radiofrequency laser ablation
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
TSC	Trial Steering Committee
UGFS	ultrasonography-guided foam sclerotherapy
VCSS	Venous Clinical Severity Score
WTP	willingness to pay

Plain English summary

Venous leg ulcers are open wounds occurring on the legs of patients with venous disease. They are common, painful and distressing and reduce patient quality of life. Leg ulcers often result from valves in the leg veins not working properly. The valves normally force blood back up towards the heart; however, blood can flow backwards (reflux) when valves do not work properly, and this can cause swelling and ulceration. Compression therapy (wrapping bandages around the legs) has been shown to help ulcers heal, but it does not treat the underlying reflux problem with the veins. Newer, less invasive, techniques (known as endovenous ablation) have taken over from surgery to correct venous reflux and are more acceptable to patients as they can be performed quickly under local anaesthetic.

The aim of the trial was to find out if treating patients with leg ulcers by early endovenous ablation (within 2 weeks) and standard compression therapy can increase ulcer healing compared with standard compression therapy and delayed endovenous ablation once the ulcer has healed.

In total, 450 people agreed to take part in this study and were treated in 20 hospitals across England. Participants were randomly allocated to either early or delayed endovenous ablation and followed up for 12 months.

The trial found that treating the veins early resulted in quicker ulcer healing than delaying treatment until the ulcer had healed. The trial also showed that participants had more time without an ulcer if the treatment was performed early rather than after ulcer healing. No safety issues with early intervention were identified.

There is some evidence that quality of life was better in the early treatment group and that people in this group had less body pain. Treating ulcers early appears likely to be more cost-effective (i.e. a better use of NHS resources) than delayed treatment.

Future work will focus on collecting longer-term follow-up data to find out if early endovenous ablation also reduces the chances of the ulcer coming back.

Scientific summary

Background

Venous ulceration is a common and costly health problem worldwide, with poor healing rates affecting patient quality of life and health service costs. Compression bandaging has been shown to improve healing rates and reduce recurrence but does not address the underlying causes of venous hypertension (e.g. superficial venous reflux). In addition, patient concordance with compression is often poor. Traditionally, varicose vein surgery has been used to treat superficial venous reflux, and this has been shown to reduce ulcer recurrence; however, no effect on ulcer healing has been demonstrated. Surgery also has low patient acceptance, but novel, minimally invasive, endovenous methods have increased in popularity in recent years. Cohort studies have suggested that early endovenous ablation of superficial venous reflux can reduce time to healing, yet no robust evidence currently exists to demonstrate the clinical effectiveness or cost-effectiveness of this approach.

Objectives

The primary objective was to determine the clinical effectiveness and cost-effectiveness of compression therapy with early endovenous ablation of superficial venous reflux compared with compression therapy with deferred endovenous ablation in patients with venous ulceration. The secondary objectives were to investigate the ulcer-free time to 1 year, assess patient quality of life and evaluate the technical success of the endovenous ablation in the group that received early ablation.

Methods

Design

This was a pragmatic, two-arm, multicentre, parallel, open randomised controlled trial with a health economic evaluation.

Setting

The setting was 20 secondary care vascular centres across England with ability to provide early endovenous ablation and established referral pathways for patients who have venous ulceration.

Participants

Written informed consent was obtained from all participants, who then underwent clinical assessment and duplex Doppler ultrasound examination to assess eligibility for entry to the trial. For patients with bilateral venous ulcers, the worse leg according to the patient was included and designated the ‘reference leg’.

Inclusion criteria

- Active leg ulceration of duration > 6 weeks but < 6 months.
- Able to give informed consent to participate in the trial after reading the patient information documentation.
- Aged ≥ 18 years.
- Ankle–brachial pressure index of ≥ 0.8.
- Primary or recurrent superficial venous reflux on colour duplex Doppler ultrasonography assessment (defined as retrograde flow of > 0.5 seconds in superficial veins and > 1 second in deep veins) deemed to warrant endovenous ablation by the treating clinician.

Exclusion criteria

- Patients who are unable to tolerate compression therapy.
- Inability of the patient to receive early endovenous ablation by recruiting centre.
- Pregnancy (female participants of reproductive age were eligible for inclusion in the trial, subject to a negative pregnancy test prior to randomisation).
- Leg ulcer of non-venous aetiology (as assessed by the responsible clinician).
- Ulcer deemed to require skin grafting (as assessed by the responsible clinician).

Randomisation

Randomisation lists were created using randomly permuted blocks and stored in a secure online location. Eligible patients were automatically assigned the next available entry in the appropriate list. Participants were randomised 1 : 1 to either early or deferred endovenous ablation.

Interventions

Participants in the early-ablation group received compression therapy and endovenous ablation of superficial venous reflux within 2 weeks of randomisation. For participants randomised to deferred ablation, treatment consisted of compression therapy followed by endovenous ablation once the ulcer had healed. Multilayer elastic compression (two, three or four layer), short-stretch compression and compression hosiery were all permitted. Ablation was allowed in the deferred ablation group if the ulcer had not healed within 6 months of randomisation. Endovenous laser ablation or radiofrequency laser ablation, ultrasonography-guided foam sclerotherapy, cyanoacrylate glue and mechanochemical endovenous ablation were all permitted; the individual ablation modality was decided by each clinician on a case-by-case basis. However, the endovenous ablation had to include ablation of truncal venous reflux (to the lowest point of incompetence) and ablation of any significant reflux identified on a further duplex Doppler ultrasonography scan performed 6 weeks after randomisation. Once the ulcer had healed, participants were provided with and advised to wear elastic stockings as per local guidelines.

Follow-up

Participants in the early-ablation group underwent duplex Doppler ultrasonography at 6 weeks post randomisation to assess the technical success of the ablation procedure. Participants were contacted on a monthly basis to determine ulcer healing dates with disease-specific [Aberdeen Varicose Vein Questionnaire (AVVQ)] and generic [EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and Short Form questionnaire-36 items (SF-36)] quality of life questionnaires at baseline, 6 weeks and 6 and 12 months.

Main outcome measures

The primary outcome measure was time to ulcer healing from randomisation, confirmed by blinded core laboratory assessment. Secondary outcomes included 24-week ulcer healing rates, ulcer-free time, Venous Clinical Severity Score (VCSS), technical success, costs and quality of life. Ulcer healing was defined as complete re-epithelialisation in the absence of a scab, with no dressing required. If the participant or clinical care teams suspected that the ulcer was healed, a series of digital photographs (once per week for up to 4 weeks) were taken and assessed by blinded clinical experts.

A within-trial cost-effectiveness analysis was undertaken at 1 year. In the base-case analysis, only complete cases were included. The price year was 2015–16 and the perspective was the UK NHS and Personal Social Services. No discounting was applied in the 1-year analysis. Only resource items related to the venous leg ulcer or treatments were included in the total mean cost. Quality-adjusted life-years (QALYs) were estimated from EQ-5D-5L using the crosswalk tariff recommended by the National Institute for Health and Care Excellence in August 2017 [EuroQol.org. *NICE position statement on the EQ-5D-5L*. 2017. URL: https://euroqol.org/nice-position-statement-on-the-eq-5d-5l/ (accessed 15 May 2019)]. Uncertainty was estimated using bootstrap methods. Sensitivity analyses were carried out using multiple imputation of missing data, using an alternative tariff for the EQ-5D-5L instrument and assuming a bivariate normal distribution for costs and QALYs. All analyses were performed on an intention-to-treat basis using Stata® v14.2 (StataCorp LP, College Station, TX, USA), with statistical significance set at the two-sided 5% level.

Results

In total, 450 participants were randomised into the trial (224 into the early-ablation group and 226 into the deferred-ablation group). An unadjusted Cox regression model, with recruitment centre as a random effect, demonstrated that ulcer healing was quicker in the early-ablation group than in the deferred-ablation group [hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.13 to 1.68; $p = 0.001$], with median time to ulcer healing being 56 (95% CI 49 to 66) days in the early-ablation group, compared with 82 (95% CI 69 to 92) days in deferred-ablation group. Adjusting for participant age, ulcer duration and size gave similar results (HR 1.42, 95% CI 1.16 to 1.73; $p = 0.001$).

Kaplan–Meier estimates of 24-week ulcer healing rates, which are unadjusted, were higher in the early-ablation group than in the deferred-ablation group (85.6%, 95% CI 80.6% to 89.8% vs. 76.3%, 95% CI 70.5% to 81.7%, respectively). Similarly, a post hoc analysis showed a 12-week healing rate of 63.5% (95% CI 57.2% to 69.8%) in the early-ablation group, compared with 51.6% (95% CI 45.2% to 58.3%) in the deferred-ablation group. At 1 year, ulcer healing had occurred in 89.8% of randomised participants overall ($n/N = 404/450$): 93.8% ($n/N = 210/224$) in the early-ablation group and 85.8% ($n/N = 194/226$) in the deferred-ablation group. There was a 7.9% (95% CI 2.3% to 13.5%) absolute difference in healing rates between the groups.

Recurrence rates at 1 year were calculated as a proportion of the participants in whom the ulcer had healed. By 1 year post randomisation, 24 of 210 (11.4%) participants in the early-ablation group and 32 of 194 (16.5%) participants in the deferred-ablation group had experienced ulcer recurrence.

Ulcer-free time was determined only in participants who completed 1 year of follow-up and the difference between the early-ablation and deferred-ablation groups was assessed using the Mann–Whitney *U*-test. Median ulcer-free time over 1 year was 306 [interquartile range (IQR) 240–328] days ($n = 204$) in the early-ablation group, compared with 278 (IQR 175–324) days ($n = 203$) in the deferred-ablation group ($p = 0.002$). The results were not affected when adjustments were made for participant age, ulcer size, ulcer duration and recruitment centre. Participants in the early-ablation group were more likely to have a longer ulcer-free time of being in a higher quartile of ulcer-free time (odds ratio 1.54, 95% CI 1.07 to 2.21; $p = 0.02$).

Mean VCSS was similar in the two trial groups at baseline {15.8 [standard deviation (SD) 3.3] in the early-ablation group and 15.7 [SD 3.1] in the deferred-ablation group}. At 6 weeks, mean VCSS was 10.5 (SD 4.7) in early-ablation group and 12.6 (SD 4.4) in the deferred-ablation group.

At baseline, AVVQ, EQ-5D-5L and SF-36 scores were similar in the early- and deferred-ablation groups. When compared over the whole follow-up period, there were significant differences in repeated measures of AVVQ score between the two groups ($p < 0.001$), with lower scores (indicating better disease-specific quality of life) seen in the early-ablation group. Significant differences over time were also observed between the groups in EuroQol-5 Dimensions index value ($p = 0.03$) and SF-36 body pain ($p = 0.05$), again with more favourable scores in those randomised to early ablation; however, differences between the groups for the other generic quality-of-life measures were not significant. The most common complications of endovenous ablation were pain and asymptomatic deep-vein thrombosis.

The base-case economic analysis (complete cases only) included 173 participants in the early-ablation group and 171 in the deferred-ablation group. This analysis showed insignificant differences in total mean cost per patient over 1 year between early and deferred ablation {mean difference £163 [standard error (SE) £318]; $p = 0.607$}. The greater initial mean cost of the early-ablation strategy was partly offset by the reduced cost of treating unhealed leg ulcers in this group. There was, however, a substantial and statistically significant gain in QALY over 1 year, with the mean difference being 0.041 (SE 0.017; $p = 0.017$). The incremental cost-effectiveness ratio of early ablation at 1 year was, therefore, £3976 per QALY, compared

with deferred ablation, with a high probability (89%) of early ablation being more cost-effective at conventional UK decision-making thresholds (currently £20,000 per QALY). Sensitivity analyses using alternative tariffs for EQ-5D-5L, a bivariate normal distribution for costs and QALYs, and multiple imputation of missing data found similar results.

Conclusions

Early endovenous ablation of superficial venous reflux in addition to compression therapy reduces the time to healing of venous leg ulcers, increases ulcer-free time and is highly likely to be cost-effective.

Implications for health care

Findings from this trial suggest that early diagnosis and endovenous ablation of superficial venous reflux in addition to compression therapy can accelerate healing of venous leg ulcers and produce health economic benefits. Implementation of early diagnosis and endovenous ablation of superficial venous reflux will require further development of care pathways between primary and secondary care.

Recommendations for research (numbered in order of priority)

1. Carry out a longer-term follow-up to determine if early endovenous ablation influences ulcer recurrence rates in the medium and long term.
2. Evaluate the benefit of early ablation for superficial venous reflux in patients with venous leg ulceration of > 6 months duration.
3. Determine the implications of deep-venous incompetence and occlusive disease and the potential role of deep-venous stenting to improve venous outflow of the limb.
4. Evaluate the optimal technique and the extent of eradication of superficial venous incompetence in patients with venous ulceration.

Trial registration

This trial is registered as ISRCTN02335796.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background of venous leg ulcers

Leg ulcers are open 'sores' on the lower limbs situated between the ankles and knees, and were defined in this trial as those that fail to heal within 6 weeks. These ulcers represent a source of great discomfort and social isolation to patients, who often complain of associated pain, odour and wound discharge. Ulcers often take many months to heal, meaning that the condition is also frustrating for health-care professionals involved in their management in hospital and community settings. In 70% of cases, the underlying cause of leg ulceration is lower limb venous disease, sometimes evident as varicose veins but often undetectable by visual examination alone.[1] The prevalence of venous leg ulcers in the adult population overall has been estimated at 0.03–1%, rising dramatically in those aged > 80 years.[2–4] As patients with venous ulceration often suffer episodes of recurrence, the number of patients at high risk of ulceration may actually be four- to fivefold higher.[5] It should also be noted that, with an ageing and increasingly obese population,[6] the incidence and prevalence of venous ulceration are both likely to increase. Treatment of the condition in the UK incurs a substantial cost burden, estimated at £400M–600M per annum,[7] although the figure could be higher.[8]

Venous ulcers are characterised by protracted healing times. Despite recent advances in the management of patients with venous ulcers, 24-week healing rates in published randomised trials are around 60–65%,[9,10] and the true population healing rates are likely to be significantly lower. Some ulcers may never heal, and patients whose ulcers do heal are at high risk of recurrent ulceration. These poor outcomes are likely to be a reflection of the severe underlying venous disease (reflux and, less commonly, obstruction) in this patient group, although inadequate assessment and suboptimal treatment of the venous disease are also likely to be important contributing factors.

Pathophysiology of venous leg ulcers

The venous circulation of the lower limb has two components: the deep and superficial systems. Blood normally flows from the superficial to the deep veins, stimulated by calf and foot muscle contractions. Blood is prevented from flowing back down the leg under the influence of gravity by 'one-way' bicuspid valves along the deep and superficial veins.

When these valves are damaged, they become incompetent, resulting in venous flow away from the heart. This results in the superficial veins usually becoming dilated and tortuous (varicose), and the resulting sustained high venous and capillary pressures lead to skin inflammation and breakdown of the skin, visible as ulceration.[11] The deep veins also have valves, which may also become incompetent and cause high venous pressure, but are not visible on the skin.

Duplex Doppler ultrasonography studies[12–14] of patients attending leg ulcer clinics suggest that around 50% of patients with venous leg ulcers have disease only of the superficial veins, with a further 30–40% having a mixture of superficial and deep-venous disease. Surgical treatment of the superficial venous reflux can benefit both of these groups of patients, in terms of reducing ulcer recurrence.[15] Approximately 5–10% of patients with venous ulcers have diseased deep-venous systems only and are not amenable to surgical correction with current technology. These patients are usually treated with compression therapy alone.

Conservative management

Ulcer healing strategies are based on efforts to reduce the reflux of blood back down the leg and into the skin, as this is considered the most significant cause of high venous pressure and ulceration in most patients. Longstanding venous hypertension has been shown to cause a number of changes to the microcirculation in the lower leg, which can contribute to the chronic skin changes or eventual ulceration associated with chronic venous disease.[16]

The mainstay of therapy for venous ulceration is compression therapy, which was first described around 2000 years ago. Compression bandaging is used to heal venous ulceration by counteracting the gravitational force on the blood, in effect temporarily replacing the incompetent valves.[17] Bandages are usually reapplied once to four times per week.

A Cochrane review[18] of the effectiveness of compression reviewed 48 randomised controlled trials (RCTs) and found that the use of compression improved healing rates compared with no compression use and that multicomponent bandages are more effective than single-component systems, with two-component systems' healing rates being equivalent to four-layer bandaging. An individual patient data meta-analysis[18] found faster healing with four-layer bandaging use than with short-stretch bandaging use, and improved healing rates at 2–4 months using high-compression stockings compared with short-stretch bandaging. In addition, the meta-analysis showed the four-layer bandaging to be more cost-effective than short-stretch bandaging.[18]

The haemodynamic benefit of compression is lost almost immediately after removal of compression, and so compression offers a treatment benefit only while in situ.[19] There are also side effects associated with compression, such as pressure damage, which can lead to reduced concordance rates, as highlighted by a recent Cochrane review.[20]

Treatment options for superficial venous reflux

The treatment of superficial venous reflux offers a logical strategy for reducing chronic venous hypertension and so improving the healing of venous leg ulcers. Diseased superficial veins can be surgically removed (or 'stripped') by open varicose vein surgery or ablated using endovenous interventions without harming the overall venous function of the leg, theoretically removing a causative factor for recurrence of the ulcer after the compression bandaging has ceased.

Open surgery

For over a century, the treatment of superficial venous reflux has involved operative ligation and stripping of the vein and avulsion of bulging varicose veins.[21] Until recent years, open surgery has been considered the definitive treatment option for superficial venous reflux. However, the operation usually requires general anaesthesia, and patients often suffer discomfort, bruising and significant time off work in the postoperative period. Long-term studies have also identified significant complications of open surgery, including nerve damage and recurrence of varicose veins, seen in > 60% of patients at 11 years in one randomised study.[22]

Endovenous interventions

In response to this high complication rate and a growing patient desire for less invasive treatments, a range of novel, minimally invasive, endovenous treatment options have been developed and have gained in popularity over the last 10–15 years. Interventions such as ultrasonography-guided foam sclerotherapy (UGFS),[23] endovenous laser ablation (EVLA)[24] or radiofrequency laser ablation (RFA)[25] can be performed using local anaesthesia in an outpatient setting. Newer endovenous interventions include mechanochemical endovenous ablation (MOCA) and cyanoacrylate glue closure. These treatments involve cannulation of the vein to be treated, usually under ultrasonography guidance, obliteration and closure of the refluxing superficial veins by either chemical (e.g. foam sclerosant, glue) or thermal ablation (e.g. RFA, EVLA, steam).

Numerous randomised studies have demonstrated that endovenous modalities result in comparable vein closure rates to open surgery, but are clearly superior in terms of complications and recovery.[26–28]

Each of the different endovenous modalities has potential advantages and potential disadvantages, although all are less invasive than traditional open surgery. This is of particular relevance to patients with venous ulcers, who are often elderly and may have several comorbidities and for whom surgical procedures involving general anaesthesia may be inappropriate. Endovenous techniques can also be performed without discontinuing anticoagulation therapy, which is increasingly prescribed in this patient population.

Existing research

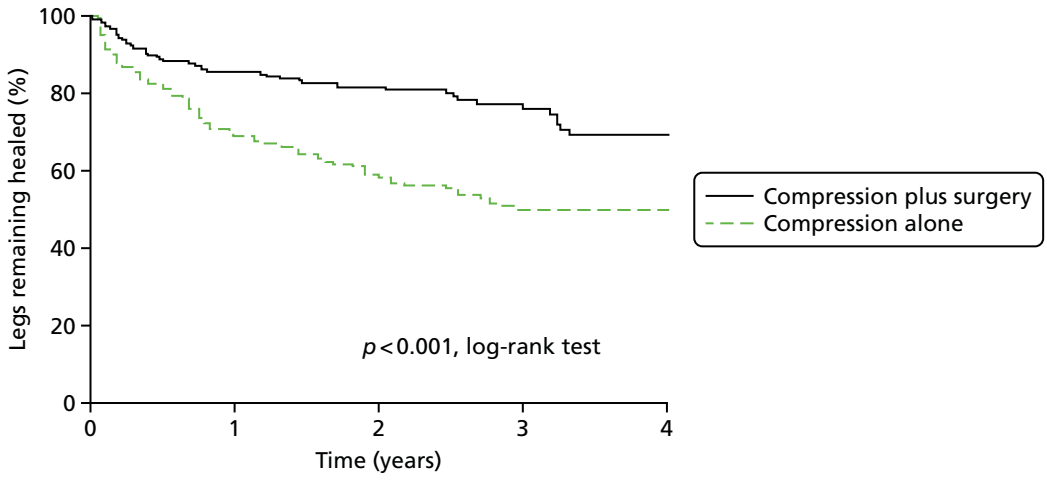
The ESCHAR randomised controlled trial

Aims and results

The most significant trial of superficial venous intervention in patients with venous ulceration is the Effect of Surgery and Compression on Healing And Recurrence (ESCHAR) trial (ISRCTN07549334).[9,15] The trial aimed to evaluate the role of traditional superficial venous surgery in reducing ulcer recurrence in patients with open or recently healed venous ulcers. Following prospective observational studies to inform power calculations, a total of 500 participants were randomised to compression therapy alone or to compression with open surgery for superficial venous reflux. The group randomised to surgical treatment had significantly lower venous ulcer recurrence rates at 4 years (*Figure 1*).

Analysis stratified by pattern of venous reflux demonstrated that this clinical benefit was present for patients with isolated superficial venous reflux and patients with superficial and segmental deep reflux. This clearly indicated that the majority of patients with venous ulceration could benefit from superficial venous intervention.

The ESCHAR trial was unable to detect an effect of surgery on ulcer healing (*Figure 2*). This finding has led many to conclude that treatment of venous reflux does not have a role in patients with open ulcers.



Numbers at risk					
Compression plus surgery	216	166	124	68	27
Compression alone	226	139	98	45	10

FIGURE 1 The ESCHAR trial: ulcer recurrence. Reproduced from Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial, Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, *et al.*,[15] vol. 335, p. 83, 2018, with permission from BMJ Publishing Group Ltd.

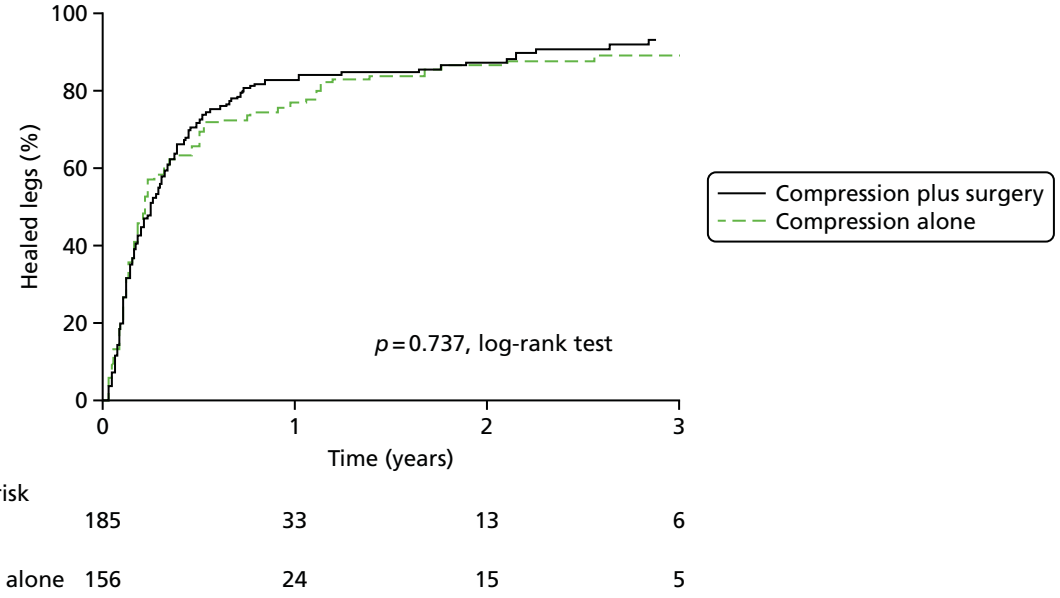


FIGURE 2 The ESCHAR trial: ulcer healing. Reproduced from Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial, Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, *et al.*,[15] vol. 335, p. 83, 2018, with permission from BMJ Publishing Group Ltd.[15]

Weaknesses

There were, however, several limitations to the evidence from the ESCHAR trial. The trial was not powered to assess ulcer healing, as both patients with open ulcers and those with healed ulcers were included. The statistical power was further weakened by a high crossover rate, as around one-fifth of participants randomised to surgery later decided that they did not want to have the operation. Moreover, participants who consented to surgery waited a median of 7 weeks for intervention and so did not receive an immediate benefit. Consequently, some smaller ulcers might have already healed with compression bandaging. Finally, some of the surgical procedures used were suboptimal when judged by current standards and the use of local anaesthetic may have meant that some legs were left with residual venous incompetence. Thus, it is likely that the benefits of treating superficial venous reflux were underestimated in this trial, particularly for the assessment of ulcer healing. The poor patient acceptance of surgery emphasises the need for a minimally invasive superficial venous treatment modality in this patient group.

Other relevant research

In a smaller Dutch randomised trial, 170 patients (200 legs) were randomised to compression alone or compression with surgical treatment of superficial reflux (including subfascial endoscopic perforator surgery).[10] Although there was no statistically significant difference between healing rates with compression and surgery, the trial was underpowered and the results were compatible with improved ulcer healing rates and greater ulcer-free time in the group randomised to surgery.

The Ulcer Surgery as Adjuvant to compression Bandaging for Leg UlcErs (USABLE) trial[29] randomised 76 patients with venous ulceration to four-layer compression bandaging or compression plus superficial venous surgery. Time to ulcer healing was similar between the groups.[29]

Despite the widespread acceptance of endovenous modalities, few published prospective studies have reported outcomes in patients with leg ulcers. The Cochrane systematic review did not identify any eligible RCTs;[30] another systematic review[31] identified one RCT[32] and, although this trial did not meet the quality criteria for inclusion in the Cochrane review, it found that endovenous thermal ablation significantly increased the probability of ulcer healing compared with compression alone [risk ratio 3.40, 95% confidence interval (CI) 1.65 to 6.98].

One retrospective cohort study of 170 patients with active or healed leg ulceration (195 legs) treated with EVLA achieved excellent healing rates and low recurrence rates of 16%, as did another study of 173 legs, which noted that ulcer healing and recurrence rates were similar to those seen with surgical stripping.[33,34]

In a prospective study of 186 patients with leg ulceration treated with UGFS, the ulcer healing rate was > 70% and the patient acceptability of treatment was excellent.[35] In a further study of foam sclerotherapy in 130 patients, a healing rate of 82% was achieved.[36]

Unsurprisingly, endovenous interventions are very acceptable to patients, and reported complication rates are low.[37] A recent meta-analysis demonstrated that clinical outcomes following endovenous interventions outcomes are comparable with those achieved with open surgery, but with lower complication rates of pain, infection and bruising, and faster/earlier return to work.[38]

Although these studies lend support to the hypothesis that early endovenous ablation to correct superficial venous reflux may accelerate venous ulcer healing, a large randomised trial is required to provide reliable evidence and guide modern practice.

Current UK national guidelines

Scottish Intercollegiate Guidelines Network: 2010

The most current ulcer-specific guidance, issued by the Scottish Intercollegiate Guidelines Network in 2010,[39] concluded that the optimal management of patients with venous ulceration includes the treatment of refluxing superficial veins to reduce the risk of ulcer recurrence based on the results of the ESCHAR trial.

National Institute for Health and Care Excellence guidelines: 2013

The National Institute for Health and Care Excellence (NICE) published guidance on the diagnosis and management of varicose veins in July 2013;[40] it recommends the referral of patients with symptomatic varicose veins (including current or healed ulceration) to a vascular service within 2 weeks. Vascular service has been defined by NICE as:

> *. . . a team of healthcare professionals who have the skills to undertake a full clinical and duplex ultrasound assessment and provide a full range of treatment.*
>
> *© NICE 2013 Varicose veins: diagnosis and management.[40] Available from www.nice.org.uk/guidance/cg168/chapter/key-priorities-for-implementation. All rights reserved. Subject to Notice of rights <https://www.nice.org.uk/terms-and-conditions#notice-of-rights>. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication*

Despite a study noting an increase in referrals to secondary care in the period after implementation, results were unable to demonstrate an impact on early referral.[40,41] The NICE guidance also recommends the use of venous duplex ultrasonography to confirm the presence of venous insufficiency and endovenous intervention as first-line treatment.[42]

National Institute for Health and Care Excellence quality standard: 2014

The NICE quality standard on the diagnosis and management of varicose veins of the legs[43] was published in August 2014 and provides specific, concise and measurable statements to improve the process and care of patients with varicose veins. This quality standard echoed the 2013 NICE guidance in terms of referral, diagnosis and treatment choice.

Rationale for the Early Venous Reflux Ablation trial

Despite the evidence that the treatment of superficial venous reflux reduces ulcer recurrence in patients with venous leg ulcers, there is currently no level 1 evidence demonstrating reductions in time to healing.[21] With this void in evidence, superficial venous reflux is often treated after ulcers have healed following conservative treatment involving compression bandaging. The danger of taking this approach is that, once the ulcer is healed and the symptoms have resolved, patients may not be referred. The resulting untreated superficial venous reflux contributes to an increased risk of ulcer recurrence, which is both costly for the health service and distressing for the patient. The previous RCT literature may have underestimated the clinical benefit of intervention, with recent prospective cohort studies of endovenous intervention in active leg ulceration clearly suggesting an adjuvant benefit compared with compression alone in terms of healing rates. Time to healing has been highlighted as the end point that is most important to patients, as demonstrated in the patient and public involvement (PPI) work (see *Appendix 1*) of this trial and even a modest improvement in ulcer healing would significantly reduce the health-service costs associated with the condition.

As the incidence and prevalence of venous ulcers are likely to increase as a result of the ageing population, it is important to clarify the role and timing of superficial endovenous ablation in venous ulceration to guide treatment recommendations and referral pathways.[44,45]

Summary of main points

Venous leg ulcers are open wounds that have a detrimental effect on the quality of life of patients. Treatment of the condition in the UK represents a substantial economic burden to the NHS and Personal Social Services, amounting to many hundreds of millions of pounds per year.

Until recently, superficial venous reflux could be treated only by open surgery. Newer, endovenous techniques have been shown to be just as effective as open surgery in terms of clinical improvement, but with reduced complications and pain. These techniques do not need to be performed under general anaesthetic and therefore may be more suitable for elderly patients with significant comorbidities. The most recent UK guidelines for varicose veins[43] recommend early referral to a vascular service for diagnosis and first-line treatment by means of endovenous interventions.

The ESCHAR trial[9,15] indicated that the majority of patients with venous ulceration could benefit from superficial venous intervention with respect to ulcer recurrence; however, the study was not powered to detect an effect on ulcer healing and therefore further research into ulcer healing was required.

Chapter 2 Methods

Research objectives

Primary objective

The primary objective was to determine the clinical effectiveness and cost-effectiveness of compression therapy with early endovenous ablation of superficial venous reflux compared with compression therapy with deferred endovenous ablation in patients with venous ulceration.

Secondary objective

The secondary objective was to investigate ulcer-free time, quality of life, and the clinical and technical success of endovenous ablation to 1 year.

Trial design

We conducted a pragmatic, multicentre, open RCT with participants randomised 1 : 1 to either (1) deferred (standard) therapy, consisting of multilayer elastic compression therapy, with deferred endovenous ablation of superficial reflux once the ulcer has healed, or (2) early endovenous ablation of superficial venous reflux (within 2 weeks) in addition to standard compression therapy.

Amendments to the protocol

Substantial amendments to the trial protocol were submitted after the initial approval, in order to increase recruitment and retention, correct the sample size calculation and clarify the health economic evaluation:

- Version 2.0, dated 6 January 2014: amended to provide a clearer definition of ulcer healing, clarify the per-protocol analyses and safety sections, and to clarify that participants could be offered endovenous ablation of superficial venous reflux in the deferred group if their ulcer had not healed at 6 months.
- Version 3.0, dated 10 March 2014: amended in order to allow the display of posters and dissemination of leaflets and participant information sheets in primary care sites.
- Version 4.0, dated 16 March 2016: amended to correct the sample size from 500 participants to 450 participants (which was originally calculated erroneously), and to allow for a reduction in the number of photograph verification visits performed if the core laboratory confirms that the ulcer is healed in order to prevent unnecessary visits and enhance participant retention.
- Version 5.0, dated 6 April 2017 [see the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 23 April 2019)]: amended to (1) incorporate a Health Technology Assessment (HTA) funding extension to allow for the collection of longer-term follow-up during October 2018 and March 2019 and (2) make revisions to the health economics section to clarify and update the protocol to reflect new National Institute for Health Research (NIHR) guidelines. The follow-up period is now complete (31 March 2019) and, at the time of publication, we are cleaning and locking the database prior to data analysis.

Ethics and research and development approvals

A favourable ethics opinion was given by the National Research Ethics Service Committee South West – Central Bristol on 15 August 2013 (reference number 13/SW/0199). For a copy of the original approval see *Report Supplementary Material 1*. Annual reports were submitted to this committee, which confirmed that the ethics approval continued to apply.

The study-wide governance review was undertaken by the Clinical Research Network North West London in August 2013. Research and development NHS approvals were granted at participating sites between October 2013 and March 2015. The trial was granted the new Health Research Authority approval on 30 June 2016.

Sponsorship

The trial was sponsored by Imperial College London.

Trial management

The trial was supported by the Imperial Clinical Trials Unit (ICTU) and the day-to-day trial management was performed by the trial manager based in the academic vascular department of Charing Cross Hospital, London. The trial manager was responsible for co-ordinating the data collection; follow-up; data cleaning; monitoring visits; communication with the sites, participants and collaborators; and answering trial-specific queries. The trial manager and chief investigator met at least monthly during the course of the trial.

Trial Management Group

The trial was supervised by the Trial Management Group, which comprises the chief investigator, lead statistician, trial statistician, health economist and trial manager. The Trial Management Group met in person or by teleconference on a regular basis.

Trial Steering Committee

An independent Trial Steering Committee (TSC) was established as per the HTA TSC terms of reference to oversee trial conduct. The membership comprises five independent members (see *Acknowledgements*), the chief investigator, trial manager and lead statistician. The TSC met at least annually or more regularly if required, as decided by the committee. For the meeting dates see *Appendix 2*.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) was established as per the HTA DMC terms of reference, to monitor trial data and safety. The membership comprised four independent members (see *Acknowledgements*). The members met once prior to the start of the trial to agree the DMC charter and then on an annual basis to review recruitment, fidelity, retention and unblinded comparative data (for both safety and efficacy). No interim analyses were planned and the trial statistician was the only member of the trial team to have access to the unblinded data. Following each meeting, the DMC recommended continuation of the trial to the TSC. For the meeting dates see *Appendix 2*.

Participants

All patients aged $\geq$ 18 years presenting with a leg ulcer of venous origin who were able to tolerate compression therapy and were suitable for endovenous ablation of superficial venous reflux could be included.

Inclusion criteria

Patients with all of the criteria listed below were deemed eligible:

- current leg ulceration duration of > 6 weeks' but < 6 months
- able to give informed consent to participate in the trial after reading the patient information documentation
- patient aged $\geq$ 18 years
- ankle–brachial pressure index (ABPI) of $\geq$ 0.8

- primary or recurrent superficial truncal venous reflux on colour duplex assessment deemed by the treating clinician to be significant enough to warrant endovenous ablation.

Patients who could not speak/understand English were eligible for inclusion. Informed consent was obtained with assistance from translation services as per standard clinical practice; however, in view of the lack of cross-cultural validation for quality-of-life tools, only healing outcome data were collected.

Exclusion criteria

Patients meeting any of the criteria listed below were ineligible:

- presence of deep-venous occlusive disease or other conditions precluding endovenous superficial venous ablation (at the discretion of the treating clinician)
- patients unable to tolerate multilayer compression therapy (as concordance with compression therapy can be variable for patients at different times, patients who were generally concordant with compression, but unable to tolerate short periods, were still deemed eligible)
- inability of the patient to receive prompt endovenous ablation by recruiting centre
- pregnancy
- leg ulcer of non-venous aetiology as assessed by the treating clinician
- patients deemed to require skin grafting as assessed by the treating clinician.

Sample size

The sample size calculation for this trial was based on the primary outcome of time to ulcer healing. In the ESCHAR trial, the 24-week healing rate in participants randomised to compression alone was approximately 60%.[46] Two prospective studies evaluating the early endovenous ablation of superficial venous reflux suggested that the 24-week healing rate may be as high as 82%.[35,36]

In order to calculate a sample size for this trial, the desirable absolute benefit associated with early endovenous ablation of superficial truncal reflux was estimated to be 15%. Assuming that the 24-week healing rate in the deferred (standard) group is 60%, to identify an absolute difference in 24-week healing rates between the two groups of 15% (60% vs. 75%), with 90% power and allowing for 10% dropout, the trial required 416 subjects (208 in each group, 254 healed leg ulcers in total).[47] To incorporate further allowances for protocol violations and unexpected dropouts, the target sample size was set at 450 participants.

Settings and locations

Participants were recruited from the vascular departments of 20 secondary care NHS trusts throughout England: Bradford Teaching Hospitals NHS Foundation Trust, Cambridge University Hospitals NHS Foundation Trust, Frimley Health NHS Foundation Trust, Gloucestershire Hospitals NHS Foundation Trust, Heart of England NHS Trust (now University Hospitals Birmingham NHS Foundation Trust), Hull and East Yorkshire Hospitals NHS Trust, Imperial College Healthcare NHS Trust, Leeds Teaching Hospitals NHS Trust, North Cumbria University Hospitals NHS Trust, North West London Hospitals NHS Trust, University Hospitals Plymouth NHS Trust, Salisbury NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Taunton & Somerset NHS Foundation Trust, The Dudley Group NHS Foundation Trust, the Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Royal Wolverhampton NHS Trust, University Hospital Birmingham NHS Trust, Worcestershire Acute Hospitals NHS Trust, and York Teaching Hospital NHS Foundation Trust. For a list of participating hospitals see *Acknowledgements, Local vascular research teams*.

Recruitment procedure

Prior to commencing the trial, information was disseminated to general practices in each recruiting region. In addition, selected primary care trusts (PCTs) not currently involved in the trial were set up as patient identification centre sites displaying posters and leaflets and disseminating patient information sheets to patients once the protocol amendment had been approved. As per the July 2013 NICE guidelines on varicose veins,[40] patients with venous ulcers were required to be referred from primary to secondary care as part of the standard care pathway.

Patients were screened from secondary care vascular, ulcer and tissue viability clinics. As part of standard care, patients are evaluated by clinical assessment and colour duplex examination. Depending on the results of these tests, the patients were given a short leaflet containing a summary of the trial and, if interested, then given the more detailed patient information sheet to read.

The details of patients who were eligible for the trial but did not agree to participate, and patients with ulcers who were not eligible for the trial, were recorded anonymously on screening logs along with a minimal data set (including age, ulcer duration and venous duplex/ABPI findings, if known, and reason for non-inclusion).

Informed consent

Patients were given a minimum of 24 hours to consider the trial in addition to the opportunity to discuss all aspects of the trial with their family and/or general practitioner (GP). Patients were then contacted by telephone by the research nurse so that any further questions could be answered. All willing patients were booked in to the leg ulcer clinic to undergo a baseline visit.

Written consent was obtained from each participant at the baseline visit. The patient information sheet and informed consent form (see *Report Supplementary Material 2*) both refer to the possibility of long-term follow-up if the trial is extended and seek permission to access to their NHS records for these purposes. With the participant's consent, a letter was also sent to the participant's GP (see *Report Supplementary Material 3*). A copy of the patient information sheet and informed consent form was filed in the participant's hospital notes and the local research file and a copy was also given to the participant.

All trial documentation contained the contact details of the Early Venous Reflux Ablation (EVRA) trial chief investigator and trial manager to enable participants to obtain further information from the trial team if required.

Baseline assessment

Once written consent was given by the participant, eligibility was confirmed and baseline data were collected by the research nurse using the case report form (CRF) (see *Report Supplementary Material 4*).

Participant demographic and contact details

Data collected included participant contact details, GP details, age, sex, ethnicity and work status. Pregnancy tests were taken by women of child-bearing potential. Participants were provided with a reminder wallet card, which contained the contact details of the local research nurse with a reminder message to call the nurse when they thought that their ulcer had healed.

General medical and ulcer history

This included body mass index (BMI), ABPI, medical history and current medications. An ulcer history was taken, including any previous ulcers and interventions.

Current ulcer and venous assessment

Ulcer duration and size

For the leg to be randomised, the duration of the current ulcer (according to the participant and available medical records) and ulcer size were recorded.

To measure the total ulcer area, tracing grids of 1 cm^2 squares were placed over all the ulcers on the randomised leg and the outside perimeter of the wounds was traced using an indelible pen. The ulcer area was determined by totalling the number of squares contained within the traced ulcer/s area. Where more than one ulcer was present, the total area was calculated by combining each individual area.

In addition, photographs of all the ulcers on the randomised leg were taken with a digital camera, alongside a measuring scale. Sony Cyber-shot DSC-WX60 16.2 Megapixel Digital Cameras (Sony Electronics Inc., San Diego, CA, USA) were provided to all sites and a simple photography protocol was detailed in the site handbook. The tracings and photographs were assigned pseudonyms (trial number) and transferred via a secure server to the trial manager.

The tracing and photograph protocol is detailed in *Appendix 3*.

Once follow-up was complete, an exact ulcer area was calculated from the wound grid and photograph by the use of a software program, ImageJ (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA; open source).[48] By reviewing the photographs and tracings in combination, a judgement was made of the most accurate measurement to be taken as the total ulcer area.

Clinical ulcer assessment

Clinical, aetiological, anatomical and pathophysiological

Clinical, aetiological, anatomical and pathophysiological (CEAP) is a descriptive classification that was developed in 1994 by an ad hoc committee of the American Venous Forum in order to standardise the classification of chronic venous disease.[49] The classification was updated in 2004 to refine some of the definitions and introduce the simpler basis CEAP.[50] All participants were classified according to the basic CEAP. An active ulcer is described by C6, and a healed ulcer as C5.

Venous Clinical Severity Score

The Venous Clinical Severity Score (VCSS) is a component of the Venous Severity Scoring System designed in 2000 by an ad hoc American Venous Forum committee consensus, in order to compliment the CEAP classification and quantify the severity of disease and subsequent improvement or decline.[51] The VCSS has 10 components (pain, varicose veins, venous oedema, skin pigmentation, inflammation, induration, compression used and active ulcer, duration, number and size), each with four categories assigned values of 0–3. The overall scores can range from 0 (lowest severity) to 30 (highest severity). A score was recorded at baseline for each participant (*Tables 1* and *2*).

Suitability for intervention

Details of venous disease were also collected, including previous deep-vein thrombosis (DVT) and pattern of venous reflux identified on the duplex ultrasound, to assess suitability for ablation. Duplex ultrasonography scanning was performed as per standard care at the randomising site.

Participant-completed questionnaires

To provide a comparator for participant-reported outcomes, enrolled participants completed three health questionnaires at baseline. The baseline health questionnaires were administered prior to the participants being told of their treatment allocation (see *Report Supplementary Material 4*).

TABLE 1 Summary of secondary outcome measures and quality-of-life tools used in the EVRA trial

Details of outcome measure	Type of assessment	Range of scores	Comments
VCSS[52]	Physician-assessed clinical severity evaluation	0–30	Higher scores indicate more severe venous disease
AVVQ[53]	Patient-reported disease-specific quality of life	0–100[a]	Higher scores indicate worse health related to varicose veins
EQ-5D-5L[55]	Patient-reported generic quality of life	0–100 (health scale)	Consists of a health scale and health index (with higher scores indicating better health)
SF-36[56]	Patient-reported generic quality of life	0–100 (for each domain)	Eight scores covering different domains of health, with higher scores indicating better health

AVVQ, Aberdeen Varicose Vein Questionnaire; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; QoL, quality of life; SF-36, Short Form questionnaire-36 items.
a Previous studies have used 0.25 standard deviations as a clinically important difference.[54]
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

EuroQol-5 Dimensions

The EuroQol-5 Dimensions (EQ-5D) is a widely recognised, generic tool to measure health outcomes and has been validated in a variety of patient groups, including those with venous leg ulcers.[58] The EQ-5D questionnaire comprises two sections; the first assesses the participant's mobility, self-care, ability to perform usual activities, pain/discomfort and anxiety/depression levels, and the second records the participant's self-rated health on a vertical score of 0 to 100 (see *Table 1*).

Short Form questionnaire-36 items

The Short Form questionnaire-36 items (SF-36) is a generic quality-of-life tool used to determine people's physical and mental health. It has been validated in many patient groups, including those with varicose veins.[56] The physical domain measures physical functioning, physical role limitations, body pain and general health, whereas the mental dimension measures vitality, social functioning, mental health role limitations and general mental health. Two separate scores are produced (separate physical/mental component summary scores), in addition to the eight separate domain scores. Each score is measured on a scale of 0 to 100 (worst to best). Scores represent the percentage of total possible score achieved (see *Table 1*).

Aberdeen Varicose Vein Questionnaire

The Aberdeen Varicose Vein Questionnaire (AVVQ) is a validated patient-reported disease-specific health questionnaire to assess quality of life in patients with varicose veins. The AVVQ comprises a diagram on which patients draw on their varicose veins and a questionnaire with 12 questions, half of which require a response for each leg. The scores range from 0 to 100 (no effect to severe effect)[53] (see *Table 1*).

Randomisation and treatment allocation

Separate randomisation lists for each centre were prepared by a statistician prior to recruitment using randomly permuted blocks in two block sizes ('ralloc' command; Stata® v14.2, StataCorp LP, College Station, TX, USA) and loaded onto the InForm™ version 4.6 (Oracle® Health Sciences, CA, USA) system. Access to the allocation sequence was strictly restricted to the statistician and appropriate members of the InForm technical support team to maintain allocation concealment.

Consenting participants were registered on the InForm integrated trial management system, a web-based data entry system maintained by the ICTU, and their eligibility for the trial verified. Once eligibility was confirmed, online randomisation was performed remotely by the research nurse.

TABLE 2 Venous Clinical Severity Score (revised)

Score	None (0)	Mild (1)	Moderate (2)	Severe (3)
Pain or other discomfort (i.e. aching, heaviness, fatigue, soreness, burning). Presumes venous origin	None	Occasional pain or other discomfort (i.e. not restricting regular daily activity)	Daily pain or other discomfort (i.e. interfering with but not preventing regular daily activities)	Daily pain or discomfort (i.e. limits most regular daily activities)
Varicose veins: 'varicose' veins must be ≥ 3 mm in diameter to qualify in the standing position	None	Few: scattered (i.e. isolated branch varicosities or clusters). Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous oedema: presumes venous origin	None	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation: presumes venous origin. Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e. vasculitis purpura)	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation: more than just recent pigmentation (i.e. erythema, cellulitis, venous eczema, dermatitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration: presumes venous origin of secondary skin and subcutaneous changes (i.e. chronic oedema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	None	1	2	≥ 3
Active ulcer duration (longest active)	N/A	< 3 months	> 3 months but < 1 year	Not healed for > 1 year
Active ulcer size: diameter (largest active)	N/A	< 2 cm	2–6 cm	> 6 cm
Use of compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: with stockings

N/A, not applicable.

Reprinted from *J Vasc Surg Venous Lymphat Disord*, vol. 1, Marston *et al.*,[52] Multicenter assessment of the repeatability and reproducibility of the revised Venous Clinical Severity Score (rVCSS), pp. 219–24, © 2013 Society for Vascular Surgery, with permission from Elsevier.

Each participant was automatically assigned the next available treatment allocation in the appropriate randomisation list and allocated a unique trial number. The randomisation ratio was 1 : 1 with participants allocated to either:

- early (within 2 weeks) endovenous ablation of superficial venous reflux in addition to compression therapy or
- deferred (standard) therapy consisting of multilayer elastic compression therapy with deferred endovenous ablation of superficial reflux once the ulcer healed.

Blinding

It was not possible to blind either the treating team or the participant to the allocated treatment. The primary outcome, time to ulcer healing, was determined by two expert assessors who were blinded to participant details, including the treatment group.

Deferred ablation (standard care): control group

Participants in the deferred (standard) care group were randomised to receive multilayer compression therapy alone with endovenous ablation of superficial reflux once ulcer healing had been confirmed. Participants whose ulcer had not healed at 6 months post randomisation or who experienced clinical deterioration in the active leg ulcer during the control treatment, could be offered endovenous interventions if it was felt that the participant would benefit from expedited endovenous ablation (at the discretion of the local responsible clinician). The post-ablation duplex ultrasonography strategy for participants in the standard care group was left to local policy.

Early ablation: interventional group

Participants in the interventional group were randomised to receive endovenous ablation of superficial truncal reflux within 2 weeks of randomisation in addition to compression therapy. Post-ablation duplex ultrasonography was performed 6 weeks from randomisation.

Standardisation of compression therapy

As a wide range of compression types are currently used within the NHS, the specific therapy was left to the discretion of individual centres and primary care professionals. Multilayer elastic (two, three or four layer), short stretch and hosiery compression were all deemed acceptable for inclusion in the trial. All participants were advised to use compression hosiery post healing, in line with local policy.

Endovenous interventions

A wide range of endovenous ablation modalities are currently available and in widespread use. The following interventions were permitted in the trial: EVLA or RFA, UGFS, mechanochemical ablation and cyanoacrylate glue closure. These interventions could be performed alone or in combination, as directed by clinical need at the discretion of the responsible vascular specialist.

It was noted that the interventional strategies varied between institutions and between individual clinicians within the same department. Heterogeneity existed for site of vein cannulation (and, therefore, the length of vein ablated), the location of intervention ('office' or clinic based vs. operating theatre), interventional strategy for subulcer venous plexus (to ablate or not), the ablation of visible varicose veins (no treatment, UGFS or surgical avulsion) and the timing of any secondary interventions. As there was neither current research evidence nor consensus as to a single, optimal endovenous interventional strategy for superficial reflux in patients with leg ulceration, local and individual variation was allowed, subject to the following stipulations:

- The endovenous strategy had to include ablation of the main truncal venous reflux.
- Truncal venous reflux had to be treated to the lowest point of incompetence, where possible.
- Significant (as deemed by the treating clinician) residual/recurrent superficial reflux on the 6-week duplex scan was to be ablated.
- Participants had to continue with multilayer compression/stockings immediately after ablation.

Participant follow-up

All randomised participants were followed up until one of the following:

- 1 year after randomisation
- the participant chose to withdraw from the trial
- death.

The trial design is summarised in *Appendix 4*.

As per standard care, participants received routine leg ulcer care in the community and/or hospitals in accordance with local policies.

Monthly telephone calls/follow-up

Participants were followed up on a monthly basis by research nurses at each local site. The aim of the telephone follow-up was to assess whether or not the reference ulcer had healed (for ulcers that were unhealed at the last follow-up), and, in the case of ulcers that were known to have healed, to confirm that the ulcer remained healed. In cases of ulcer recurrence, the telephone follow-up was used to ascertain the date of recurrence and of subsequent healing. Information on utility and resource use, dressing changes, adverse events (AEs) and serious adverse events (SAEs) were also collected.

Six-week clinic visit

All participants underwent a clinical assessment of the reference leg at 6 weeks post randomisation to determine ulcer healing, in addition to VCSS evaluation and documentation of the current ulcer compression regimen. A wound tracing was drawn and photographs were taken to document the size of any unhealed ulcers. Disease-specific and generic quality of life were assessed by means of self-completed questionnaires (AVVQ, EQ-5D and SF-36).

Venous duplex ultrasonography was performed in participants in the early-ablation group to verify if any residual superficial venous reflux was present and guide whether or not further interventions were warranted.

Participant withdrawal

Participants could withdraw from the trial at any time without giving a reason; however, efforts were made to identify the reason for withdrawal whenever possible.

Participants who expressed a wish to withdraw from the trial visits were asked to confirm if they agreed to the trial team retaining their existing trial data and accessing trial-related NHS data; this was documented in the patient notes. If possible, participants were asked for permission to retain primary outcome data.

Participants who declined endovenous ablation remained in the trial for assessment of primary and secondary outcomes [and analysis on intention to treat (ITT)] unless they specifically withdrew their consent.

Measurement and verification of primary outcome measure

Time to healing of the reference ulcer (blinded)

The primary outcome measure of this trial was time from randomisation to complete healing of ulcers on the reference leg. Healing was defined in the protocol as complete re-epithelialisation of all ulceration on the randomised leg in the absence of a scab (as defined in the ESCHAR trial) with no dressing required.

If either the community nurse or the participant believed that ulcer healing had been achieved, they were asked to contact the local research centre immediately to trigger an urgent verification assessment by the research nurse within 1 week.

Ulcer healing was verified by clinical assessment and digital photography repeated weekly for 4 weeks, unless otherwise agreed by the trial manager. Digital photographs were assigned pseudonyms by trial number only and transferred via a secure server to the ICTU.

All digital images were assessed by two vascular surgeons blinded to treatment allocation. Each independently assessed the reference ulcer using a predefined set of decision rules based on those utilised in Venous leg Ulcer Study IV (VenUS IV)[59] (see *Appendix 5*) to allocate each to one of three categories (healed, not healed or unsure). Disagreements were resolved through discussion with a third blinded expert reviewer.

When a reference ulcer was deemed to have healed, the date of the photograph in which healing was recorded was taken to be the date of healing. If healing was confirmed at the first verification visit, the date of healing notification (by participant or community nurse) was taken as the date of ulcer healing.

Measurement and verification of secondary outcome measures

Ulcer healing

The number of ulcers healed at 24 weeks was reported, in addition to time to ulcer healing, to allow comparison with other published studies.

Ulcer recurrence/ulcer-free time

Participant-reported ulcer recurrence on the reference leg was recorded by the research nurses for up to 12 months from randomisation or until trial exit, by means of monthly telephone calls to the participant. Recurrence was verified using patient notes from recent clinic visits whenever possible. When there had been a recurrence of venous leg ulceration on the reference leg, the dates of recurrence and subsequent healing, if applicable, were recorded and used to determine ulcer-free time.

Health-related quality of life

In addition to the baseline assessment, health-related quality of life (HRQoL) was measured at 6 weeks, 6 months and 12 months using questionnaires either administered in clinic by the research nurse or sent by mail to the participant along with a pre-addressed and prepaid envelope. Each questionnaire pack was identical in content to the baseline questionnaire pack containing the EQ-5D, SF-36 and AVVQ. When necessary, reminder letters were sent by post to participants if the questionnaires had not been returned.

Utility and resource use

Participant-reported utility and resource use was collected by the research nurses up to 12 months from randomisation or trial exit via monthly telephone calls to the participant, or at clinic visits if these occurred as part of clinical care. The participants were provided at baseline with diaries in which any visits to health-care providers could be recorded. All utility and resource use data were collected, whether or not deemed to be related to the reference leg.

Markers of clinical success

Venous Clinical Severity Score

In addition to the baseline visit, the VCSS was assessed by the research nurse or treating clinician at the 6-week clinic visit to allow comparison with the baseline score.

Ablation success

Local principal investigators assessed the presence of residual/recurrent truncal superficial venous reflux in the early-ablation group at 6 weeks by means of a venous duplex. Residual reflux and any recanalised segments were noted. When the truncal vein was not successfully closed, further endovenous ablation procedures were organised. For other patterns of residual or recurrent reflux (such as reflux in tributaries or perforating veins), the decision whether or not to perform additional endovenous interventions was left to the discretion of the treating clinician.

Safety monitoring of early ablation

Adverse events

The research nurses collected data regarding the occurrence of AEs during the monthly telephone calls and from clinic or surgery notes, and reported these to the ICTU via the web-based data capture system. Only AEs deemed by the local principal investigator to be related to the trial intervention or compression were recorded. The AEs thought to be related to the interventions are summarised in *Table 3*. AEs were reviewed and categorised by the trial manager and chief investigator as procedural complications.

Serious adverse events

As per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice (ICH–GCP) guidelines, SAEs were defined as those AEs that result in death; are life-threatening; require inpatient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; are cancer; or are other important medical events in the opinion of the responsible investigator (i.e. not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or more of the outcomes described previously). All SAEs were recorded, whether or not deemed by the local principal investigator to be related to the trial intervention or compression.

The research nurses collected data regarding the occurrence of all SAEs via the monthly telephone calls, clinic or surgery notes, and hospital admission records. These were reported to the ICTU via the web-based data capture system within 24 hours of the nurses becoming aware of the event and reviewed by the chief investigator.

All SAEs were also reported by the trial manager to the sponsor and chairperson of the DMC. SAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA®) version 20.0 [URL: www.meddra.org (accessed 15 May 2019). MedDRA® terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. MedDRA® trademark is registered by the International Federation of Pharmaceutical Manufacturers and Associations on behalf of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use].

TABLE 3 Adverse events expected to be related to the intervention

Systemic	Local
Allergic reaction required local/no treatment	Bleeding requiring intervention
Migraine	Blistering of skin
Visual disturbance	Pressure damage
Fainting	Nerve damage
Cough/chest tightness	DVT
Systemic infection	Haematoma
Pulmonary embolism	Participant-reported paraesthesia
Transient ischaemic attack	Pigmentation of skin
Stroke	Superficial thrombophlebitis
	New ulcer
	Deterioration of ulcer
	Wound infection

Participant communications

Participants were kept updated on trial progress via the trial Facebook (Facebook, Inc., Menlo Park, CA, USA) and Twitter (Twitter, Inc., San Francisco, CA, USA) accounts. Two participant newsletters were circulated during the follow-up stage (for participants who had not withdrawn from the trial), to keep them updated with trial progress. A newsletter summarising the main results from the EVRA trial was also sent to non-withdrawn participants.

Statistical methods

The trial analysis was carried out on an ITT basis (all participants remained in the group allocated at randomisation). Histograms and box plots were used to check the distribution and possible outliers for continuous variables. Mathematical transformations were applied, when appropriate, in order to render the continuous variables distribution normally distributed. Continuous variables that follow an approximately normal distribution were summarised using means and standard deviations (SDs). Skewed continuous variables were summarised using medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages.

All hypothesis testing was planned to be two-tailed with a 5% significance level and no adjustment for multiple testing. Analyses were performed using Stata v14.2.

As the randomisation was stratified by centre, when possible, analyses are adjusted by trial centre. Potentially, this is done by including trial centre as either a fixed or a random effect in any regression models. As the centres that participated in the trial could be viewed as a random sample of all possible trial centres, random-effects models were preferred. However, in cases where random-effects models could not be fitted (e.g. owing to lack of convergence), trial centre was included in models as a fixed effect.

Baseline data

Baseline characteristics, including demographics, medical history, ulcer history and details of current ulcers, were summarised by treatment group using appropriate descriptive methods for all randomised participants. Ulcer duration was calculated as the difference between the date the current ulcer appeared

(best estimate based on medical records, referral letters and participant recollection) and the date of randomisation. Deep vein reflux and/or obstruction was defined as iliac, femoral, popliteal or infrapopliteal deep vein reflux as shown on duplex scan [for details, see the statistical analysis plan on the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 18 April 2019)].

Trial completion

Reasons for trial exit were taken from the end-of-trial form and included completed trial (to 12 months), lost to follow-up, withdrawn and death.

Statistical analysis

Primary end point

The primary outcome was time to complete healing and we tested the hypothesis that there was no difference in time to ulcer healing between deferred- and early-ablation groups using a Cox proportional hazards model. As the randomisation was stratified by centre, centre was also included in the model as a random effect (shared frailty). The proportional hazards assumption was assessed graphically – by plotting $-\ln\{-\ln[\hat{S}(t)]\}$ versus $\ln(t)$ and checking that the curves for each level of the covariate are parallel – and also numerically using Grambsch and Therneau tests. Kaplan–Meier (KM) survival curves were also presented and, as a subsidiary analysis, we investigated the effect of participant age, ulcer size at baseline and duration of time to complete healing using Cox regression, with centre included in the model as a random effect to adjust for potential centre effect [for details, see the statistical analysis plan on the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 18 April 2019)].

Participants were censored at the time of last follow-up if they had died, withdrawn or were lost to follow-up before primary ulcer healing. The follow-up time was 1 year after randomisation, and thus observations of participants with an unhealed primary ulcer at 1 year after randomisation were also censored.

Secondary end points

Recurrence/ulcer-free time to 1 year and 24-week ulcer healing rate

The effect of the trial intervention on ulcer-free time was investigated after adjusting for potential confounders [for details, see the statistical analysis plan on the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 18 April 2019)], using multiple linear regression if the assumption of normality was met. If the assumption of normality was not met (there is no suitable transformation), ulcer-free time was categorised and analysed using appropriate regression methods to adjust for potential confounders. The number of ulcers healed at 24 weeks and associated 95% CIs were obtained from the KM analysis.

One-year ulcer-free time (in days) in those who had completed follow-up to 1 year was calculated as total follow-up time (i.e. 1 year) minus the total duration of ulcers, including the primary ulcer and any recurrences.

Quality of Life

The AVVQ was scored in accordance with the manual.[53]

The SF-36 was scored using QualityMetric Health Outcomes™ scoring software 4.0 (QualityMetric, Lincoln, RI, USA) for the physical health and mental health dimensions and all eight scales: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health.

The index-based values ('utilities') were calculated by the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), crosswalk index value calculator downloaded from the EQ-5D official website.

The HRQoL scores were presented using line plots for each trial group to illustrate trends in AVVQ score, SF-36 and EQ-5D-5L over time. We planned to report the means and 95% CI of means, or medians and interquartiles, at each time point (including baseline and 6 weeks and 6 and 12 months after randomisation),

depending on the distribution of the data. Mixed models with time, age, ulcer size and duration as fixed effects, and trial centre and patient as nested random effects, were used to estimate differences in HRQoL scores between the trial groups at each time point and to calculate an overall *p*-value for the difference in HRQoL scores between the trial groups.

Markers for clinical success: Venous Clinical Severity Score

Clinical success was assessed using the VCSS, which was measured at baseline and 6 weeks post randomisation. Any change in VCSS was compared between the two groups using the *t*-test (assuming that change in VCSS is normally distributed) or appropriate non-parametric test (if change in VCSS is not normally distributed). The VCSS at 6 weeks post randomisation and baseline is summarised using box plots for both groups (see *Figure 11*).

Markers for clinical success: clinical, aetiological, anatomical and pathophysiological

The change in clinical classification in the CEAP score from baseline to 6 weeks post randomisation is reported (see *Table 17*) and the chi-squared test was used to compare the two groups.

Safety data

The safety data, including AEs and SAEs, were provided in a tabular format for the two groups [for details, see the statistical analysis plan on the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 18 April 2019)]. AEs were summarised by description and outcome and SAEs were summarised by SAE reason, frequency, severity, relationship to treatment, outcome and expectedness.

Sensitivity analysis

As a sensitivity analysis, a per-protocol analysis was performed by excluding participants with protocol deviations. This sensitivity analysis covered all primary and secondary outcomes.

Missing data

There was no imputation of missing data for the primary end point (time to healing) or the secondary end points of 24-week healing rate and ulcer-free time. However, multiple imputation of the quality-of-life measures and measures of clinical success was performed using chained equations as a sensitivity analysis.[60] The number of missing data were reported.

Health economic analysis

Overview of within-trial economic analysis

The within-trial health economic analysis compared early endovenous ablation with deferred endovenous ablation for superficial venous truncal reflux in patients with venous ulceration, within the 1-year time horizon of the clinical trial. A cost–utility analysis was performed. No subgroup analyses were undertaken. The analyses were performed from the perspective of the NHS and Personal Social Services in accordance with NICE methods guidance.[61]

The total cost per patient aimed to include only items related to the endovenous ablation procedure or venous leg ulcer. The price year was 2015/16. No discounting was applied as the follow-up is 1 year. The trial was reported in accordance with guidelines for economic evaluation.[62] See Husereau *et al.*[62] for the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and the project web page [www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 18 April 2019)] for the health economic plan.

Data

Data were collected in the CRF by case note review and from questionnaires. The primary outcome measure was the quality-adjusted life-years (QALYs) gained at 1 year. Health state utilities were calculated from the EQ-5D-5L questionnaire administered to participants at baseline, and at 6 weeks and 6 and 12 months post randomisation. The base-case economic analysis uses the crosswalk tariff.[63] This is an algorithm that maps the EQ-5D-5L responses to the three-level responses and then values those health

states using the original EQ-5D-3L tariff developed by Dolan.[64] This tariff was available from the EuroQol group and was recommended by NICE at the time of these analyses.[65] As a sensitivity analysis, an alternative five-level tariff recommended by Devlin *et al.*[55] was used. QALYs were estimated for each participant to 1 year as the 'area under the curve' of EQ-5D-5L index values.

Resource use items were recorded for each participant at monthly follow-up telephone calls. The health-care resource use collected in the trial and the assumptions made in the economic analysis are presented in *Table 4*.

TABLE 4 Resource use items collected in the trial and assumptions made in the analysis

Resource use	Description
Trial vein ablation procedures	Time in operating theatre and the type of procedure (UGFS, RFA, EVLA or MOCA) were recorded. Participants could have more than one trial vein ablation procedure. Staff procedure costs were calculated from the time in operating theatre (recorded in the CRF) multiplied by standard unit costs (see *Appendix 6*)
Dressings and bandages for wound healing	Dressings: classified in the CRF as NA dressing, Inadine™ [Systagenix (KCI company), San Antonio, TX, USA] (iodine impregnated), or other. For estimating costs, it was assumed that dressings were changed twice per week until wound healing Compression: the CRF recorded if the participant used compression bandages, stockings or no compression. If bandages, it was assumed that these were changed at each dressing change. Participants who used compression stockings were assumed to own two pairs (one to wash and one to wear), and that both were replaced every 3 months (Karen Dhillon, Imperial College London, 2017, personal communication). Bandages were assumed to have been used if the CRF did not state which mode of compression was applied (as these are the most common type of compression therapy in use)
Compression therapy to prevent recurrence after wound healing	The costs of compression therapy post healing were estimated in line with local policy. For estimating costs, it was assumed that stockings were changed every 3 months (Karen Dhillon, personal communication)
Visits to a district nurse or primary care nurse	All these visits, for any reason, were included in the total cost
Visits from a district nurse	All these visits, for any reason, were included in the total cost
Hospital admissions (inpatient and day case)	The trial collected data on the reason for the admission and any procedure undertaken as free text. Admissions were classified as 'vein related' if one of the text fields included one of these keyword fragments: 'leg ulcer, vein, rf, abla, evlt, evla, sclero, screlo, vnus, foam, ugfs, angio, rehab, physio, conval, skin, antibio, sepsis, septic, infection, dvt' (the list takes account of spelling errors in the text field). Vein ablation procedures were identified if one of the text fields included one of the following keywords: 'vein, rf, abla, evlt, evla, sclero, screlo, vnus, foam, ugfs'. Admissions were cross-checked against protocol ablations so as not to double count the same event. The exact date of the admission was not recorded in the admissions CRF, only the month after randomisation. It was assumed that if two vein ablation procedures occurred in the same month, then they were duplicate records
Outpatient visits	Outpatient visits were recorded, along with free text indicating the reason for the consultation and any procedure undertaken. Outpatient visits were classified as 'not vein related' if the reason for the consultation or the procedure contained one of these keywords: 'tia, hernia, aaa, asth, aneurysm, ankle, opthal, arthritis, breast, bowel, bereavement, eye, breath, carpal, cpap, cancer, chest, colorectal, diab, diet, head, ent, endoscopy, endocrin, fall, fracture, gynae, gastro, heamat, hearing, heart, hyperdermic, immo, testic, kidney, knee, lung, lymph, facial, nasal, oncol, ortha, ortho, urology, pacemaker, parkinson, pessary, cateract, rheuma, renal, respiratory, reveal, recell, rhemat, spinal, sleep, wrist, thumb, shoulder, abdo, aorta, deaf, memory, migrane, ovary' (note that ReCell and REVEAL are other concurrent clinical trials[66,67])

continued

TABLE 4 Resource use items collected in the trial and assumptions made in the analysis (*continued*)

Resource use	Description
	Vein procedures in outpatients were identified if one of the text fields included one of the following keywords: 'sclero, foam, ugfs' Outpatient visits were cross-checked against protocol ablations so as not to double count the same event. The exact date of the outpatient consultation was not recorded in the CRF, only the month after randomisation. It was assumed that if two vein ablation procedures occurred in the same month, then they were duplicate records
Visits to and from the GP	All these visits were included in the total cost, for any reason
Use of antiplatelet and anticoagulant medicines	The CRF recorded the drug used each month, but did not record the dose. It was assumed that doses (taking account age, sex and weight) were as recommended by the *British National Formulary*[68]
Physiotherapy and occupational therapy	All these visits, for any reason, were included in the total cost
Home care visits (auxiliary nursing)	All these visits, for any reason, were included in the total cost
Home help visits for (personal care)	All these visits, for any reason, were included in the total cost
Out-of-pocket, informal care and personal expenses	Time lost from work and normal activities, informal care and whether or not out-of-pocket expenses were incurred were recorded in the CRF. These were tabulated but not included in the NHS and Personal Social Services total costs

NA, non-adherent; REVEAL, Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification.

Ulcer-related health-care use

The participants in this trial tended to be elderly with comorbidities and, therefore, significant users of health-care resources. To obtain a precise estimate of the effect of the intervention on health-care use, and avoid statistical 'noise', the trial aimed to include only resource use related to the ulcer. The trial CRF collected the reason for the use of health-care resources and the procedure undertaken as free text. Keywords indicating ulcer-related activity included ulcer care, skin care, leg care, venous procedures, angiography, infection, rehabilitation, DVT and related keywords (see *Table 4*). Ulcer-related health care was included in the total cost per patient, whereas non-ulcer-related health care was tabulated but not included in total cost. Non-ulcer-related care was excluded from inpatient admissions, day case admissions and outpatient consultations. These health-care resources and costs, along with out-of-pocket expenses and time lost from usual activities, were tabulated but not included in the total mean cost per patient. It was assumed that all district nurse visits, primary care visits, physiotherapy and occupational therapy were definitely or probably ulcer related.

Unit costs

Costs were estimated by multiplying resource use by unit costs obtained from published literature, England and Wales Healthcare Resource Group costs and manufacturers' list prices for catheters and other disposable kit (see *Appendix 6*).

Handling of missing data

A small number of trial data were missing because of withdrawal or for other reasons. The extent and pattern of missing data were assessed. Costs and EQ-5D-5L index were set to zero after the date of death.

For the cost-effectiveness analysis, the base case uses 'complete cases' in an ITT analysis. A participant was considered to be a complete case if he or she completed all the EQ-5D questions at baseline, 6 weeks, 6 months and 1 year, and did not withdraw from the trial before 1 year.

As a sensitivity analysis, multiple imputation using chained equations was used to impute the remaining missing data by regression, under the assumption of 'missingness at random'.[60] This means that missing costs are considered predictable from observed data, plus or minus a random error. For each participant lost to follow-up, costs 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).[60]

Handling of protocol deviations

In the clinical trial, 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 ($n/N = 40/59$ patients in the early-intervention group and $n/N = 34/58$ in the deferred-intervention group). A sensitivity analysis was carried out excluding these participants.

Cost-effectiveness analysis

The difference in mean total costs and mean total QALYs per participant between the treatment groups was estimated using bivariate normal regression (seemingly unrelated regression using the Stata command 'surreg'), including baseline EQ-5D-5L in the QALY regression.[69]

The incremental cost-effectiveness ratio (ICER) was calculated. The probability that early ablation was more cost-effective than deferred ablation was estimated at different cost-effectiveness thresholds using two methods. The first method assumed bivariate normality in the distribution of total costs and QALYs. The second method used the bootstrapping method, with 1000 Monte Carlo resamples. The bootstrap was used only for the analysis of complete cases. Bootstrap combined with multiple imputation can be very computationally demanding. If 1000 bootstrap resamples were used with 10 multiple imputations, 10,000 data sets would need to be generated and analysed.[70]

Sensitivity analyses

Five models were estimated: (1) base case – complete cases with bootstrap standard errors (SEs) and crosswalk EQ-5D tariff; (2) complete case with bivariate normal SEs and crosswalk EQ-5D tariff; (3) multiple imputation with bivariate normal SEs and crosswalk EQ-5D tariff; (4) complete case with bootstrap SEs and EQ-5D-5L tariff estimated by Devlin *et al.*;[55] and (5) as model 1, excluding participants with protocol deviations.

Database and data processing

InForm database

Data were collected and managed using InForm, an electronic data capture system built around an Oracle database. The InForm system includes automated range checks and validation rules for data entry to help ensure data accuracy. A computer-generated audit trail is in place, which records the date, time, operator, operation and previous value of all manipulation of clinical data.

InForm storage and management was undertaken by the Imperial College London information and communication technologies team. InForm sits on a server behind a firewall connected to the college storage area network. The data are backed up regularly to removable media, allowing for disaster recovery. In addition to the college backup facility, every 20 minutes the activity logs for the trial are moved to another server in a different location to facilitate rapid recovery of data, should it become necessary (e.g. in a disaster recovery scenario).

Data were entered remotely into the database by research nurses at each site. Access to InForm is web based with role- and site-based security applied.

Data queries

During the recruitment and follow-up phases, inconsistent, implausible or missing data were investigated by the trial manager and further validation checks were carried out periodically by the trial statistician.

The trial manager performed quality control checks on the first two CRFs and participant questionnaires entered at each site to ensure the accuracy of data input and that data entry processes had been understood. Ongoing data checks using source data verification were performed at each monitoring visit as per the EVRA monitoring plan. Missing forms and data were flagged by the trial manager periodically and distributed to the appropriate sites on a regular basis.

Data cleaning

The data cleaning process included the following:

- ensuring that missing/unknown values are labelled accurately
- further ensuring that spurious values have not been included into data fields
- check of inconsistencies in data not flagged by inbuilt edit checks
- review of 100% of comments by the trial manager
- review of 100% of anonymised duplex reports by the chief investigator assisted by the trial manager, to ensure that they were entered into InForm correctly
- review of 100% of the data for the primary end point, final ulcer healing date, by an independent trial manager, to ensure that they were entered into InForm correctly.

Final data checks were performed by the statistician once the database had been soft locked before hard lock was complete. All outstanding queries were resolved prior to the database hard lock.

Chapter 3 Clinical results

Screening and recruitment

Recruitment commenced in October 2013 and was completed at the end of September 2016. In total, 6555 patients were screened for potential inclusion in the trial and, of these, 450 (6.9%) were randomised. The reasons for exclusion are presented in the Consolidated Standards of Reporting Trials (CONSORT) diagram (*Figure 3*).

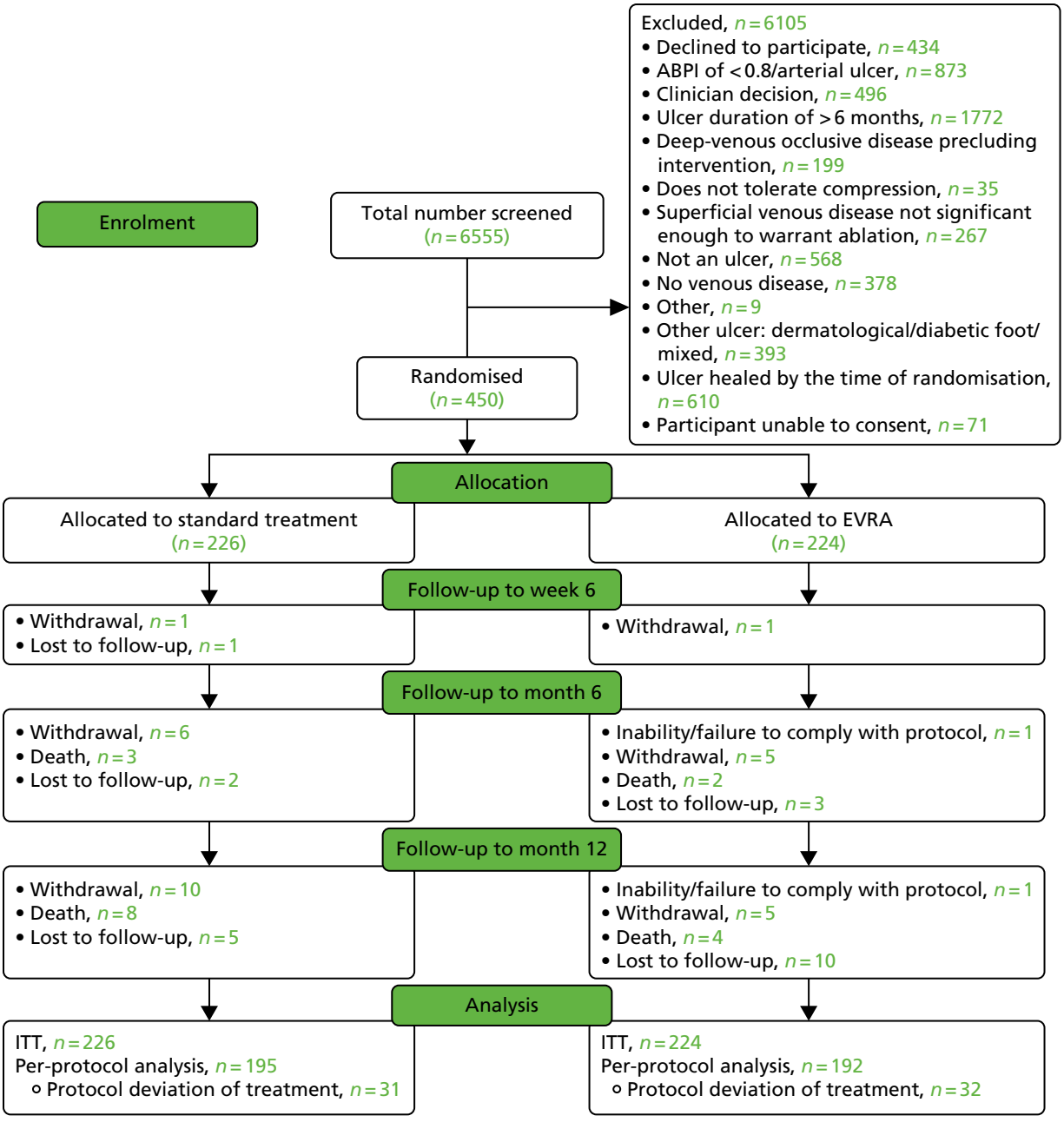


FIGURE 3 Consolidated Standards of Reporting Trials diagram of the trial population. The cumulative number of participants who had withdrawn, died, had failed to comply with the protocol or had been lost to follow-up by each time point are presented. Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

Trial site recruitment

Ten sites were initially activated for recruitment, with a further 11 sites activated as it became apparent that the original sites would be unable to reach their recruitment targets. Over the recruitment period, 21 sites participated in the trial, with one site failing to recruit any participants.

Appendix 7 shows the total number of participants recruited per site in order of the total number of weeks recruiting. The first six sites opened benefited from a dedicated part-time research nurse, whereas the remaining sites were supported by Clinical Research Network or local research nurses working across multiple studies.

Appendix 8 details the overall recruitment per month against the targets. At trial commencement, the monthly target recruitment was 24 participants per month. When it became apparent that this was not achievable (October 2015), the target was reduced to 13 participants per month, adding an additional 8 months to the recruitment period. The target of 450 participants was achieved on 30 September 2016.

Follow-up

Follow-up of the last recruited participant was competed on 28 September 2017. A total of 407 participants attended the 12-month follow-up and the median follow-up period for both the deferred- and early-ablation groups was 365 (IQR 364–370) days. *Figure 3* details the trial exit time points. The cumulative numbers of participants who had withdrawn, died, failed to comply with the protocol or been lost to follow-up by each time point are presented.

Ineligible participants

Six ineligible participants were randomised to the trial: two participants in the early-ablation group (one with leg ulceration of > 6 months' duration and one with no active ulceration) and four participants in the deferred-ablation group (two participants with leg ulceration of > 6 months' duration, one participant with no active leg ulceration and one participant with deep-venous occlusive disease). These participants were included in the ITT analysis but excluded from the per-protocol analysis (see *Figure 3*).

Baseline characteristics of participants by trial group

The baseline characteristics, medical history, current medication, ulcer history and baseline compression therapy are summarised in *Tables 5–7*. The two trial groups were well matched in terms of baseline characteristics, including the following potential prognostic factors: ulcer duration, ulcer size, participant age and history of DVT.

Slightly more men than women were randomised (55% vs. 45%). The mean participant BMI was 30.3 kg/m^2 (clinically obese).

The baseline ulcer characteristics are summarised in *Table 8*. Ulcer duration was slightly greater in participants randomised to early ablation [median 3.2 months (IQR 2.3–4.2 months)] than in the deferred-ablation group [median 3.0 months (IQR 1.7–4.2 months)]. The median ulcer size in the early-ablation group was 2.4 cm^2 (IQR 1.0–7.1 cm^2), compared with 2.9 cm^2 (IQR 1.1–8.2 cm^2) in the deferred-ablation group.

TABLE 5 Baseline characteristics between the early and deferred ablation group

Characteristic	Early (*N* = 224)	Deferred (*N* = 226)	Total (*N* = 450)
Age (years), mean (SD)	67.0 (15.5), *n* = 224	68.9 (14.0), *n* = 226	68.0 (14.8), *n* = 450
Height (cm), mean (SD)	171.9 (11.1), *n* = 220	170.5 (10.8), *n* = 220	171.2 (11.0), *n* = 440
Weight (kg), mean (SD)	89.5 (25.6), *n* = 218	88.8 (24.1), *n* = 219	89.1 (24.9), *n* = 437
BMI (kg/m^2), mean (SD)	30.1 (7.8), *n* = 218	30.4 (7.4), *n* = 219	30.3 (7.6), *n* = 437
Sex, *n* (%)			
Female	97 (43.3)	106 (46.9)	203 (45.1)
Male	127 (56.7)	120 (53.1)	247 (54.9)
Smoking, *n* (%)			
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, *n* (%)			
White	206 (92.0)	208 (92.0)	414 (92.0)
Mixed	1 (0.4)	0 (0.0)	1 (0.2)
Asian	11 (4.9)	12 (5.3)	23 (5.1)
Black	3 (1.3)	5 (2.2)	9 (1.8)
Other	3 (1.3)	1 (0.4)	4 (0.9)
EQ-5D, mean (SD)			
Health state score	70.2 (17.7), *n* = 222	70.1 (17.1), *n* = 225	70.2 (17.4), *n* = 447
Index value	0.7 (0.2), *n* = 222	0.7 (0.2), *n* = 226	0.7 (0.2), *n* = 448
SF-36, mean (SD)			
Physical function	37.3 (12.0), *n* = 223	37.5 (12.5), *n* = 225	37.4 (12.2), *n* = 448
Role-physical	39.0 (12.2), *n* = 223	39.7 (12.1), *n* = 224	39.4 (12.2), *n* = 447
Body pain	41.3 (11.1), *n* = 223	41.6 (11.9), *n* = 224	41.4 (11.5), *n* = 447
General health	45.8 (9.2), *n* = 223	46.0 (9.8), *n* = 225	45.8 (9.5), *n* = 448
Vitality	48.2 (10.2), *n* = 222	47.8 (10.6), *n* = 224	48.0 (10.4), *n* = 446
Social functioning	42.6 (12.4), *n* = 223	42.4 (13.5), *n* = 224	42.5 (13.0), *n* = 447
Role-emotional	42.7 (13.8), *n* = 222	43.7 (13.6), *n* = 224	43.2 (13.7), *n* = 446
Mental health	49.2 (10.3), *n* = 222	49.3 (10.7), *n* = 224	49.2 (10.5), *n* = 446
Physical component summary	38.5 (9.9), *n* = 222	38.8 (10.8), *n* = 223	38.6 (10.4), *n* = 445
Mental component summary	49.2 (10.9), *n* = 222	49.4 (11.6), *n* = 223	49.3 (11.2), *n* = 445
Total AVVQ, mean (SD)	44.1 (9.0), *n* = 200	44.3 (8.7), *n* = 192	44.2 (8.8), *n* = 392

Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

TABLE 6 Summary of medical history and concurrent medication

Variable	Early (*N* = 224)	Deferred (*N* = 226)	Total (*N* = 450)
Previous pregnancy, *n* (%)[a]			
Yes	85 (87.6)	91 (85.9)	172 (86.7)
History of DVT in pregnancy (yes)	1 (1.2)	2 (2.2)	3 (1.7)
No	12 (12.4)	15 (14.)	27 (13.3)
Hormone therapy, *n* (%)[a]			
None	66 (29.5)	71 (31.4)	137 (30.4)
Previous HRT	16 (7.1)	15 (6.6)	31 (6.9)
Current HRT	1 (0.4)	3 (1.3)	4 (0.9)
Previous OC	21 (9.4)	21 (9.3)	42 (9.3)
Current OC	2 (0.9)	1 (0.4)	3 (0.7)
Previous rheumatoid disease, *n* (%)			
No	204 (91.1)	212 (93.8)	416 (92.4)
Yes	20 (8.9)	14 (6.2)	34 (7.6)
Previous DVT in either leg, *n* (%)			
No	206 (92.0)	203 (89.8)	409 (90.9)
Yes	18 (8.0)	23 (10.2)	41 (9.1)
Previous DVT in trial leg, *n* (%)			
No	206 (93.3)	203 (93.4)	409 (93.2)
Yes	15 (6.7)	15 (6.6)	30 (6.8)
Current antiplatelet therapy, *n* (%)			
None	172 (76.8)	179 (79.2)	351 (78.0)
Aspirin	49 (21.9)	44 (19.5)	93 (20.7)
Clopidogrel	5 (2.2)	5 (2.2)	10 (2.2)
Other	1 (0.4)	0 (0)	1 (0.2)
Current anticoagulation therapy, *n* (%)			
None	196 (87.5)	189 (83.6)	385 (85.6)
Warfarin	25 (11.2)	32 (14.2)	57 (12.7)
New oral anticoagulants	2 (0.9)	4 (1.8)	6 (1.3)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Current steroids, *n* (%)			
No	211 (94.2)	220 (97.4)	431 (95.8)
Yes	13 (5.8)	6 (2.7)	19 (4.2)
Current trental (pentoxifylline), *n* (%)			
No	224 (100)	226 (100)	450 (100)
Yes	0 (0)	0 (0)	0 (0)
Diabetes, *n* (%)			
No	190 (84.8)	198 (87.6)	388 (86.2)
Yes	34 (15.2)	28 (12.4)	62 (13.8)

HRT, hormone replacement therapy; OC, oral contraception.
a Female only.
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

TABLE 7 Summary of ulcer history and baseline compression

Variable	Early (*N* = 224)	Deferred (*N* = 226)
Previous ulcer (yes), *n* (%)		
No	106 (47.3)	108 (48.0)
Yes	118 (52.7)	117 (52.0)
Ulcer dressing, *n* (%)		
NA	64 (28.6)	55 (24.3)
Inadine	28 (12.5)	25 (11.1)
Other	131 (58.5)	146 (64.6)
Missing	1 (0.4)	0 (0)
Baseline compression, *n* (%)		
None[a]	3 (1.3)	7 (3.1)
KTwo (Urgo Limited, Loughborough, UK)	32 (14.3)	29 (12.8)
Three-layer bandage	42 (18.8)	41 (18.1)
Four-layer bandage	59 (26.3)	59 (26.1)
European short stretch	43 (19.2)	36 (15.9)
Stocking, *n* (%)	42 (18.8)	53 (23.5)
Other	2 (0.9)	1 (0.4)
Missing	1 (0.4)	0 (0)
Time of wearing, *n* (%)		
Day and night	196 (87.5)	185 (81.9)
Day only	25 (11.2)	39 (17.3)
Missing	3 (1.3)	2 (0.9)

NA, non-adherent.
a For participants not treated with compression at baseline, compression therapy was commenced at randomisation.
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

TABLE 8 Characteristics of current ulcer

Characteristic	Early (*N* = 224)	Deferred (*N* = 226)
Ulcer duration (months), median (IQR)[a]	3.2 (2.3–4.2)	3.0 (1.7–4.2)
Trial ulcer leg, *n* (%)		
Right	107 (47.8)	115 (50.9)
Left	117 (52.2)	111 (49.1)
Ulcer location, *n* (%)		
Lateral	92 (41.1)	93 (41.2)
Medial	116 (51.8)	118 (52.2)
Circumferential	9 (4.0)	7 (3.1)
Missing	7 (3.1)	8 (3.5)
Ulcer size (cm^2), median (IQR)[b]	2.4 (1.0–7.1)	2.9 (1.1–8.2)

continued

TABLE 8 Characteristics of current ulcer (*continued*)

Characteristic	Early (*N* = 224)	Deferred (*N* = 226)
Duplex ultrasound scan: deep vein, *n* (%)		
Normal	150 (67.0)	157 (69.5)
Abnormal[c]	74 (33.0)	69 (30.5)
Reflux	74 (100)	69 (100)
Outflow obstruction	0 (0)	0 (0)
CEAP score: clinical signs – grade, *n* (%)		
C_5	1 (0.4)	1 (0.4)
C_6	224 (99.6)	225 (99.6)
CEAP score: clinical signs – presentation, *n* (%)		
Asymptomatic	0 (0)	0 (0)
Symptomatic	224 (100)	226 (100)
Aetiological classification, *n* (%)		
Primary	217 (96.9)	214 (94.7)
Secondary	7 (3.1)	12 (5.3)
Deep	0 (0)	0 (0)
No venous cause	0 (0)	0 (0)
Anatomical distribution, *n* (%)		
Superficial	220 (98.2)	221 (97.8)
Perforator	3 (1.3)	3 (1.3)
Deep	1 (0.4)	2 (0.9)
Pathophysiological dysfunction, *n* (%)		
Reflux	224 (100)	226 (100)
Obstruction	0 (0)	0 (0)
Both	0 (0)	1 (0.4)
No venous cause	0 (0)	0 (0)
VCSS, median (IQR)	15 (14–18)	16 (14–18)
Palpable pedal pulses, *n* (%)		
No	15 (6.7)	14 (6.2)
Yes	209 (93.3)	212 (93.8)

a Ulcer duration as reported by participant.
b Ulcer size evaluated using digital planimetry from standardised digital photographs by assessor blinded to intervention group.
c Defined as presence of retrograde flow in common femoral, femoral or popliteal veins of > 1-second duration after augmentation. A participant can have both deep vein reflux and obstruction.

The six ineligible participants included two participants who had a healed ulcer at the time of randomisation (which was confirmed after randomisation). The ineligible participant with deep-venous occlusive disease was confirmed to have both deep vein reflux and outflow obstruction by baseline duplex ultrasonography scan. In general, ulcer characteristics were well matched between the two groups.

Table 9 details the patterns of superficial truncal venous reflux at baseline.

TABLE 9 Summary of truncal venous reflux patterns at baseline

Pattern of superficial reflux at baseline	Early (*N* = 224), *n* (%)	Deferred (*N* = 226), *n* (%)
GSV reflux alone	123 (54.9)	125 (55.4)
SSV reflux alone	25 (11.2)	30 (13.3)
GSV and SSV reflux	65 (29.0)	56 (24.8)
Other pattern of reflux[a]	11 (4.9)	15 (6.6)

GSV, great saphenous vein; SSV, short saphenous vein.
a Accessory saphenous, perforator vein or tributary vein reflux.
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

Interventions

Ablation method and timing of the first ablation are summarised in *Table 10*. There were 55 participants who did not undergo ablation in the deferred-intervention group and seven in the early-ablation group, including one in whom the procedure was abandoned before completion. The most common intervention was UGFS alone (47%), followed by endothermal ablation alone (29%).

Among the 55 participants in the deferred-ablation group who did not undergo endovenous ablation up to 1 year, 19 participants died, withdrew or were lost to follow-up from the trial and 36 participants completed the trial, including 27 participants with healed ulcer and nine participants with unhealed ulcer at 1 year (*Table 11*).

TABLE 10 Summary of endovenous ablation procedures performed

Variable	Early (*N* = 224)	Deferred (*N* = 226)
Interventional ablation type,* n *(%)		
No ablation	6 (2.7)	55 (24.3)
Endothermal only[a]	71 (31.7)	54 (23.9)
UGFS only[b]	111 (49.6)	100 (44.3)
MOCA only	5 (2.2)	1 (0.4)
Endothermal[a] and UGFS[b]	27 (12.1)	16 (7.1)
MOCA and UGFS[b]	3 (1.3)	0 (0)
Abandoned ablation	1 (0.5)	0 (0)
Timing of first ablation procedure,*[c] n *(%)		
No ablation	6 (2.7)	55 (24.3)[d]
Within 2 weeks	203 (90.6)	1 (0.4)
Before ulcer healing	200	1[e]
After ulcer healing	3	0
Between 2 and 4 weeks	9 (4.0)	1 (0.4)
Before ulcer healing	9	1[e]
After ulcer healing	0	0

continued

TABLE 10 Summary of endovenous ablation procedures performed (*continued*)

Variable	Early (*N* = 224)	Deferred (*N* = 226)
Between 4 weeks and 6 months	6 (2.7)	103 (45.6)
Before ulcer healing	4	4[e]
After ulcer healing	2	99
After 6 months	0 (0)	66 (29.2)
Before ulcer healing	0	19
After ulcer healing	0	47

a Endovenous thermal ablation procedures included laser and radiofrequency ablation.
b UGFS to treat tributary veins or subulcer venous plexus performed as per the standard technique of the treating clinician.
c Timing of first endovenous ablation only. Timing of any additional ablations was left to the discretion of treating clinicians.
d Among the 55/226 (24.3%) participants in the deferred-ablation group who were not treated by 12 months post randomisation, the ulcer was healed in 27 and not healed in nine; the remaining 19 participants had either died (*n* = 7), withdrawn (*n* = 7) or were lost to follow-up (*n* = 5). Among the 27 participants with healed ulcers, 16 participants declined ablation, three were no longer deemed to be suitable for ablation (as decided by the treating clinician), six were on the waiting list for ablation and may have been treated after 12 months; in the case of the remaining two participants, the reasons for not receiving ablation are unclear.
e Reasons for ablation before ulcer healing in six participants in the deferred-ablation group were clinical deterioration of ulcer (*n* = 3), participant request for ablation (unwilling to continue with deferred ablation strategy) (*n* = 2) and participant treated early in error (*n* = 1).

TABLE 11 Summary of participants not having endovenous ablation

Completion of the trial	Deferred (*N* = 55)	Early (*N* = 6)
Yes, *n* (%)	36 (65.5)	2 (33.3)
Ulcer healed by 12 months	27	2
Ulcer not healed by 12 months	9	0
No, *n* (%)	19 (34.5)	4 (66.7)
Withdrawal	7	3
Death	7	1
Other	5	0

Regarding the timing of ablation, the majority of participants (90.6%) in the early-ablation group underwent ablation within 2 weeks of randomisation. In the deferred-ablation group, one participant was treated before 2 weeks and five participants were treated prior to ulcer healing between 2 weeks and 6 months. The reasons for the ablation before ulcer healing in the six participants in the deferred-ablation group were clinical deterioration of ulcer (*n* = 3), participant request for intervention (participant unwilling to continue with deferred ablation strategy) (*n* = 2) and participant treated early in error (*n* = 1).

Primary outcome: ulcer healing

Figure 4 shows the KM curve for time to ulcer healing. Among the 450 participants were two ineligible participants whose ulcer had healed by the time of randomisation and who did not contribute to the survival analysis. The median healing time was 56 (95% CI 49 to 66) days and 82 (95% CI 69 to 92) days in the early- and deferred-ablation groups, respectively.

The proportional hazards assumption, assessed graphically, by plotting $-\ln\{-\ln[\hat{S}(t)]\}$ versus $-\ln(t)$, and numerically, using Grambsch and Therneau tests, was not violated.

Table 12 shows the Cox proportional hazards regression results. In the univariate model, with trial centre as a random effect, the hazard ratio (HR) for ulcer healing in the early-ablation group is 1.38 (95% CI 1.13 to 1.68) ($p = 0.001$) compared with participants randomised to deferred ablation. After further adjusting for age, ulcer duration and ulcer size at baseline, the HR is 1.42 (95% CI 1.16 to 1.73) ($p = 0.001$).

The HRs from the multivariable Cox regression model for specific (pre-planned) subgroups are presented in *Figure 5*. There is considerable consistency except for ulcer duration, where an interesting trend is observed. In the prespecified subgroup analysis to investigate any differential treatment effects of ulcer duration, the HR in the early ablation group increases across the quartiles of ulcer duration. In the first and second quartiles of ulcer duration, early ablation does not make a difference to ulcer healing relative to deferred ablation. However, this study is not powered to investigate any interactions and thus the above finding will need further studies to confirm.

Figure 6 shows the HRs for different treatments in the early ablation group compared with deferred ablation. As numbers in the MOCA only group, endothermal and UGFS group, and MOCA and UGFS group are small, the three ablation groups are merged into one group as 'other ablation'. The HRs for the groups of endothermal only, UGFS only and other treatment are consistent.

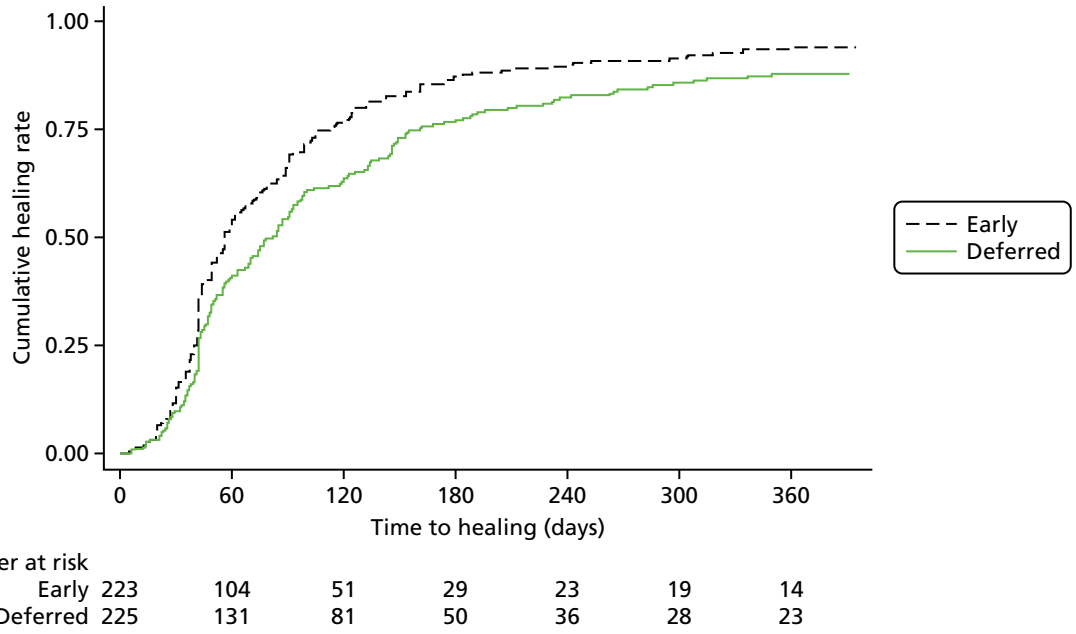


FIGURE 4 Kaplan–Meier curve showing ulcer healing time in the early- and deferred-ablation groups ($p = 0.001$, log-rank test). Ulcer healing rates were greater in participants randomised to early ablation. Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

TABLE 12 Time to ulcer healing in participants with venous ulceration (Cox regression model)

			Univariable model[b]		Multivariable model[c]	
Variable	*N*[a]	*n*[a]	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treatment						
Deferred group	226	194	Reference		Reference	
Early group	224	210	1.38 (1.13 to 1.68)	0.001	1.42 (1.16 to 1.73)	0.001
Age (years)	448	402	1.00 (0.99 to 1.00)	0.25	1.00 (0.99 to 1.01)	0.69
Ulcer duration (months)						
First quartile (0.9–2.2)	113	102	Reference		Reference	
Second quartile (2.3–3.1)	114	101	1.01 (0.77 to 1.33)	0.96	1.00 (0.76 to 1.33)	0.97
Third quartile (3.1–4.2)	111	105	1.11 (0.85 to 1.47)	0.44	1.14 (0.86 to 1.51)	0.35
Fourth quartile (4.2–8.4)	112	96	0.75 (0.56 to 0.99)	0.04	0.79 (0.59 to 1.05)	0.10
Ulcer size (cm^2)						
First quartile (0.4–1.5)	113	108	Reference		Reference	
Second quartile (1.6–2.9)	112	108	0.79 (0.61 to 1.04)	0.09	0.72 (0.55 to 0.95)	0.02
Third quartile (3–7.5)	113	101	0.52 (0.40 to 0.69)	< 0.001	0.51 (0.38 to 0.67)	< 0.001
Fourth quartile (8–235)	112	87	0.31 (0.23 to 0.41)	< 0.001	0.29 (0.22 to 0.39)	< 0.001

a *N*, total number of participants; n, number of participants with healing ulcer.
b Adjusted by centre (centre included in the model as a random effect).
c Adjusted by centre, age, ulcer size and duration (centre included in the model as random effect and age, ulcer size and duration as fixed effects).

Secondary outcomes

Ulcer-free time to 1 year

Of the 450 participants, 407 attended the 12-month follow-up visit and were included in the analysis of ulcer-free time to 1 year. There were 203 and 204 participants in the deferred- and early-ablation groups, respectively. The median ulcer-free time to 1 year was 278 (IQR 175–324) days and 306 (IQR 240–328) days in the deferred- and early-ablation groups, respectively.

As the ulcer-free time to 1 year did not follow a normal distribution and mathematical transformation was not possible because of a few participants with zero days ulcer-free time, ulcer-free time to 1 year was categorised (into quartiles) and ordinal regression was used to assess the difference between the treatment groups. The proportionality assumption was not violated (assessed using the Brant test). The results are presented in *Table 13*. In the univariable analysis, with trial centre as a random effect, the odds ratio (OR) for being in a higher quartile was 1.60 (95% CI 1.13 to 2.27) for the early-ablation group. Further adjustment for age, ulcer duration and size at baseline did not affect the result. The OR in the multivariable model is 1.54 (95% CI 1.07 to 2.21; $p = 0.02$).

Figure 7 shows the results of ordinal logistic regression in different subgroups. The results are consistent across different subgroups. The pattern observed is similar to that seen in the subgroup analysis by ulcer size and duration.

Figure 8 shows the ORs for the treatment effect on ulcer-free time by type of endovenous ablation. The ORs are consistent in the groups of endothermal only and UGFS only, whereas the OR in the other treatment group is 1.06 (95% CI 0.56 to 2.02). The lack of treatment effect here may be due to the small number in the other treatment group.

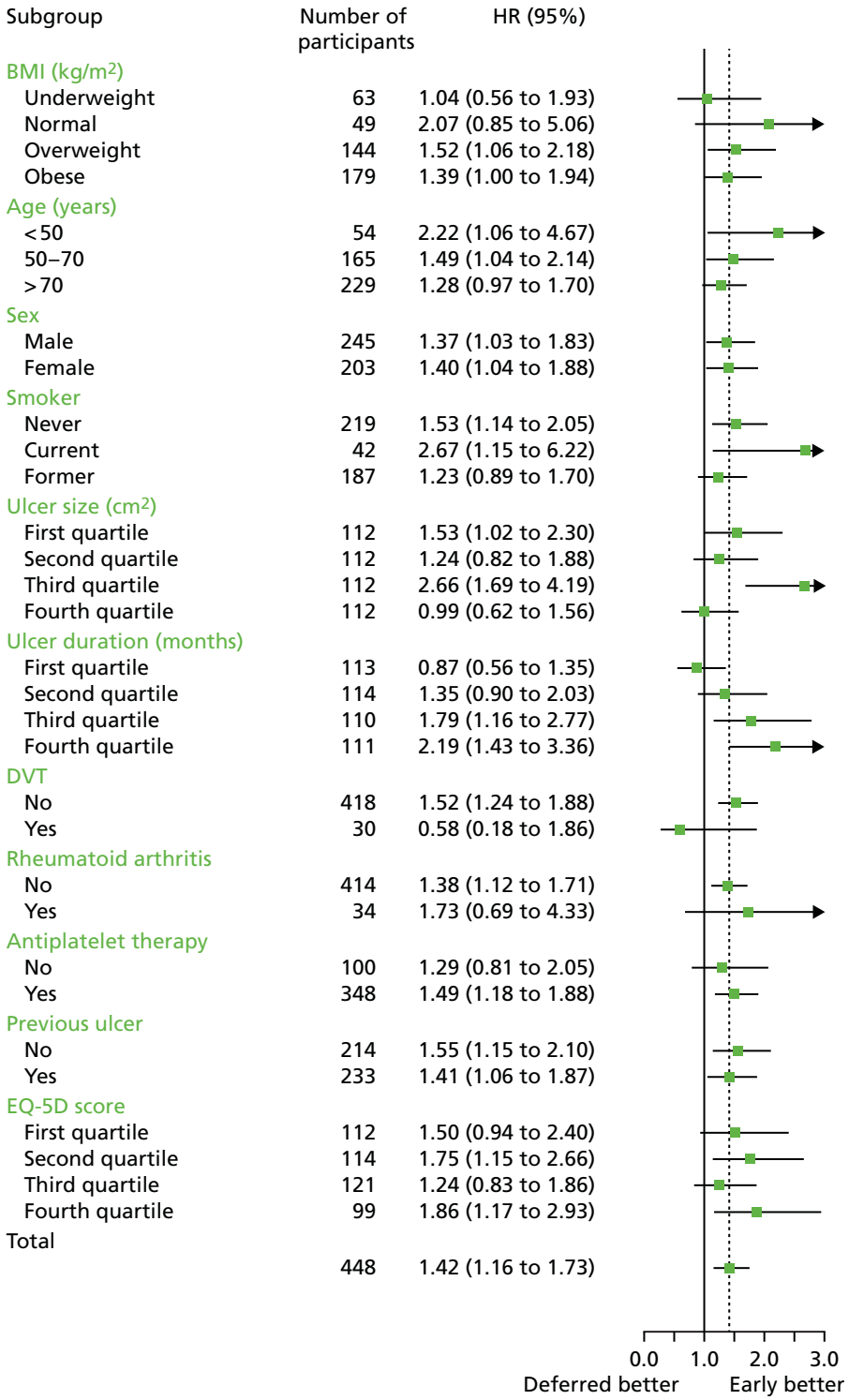


FIGURE 5 Forest plot of subgroup analysis for primary outcome. The healing advantage in prespecified subgroups was consistent with the overall healing benefit observed with early ablation. The broken line indicates overall HR for ulcer healing in entire study population. Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

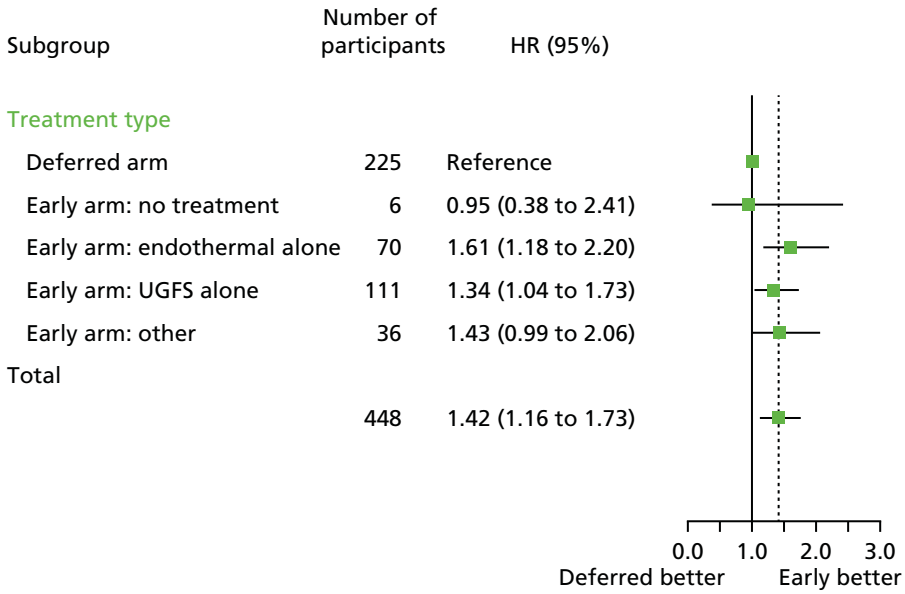


FIGURE 6 Forest plot of different endovenous ablation techniques for primary outcome. The healing advantage in prespecified subgroups treated with different ablation techniques was consistent with the overall healing benefit. The broken line indicates overall HR for ulcer healing in entire study population. Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

TABLE 13 Ordinal logistic regression for ulcer-free time to 1 year (quartiles) in participants with venous ulceration

	Univariable model[a]		Multivariable model[b]	
Variable	Coefficient (95% CI)	*p*-value	Coefficient (95% CI)	*p*-value
Treatment group				
Deferred	Reference		Reference	
Early	1.60 (1.13 to 2.27)	0.009	1.54 (1.07 to 2.21)	0.02
Age (years)	0.99 (0.98 to 1.00)	0.14	1.00 (0.98 to 1.01)	0.57
Ulcer duration (months)				
First quartile (0.9–2.2)	Reference		Reference	
Second quartile (2.3–3.1)	0.87 (0.53 to 1.44)	0.59	0.94 (0.56 to 1.56)	0.80
Third quartile (3.1–4.2)	0.94 (0.57 to 1.55)	0.82	0.96 (0.58 to 1.60)	0.89
Fourth quartile (4.2–8.4)	0.55 (0.33 to 0.92)	0.02	0.64 (0.38 to 1.08)	0.10
Ulcer size (cm^2)				
First quartile (0.4–1.5)	Reference		Reference	
Second quartile (1.6–2.9)	0.50 (0.30 to 0.82)	0.006	0.48 (0.29 to 0.79)	0.004
Third quartile (3–7.5)	0.23 (0.14 to 0.39)	< 0.001	0.23 (0.14 to 0.39)	< 0.001
Fourth quartile (8–235)	0.09 (0.05 to 0.16)	< 0.001	0.10 (0.06 to 0.17)	< 0.001

a Adjusted by centre (centre included in the model as a random effect).
b Adjusted by centre, age, duration and size (centre included in the model as random effect and age, ulcer duration and size as fixed effects).

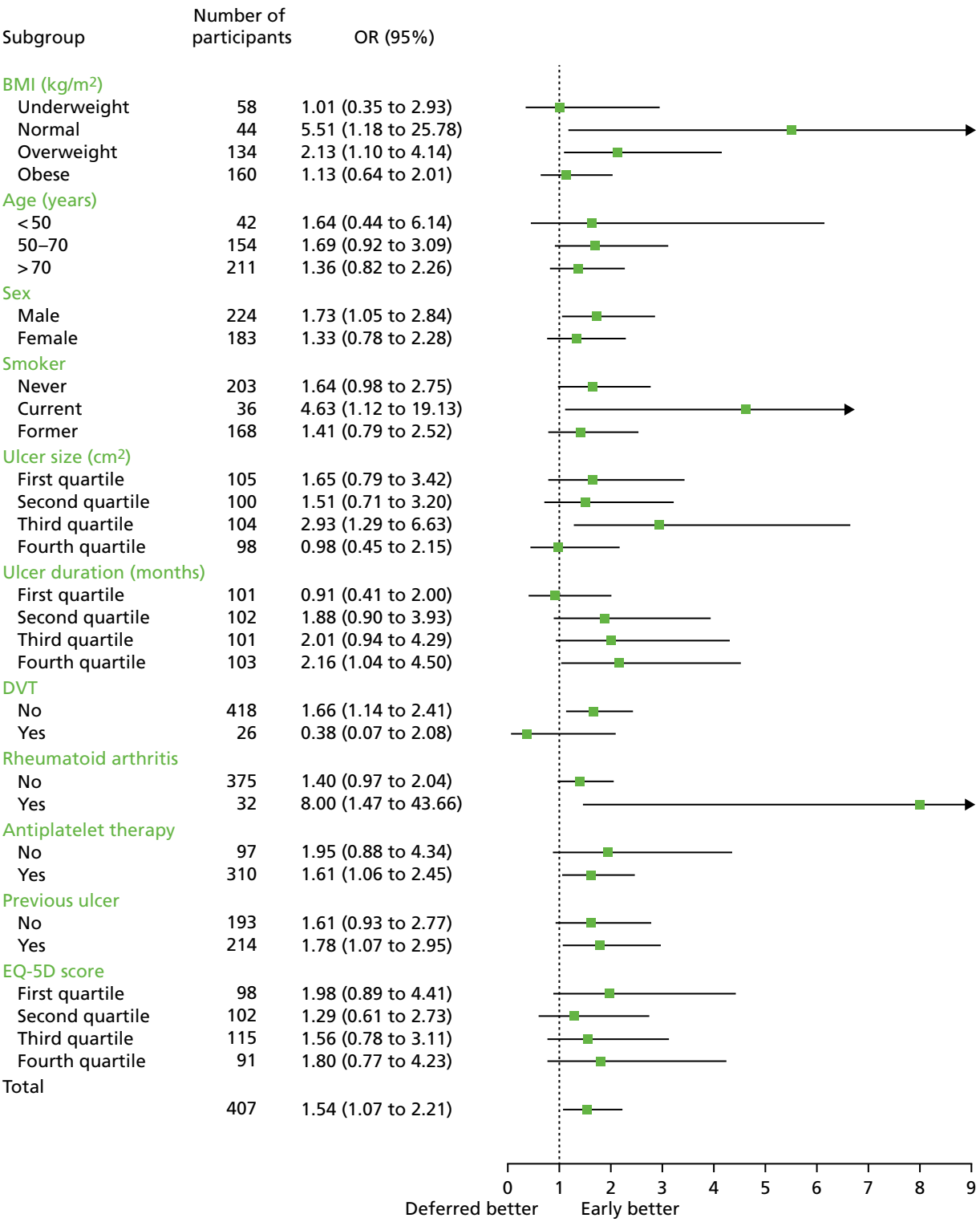


FIGURE 7 Forest plot showing the treatment effect on ulcer-free time by predefined subgroups.

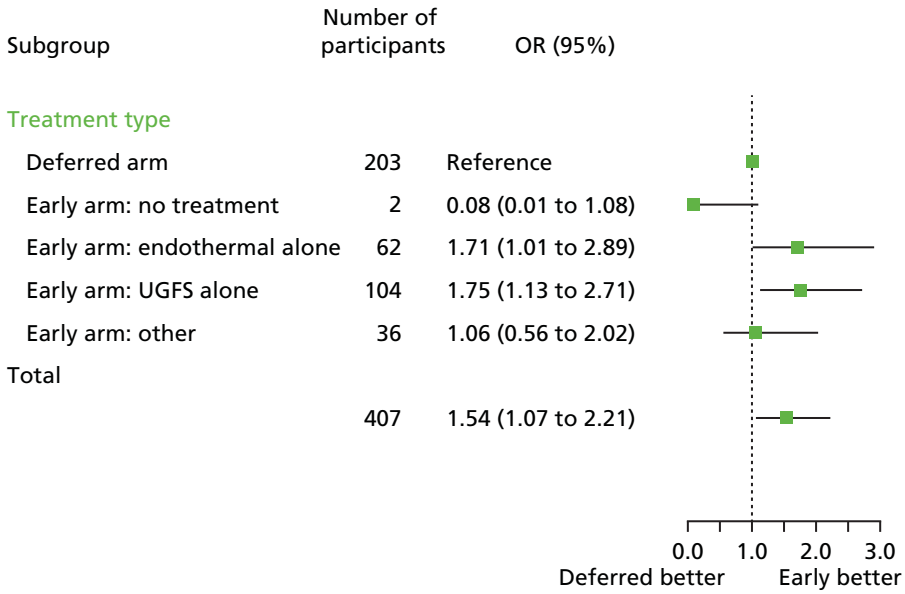


FIGURE 8 Forest plot showing the treatment effect on ulcer-free time by different ablation techniques.

Ulcer healing at 12 and 24 weeks

The unadjusted KM time-to-event ulcer healing analysis can be seen in *Table 14*. The healing rates at 24 weeks were higher in the early-ablation group (85.6%, 95% CI 80.6% to 89.8%) than in the deferred-ablation group (76.3%, 95% CI 70.5% to 81.7%).

In a post hoc analysis to allow comparison with published studies, the 12-week ulcer healing rate was 63.5% (95% CI 57.2% to 69.8%) in the early-ablation group and 51.6% (95% CI 45.2% to 58.3%) in the deferred group. A total of 404 (89.8%) of 450 randomised participants had healed by 1 year post randomisation [210/224 (93.8%) in the early-ablation group and 194/226 (85.8%) in the deferred-ablation group]. The absolute difference in healing rates between the groups was 7.9% (95% CI 2.3% to 13.5%).

TABLE 14 Summary of 12- and 24-week ulcer healing rates and ulcer-free time

Variable	Early (*N* = 224)	Deferred (*N* = 226)
Ulcer healing rate[a] (95% CI) (%)		
12 weeks	63.5 (57.2 to 69.8)	51.6 (45.2 to 58.3)
24 weeks	85.6 (80.6 to 89.8)	76.3 (70.5 to 81.7)
Number of participants with a healed ulcer at 12 months, *n* (%)	210 (93.8)	194 (85.8)
Number of participants with recurrent ulcer, *n* (%)[b]	24 (11.4)	32 (16.5)
Ulcer-free time (days), median (IQR)	306 (240–328), *n* = 204	278 (175–324), *n* = 203

a Data presented as estimation by KM curve (95% CI).
b Proportion of participants with ulcer healed at 12 months.

Quality of life

Table 15 and *Figures 9* and *10* summarise the HRQoL data at baseline, 6 weeks and 6 and 12 months for the two trial groups. The AVVQ has scores ranging from 0 to 100, with 0 representing the best score and 100 the worst score, whereas, for EQ-5D and SF-36, the higher the score, the better the HRQoL. A decreasing trend of AVVQ score across time is observed for both the deferred- and early-ablation groups.

TABLE 15 Summary of quality of life (AVVQ, EQ-5D, SF-36) at baseline and at 6 weeks and 6 and 12 months after randomisation

Variable	Baseline	6 weeks	6 months	12 months	*p*-value[a]
Early, *n*	226	21	204	199	
Deferred, *n*	224	219	208	203	
AVVQ score, mean (SD)					
Deferred	44.3 (8.7), *n* = 192	41.2 (9.3), *n* = 170	39.5 (10.3), *n* = 140	34.3 (10.4), *n* = 130	
Early	44.1 (9.0), *n* = 200	39.4 (10.2), *n* = 176	34.6 (9.4) *n* = 139	32.4 (8.3), *n* = 127	
Difference (95% CI)[b]	–0.2 (–2.0 to, 1.6)	–2.1 (–4.0 to –0.2)	–4.8 (–6.9 to –2.7)	–1.8 (–4.0 to 0.3)	0.0008
EQ-5D health score, mean (SD)					
Deferred	70.1 (17.1), *n* = 225	71.1 (18.7), *n* = 205	71.4 (19.6), *n* = 193	73.7 (17.4), *n* = 184	
Early	70.2 (17.7), *n* = 222	72.7 (18.6), *n* = 212	74.1 (15.8), *n* = 185	74.8 (16.9), *n* = 183	
Difference (95% CI)[b]	0.1 (–3.1 to 3.4)	1.7 (–1.6 to 5.1)	1.8 (–1.6 to 5.2)	1.3 (–2.1 to 4.8)	0.72
EQ-5D index value, mean (SD)[c]					
Deferred	0.73 (0.2), *n* = 226	0.75 (0.2), *n* = 208	0.76 (0.2), *n* = 192	0.80 (0.2), *n* = 182	
Early	0.73 (0.2), *n* = 222	0.79 (0.2), *n* = 211	0.81 (0.2), *n* = 186	0.83 (0.2), *n* = 184	
Difference (95% CI)[b]	–0.01 (–0.04 to 0.03)	0.04 (0.00 to 0.08)	0.04 (0.00 to 0.08)	0.03 (–0.01 to 0.07)	0.03
SF-36 physical function score, mean (SD)					
Deferred	37.5 (12.5), *n* = 225	37.4 (13.0), *n* = 207	37.4 (13.7), *n* = 193	38.7 (13.4), *n* = 180	
Early	37.3 (12.0), *n* = 223	39.1 (12.7), *n* = 212	39.1 (12.8), *n* = 187	39.4 (12.9), *n* = 182	
Difference (95% CI)[b]	–1.0 (–3.1 to 1.1)	1.0 (–1.2 to 3.1)	0.7 (–1.5 to 2.8)	0.3 (–1.9 to 2.6)	0.09
SF-36 role-physical score, mean (SD)					
Deferred	39.7 (12.1), *n* = 224	41.4 (12.7), *n* = 207	42.4 (12.7), *n* = 192	44.3 (12.9), *n* = 180	
Early	39.0 (12.2), *n* = 223	40.3 (12.5), *n* = 211	43.6 (12.6), *n* = 187	43.0 (12.7), *n* = 181	
Difference (95% CI)[b]	–1.3 (–3.5 to 0.9)	–1.7 (–4.0 to 0.6)	0.4 (–2.0 to 2.7)	–1.7 (–4.1 to 0.7)	0.28

continued

TABLE 15 Summary of quality of life (AVVQ, EQ-5D, SF-36) at baseline and at 6 weeks and 6 and 12 months after randomisation (*continued*)

Variable	Baseline	6 weeks	6 months	12 months	*p*-value[a]
SF-36 body pain score, mean (SD)					
Deferred	41.6 (11.9), *n* = 224	44.3 (12.3), *n* = 207	45.9 (12.2), *n* = 193	47.8 (11.2), *n* = 180	
Early	41.3 (11.1), *n* = 223	46.6 (10.6), *n* = 212	48.2 (11.0), *n* = 187	49.3 (11.0), *n* = 182	
Difference (95% CI)[b]	–0.5 (–2.6 to 1.6)	2.2 (0.1 to 4.4)	2.1 (–0.2 to 4.3)	1.1 (–1.1 to 3.3)	0.05
SF-36 general health score, mean (SD)					
Deferred	46.0 (9.8), *n* = 225	45.6 (9.2), *n* = 207	44.5 (10.1), *n* = 193	45.1 (10), *n* = 181	
Early	45.8 (9.2), *n* = 223	45.7 (9.1), *n* = 212	44.9 (9.8), *n* = 187	45.3 (10), *n* = 183	
Difference (95% CI)[b]	–0.3 (–2.0 to 1.5)	0.0 (–1.8 to 1.8)	0.0 (–1.9 to 1.8)	0.4 (–1.5 to 2.3)	0.86
SF-36 vitality score, mean (SD)					
Deferred	47.8 (10.6), *n* = 224	47.5 (11.3), *n* = 207	48.8 (10.8), *n* = 193	49.6 (9.8), *n* = 179	
Early	48.2 (10.2), *n* = 222	49.1 (10.0), *n* = 212	49.4 (9.5), *n* = 187	50.5 (9.4), *n* = 182	
Difference (95% CI)[b]	0.1 (–1.7 to 2.0)	1.4 (–0.5 to 3.3)	0.0 (–1.9 to 2.0)	0.9 (–1.0 to 2.9)	0.31
SF-36 social functioning score, mean (SD)					
Deferred	42.4 (13.5), *n* = 224	44.0 (12.1), *n* = 207	44.7 (12.5), *n* = 193	47.3 (11.4), *n* = 181	
Early	42.6 (12.4), *n* = 223	44.9 (11.6), *n* = 212	47.0 (10.5), *n* = 186	47.4 (10.7), *n* = 182	
Difference (95% CI)[b]	–0.1 (–2.3 to 2.0)	0.6 (–1.6 to 2.8)	1.5 (–0.8 to 3.7)	–0.4 (–2.7 to 2.0)	0.40
SF-36 role-emotional score, mean (SD)					
Deferred	43.7 (13.6), *n* = 224	45.9 (13.3), *n* = 207	45.1 (13.2), *n* = 193	47.5 (12.2), *n* = 179	
Early	42.7 (13.8), *n* = 222	46.1 (12.8), *n* = 212	47.2 (12.2), *n* = 187	45.9 (13.0), *n* = 182	
Difference (95% CI)[b]	–1.4 (–3.8 to 1.0)	0.0 (–2.5 to 2.5)	1.7 (–0.9 to 4.2)	–1.7 (–4.3 to 0.9)	0.08
SF-36 mental health score, mean (SD)					
Deferred	49.3 (10.7), *n* = 224	49.2 (10.8), *n* = 207	49.5 (10.4), *n* = 193	50.7 (10.1), *n* = 179	
Early	49.2 (10.3), *n* = 222	50.6 (10.4), *n* = 212	51.7 (9.7), *n* = 187	51.0 (9.3), *n* = 182	
Difference (95% CI)[b]	–0.2 (–2.1 to 1.7)	1.3 (–0.7 to 3.2)	1.7 (–0.3 to 3.7)	–0.2 (–2.2 to 1.8)	0.07

TABLE 15 Summary of quality of life (AVVQ, EQ-5D, SF-36) at baseline and at 6 weeks and 6 and 12 months after randomisation (*continued*)

Variable	Baseline	6 weeks	6 months	12 months	*p*-value[a]
SF-36 physical component summary score, mean (SD)					
Deferred	38.8 (10.8), *n* = 223	39.6 (11.6), *n* = 207	40.4 (12.1), *n* = 193	41.8 (12.0), *n* = 178	
Early	38.5 (9.9), *n* = 222	40.4 (10.2), *n* = 212	41.5 (11.5), *n* = 187	42.1 (11.6), *n* = 181	
Difference (95% CI)[b]	–0.8 (–2.8 to 1.1)	0.3 (–1.7 to 2.2)	0.3 (–1.7 to 2.3)	0.3 (–1.7 to 2.3)	0.41
SF-36 mental component summary score, mean (SD)					
Deferred	49.4 (11.6), *n* = 223	50.2 (11.0), *n* = 207	50.2 (10.4), *n* = 193	52.0 (10.0), *n* = 178	
Early	49.2 (10.9), *n* = 222	51.1 (10.4), *n* = 212	52.2 (9.8), *n* = 187	51.6 (9.5), *n* = 181	
Difference (95% CI)[b]	–0.3 (–2.2 to 1.7)	0.9 (–1.1 to 2.9)	1.5 (–0.5 to 3.6)	–0.7 (–2.7 to 1.4)	0.09

a *p*-value for the overall difference between the two groups over the whole trial period.
b Difference between two groups estimated using a mixed model with adjustment for time, age, ulcer duration and size as fixed effects, with trial centre and participant as random effects. Deferred-ablation group used as reference.
c EQ-5D index calculated using the value set for England.[57]
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

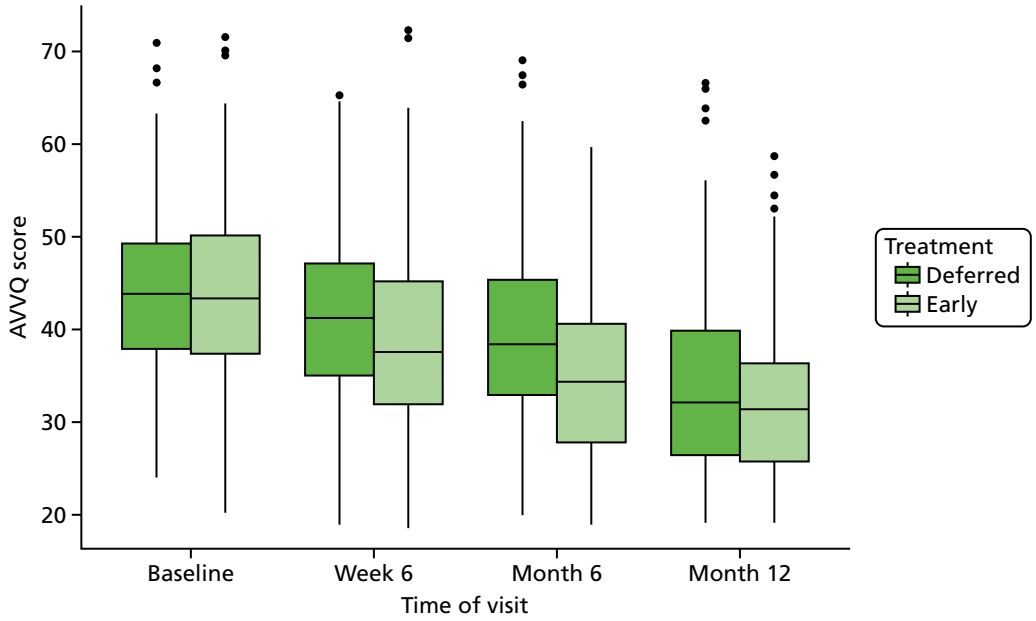


FIGURE 9 The changes in AVVQ score over time in the early- and deferred-ablation groups.

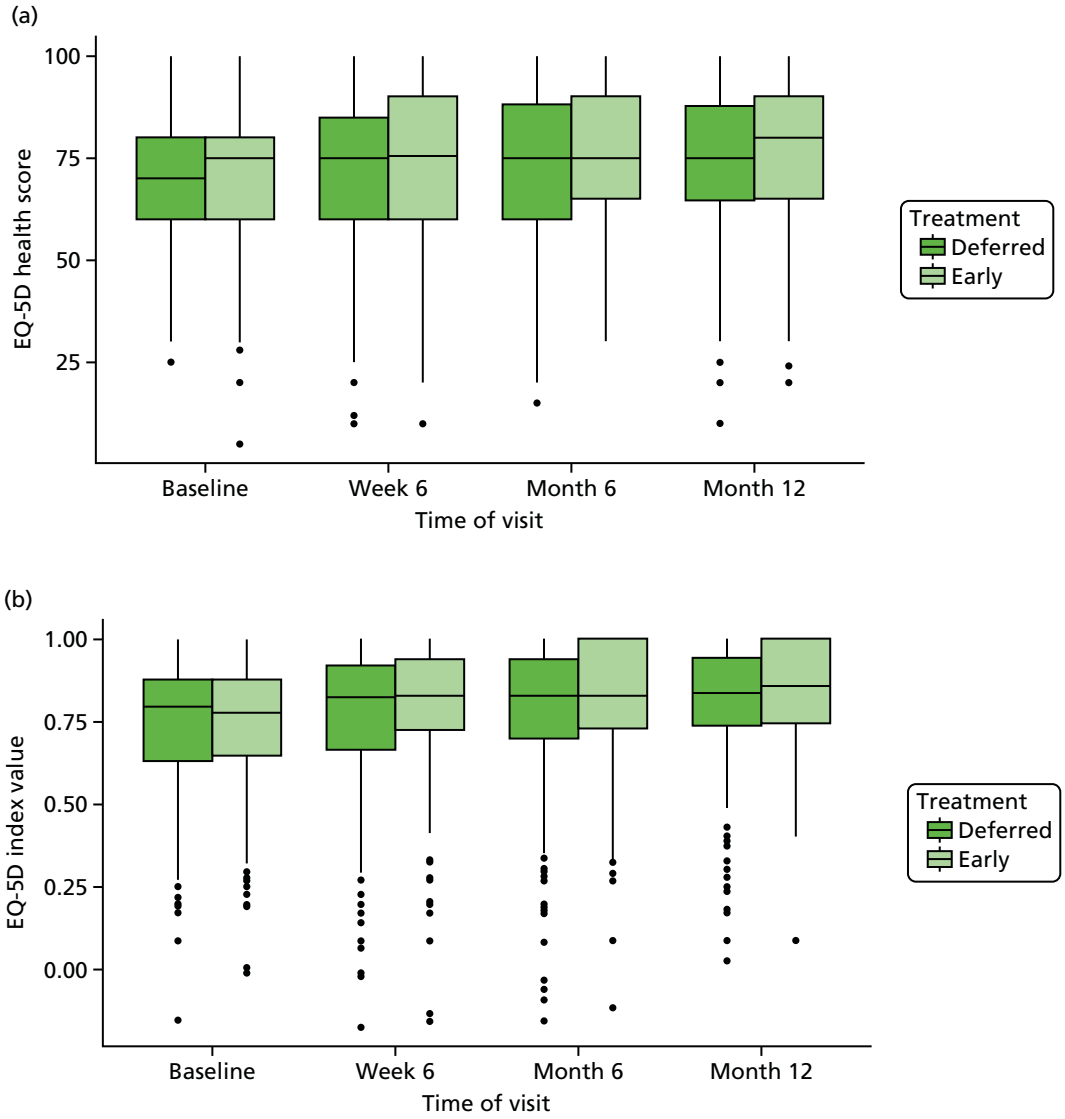


FIGURE 10 The changes in EQ-5D: (a) health score and (b) index value over time in the early- and deferred-ablation groups.

At baseline, AVVQ, EQ-5D-5L and SF-36 scores were similar in the early- and deferred-ablation groups. Overall, there was a significant difference in mean AVVQ scores between the treatment groups over time ($p < 0.001$), with lower mean scores, suggesting better disease-specific HRQoL, in the early-ablation group. There was a significant difference over time in mean EQ-5D index value between the treatment groups ($p = 0.03$), with more favourable scores in those randomised to early ablation, and in mean SF-36 body pain ($p = 0.05$). Observed differences between the groups for the other generic HRQoL measures were not statistically significant. However, as there was no control for multiple testing, these results should be interpreted with caution.

Table 16 summarises the HRQoL data with multiple imputation of missing values, which produces similar values.

TABLE 16 Summary of quality-of-life outcomes with multiple imputation of missing values

Variable	Baseline	6 weeks	6 months	12 months
AVVQ score, mean (SD)				
Early ablation	44.0 (9.0)	39.1 (10.2)	34.9 (10.1)	33.0 (9.7)
Deferred ablation	44.2 (8.9)	41.2 (9.7)	39.4 (10.3)	34.8 (10.8)
Difference (95% CI)[a]	–0.2 (–2.1 to 1.7)	–2.2 (–4.7 to 0.3)	–4.5 (–6.5 to –2.5)	–1.8 (–4.1 to 0.5)
EQ-5D health score, mean (SD)				
Early ablation	70.2 (17.7)	72.6 (18.7)	73.6 (16.3)	74.8 (17.5)
Deferred ablation	70.0 (17.1)	70.7 (19.1)	71.5 (19.4)	73.0 (17.8)
Difference (95% CI)[a]	0 (–3.3 to 3.3)	1.8 (–1.8 to 5.4)	1.8 (–2.0 to 5.7)	1.8 (–1.6 to 5.1)
EQ-5D index value, mean (SD)[b]				
Early ablation	0.73 (0.2)	0.79 (0.2)	0.81 (0.2)	0.83 (0.2)
Deferred ablation	0.73 (0.2)	0.74 (0.2)	0.77 (0.2)	0.80 (0.2)
Difference (95% CI)[a]	–0.01 (–0.05 to 0.03)	0.04 (0 to 0.09)	0.04 (0 to 0.08)	0.03 (–0.01 to 0.07)
SF-36 physical function score, mean (SD)				
Early ablation	37.4 (12.0)	39.1 (12.9)	39.4 (12.9)	39.7 (13.3)
Deferred ablation	37.5 (12.5)	37.4 (13.0)	37.9 (13.6)	38.3 (13.7)
Difference (95% CI)[a]	–1.0 (–3.2 to 1.1)	0.8 (–1.4 to 3.1)	0.6 (–1.7 to 3.0)	0.7 (–1.6 to 3.0)
SF-36 role-physical score, mean (SD)				
Early ablation	39.1 (12.2)	40.3 (12.6)	43.6 (12.6)	43.3 (12.9)
Deferred ablation	39.7 (12.1)	41.5 (12.6)	42.6 (12.8)	43.8 (13.1)
Difference (95% CI)[a]	–1.2 (–3.5 to 1.0)	–1.9 (–4.1 to 0.4)	0.4 (–2.6 to 3.3)	–0.9 (–3.4 to 1.5)
SF-36 body pain score, mean (SD)				
Early ablation	41.3 (11.1)	46.6 (10.6)	48.3 (11)	49.4 (11.1)
Deferred ablation	41.6 (11.9)	44.0 (12.2)	46.1 (12)	47.5 (11.5)
Difference (95% CI)[a]	–0.5 (–2.6 to 1.6)	2.4 (0 to 4.7)	2.1 (–0.2 to 4.4)	1.9 (–0.3 to 4.0)
SF-36 general health score, mean (SD)				
Early ablation	45.8 (9.2)	45.5 (9.1)	44.8 (9.8)	45.1 (10.0)
Deferred ablation	46.0 (9.8)	45.5 (9.3)	44.7 (10.2)	44.6 (10.2)
Difference (95% CI)[a]	–0.3 (–2.1 to 1.5)	–0.1 (–1.9 to 1.8)	–0.1 (–2.1 to 2.0)	0.4 (–1.4 to 2.2)
SF-36 vitality score, mean (SD)				
Early ablation	48.2 (10.2)	49.0 (10.2)	49.1 (9.6)	50.2 (9.7)
Deferred ablation	47.9 (10.5)	47.4 (11.2)	48.7 (10.7)	49.0 (10.0)
Difference (95% CI)[a]	0.1 (–1.7 to 2.0)	1.3 (–0.6 to 3.2)	0.2 (–2.0 to 2.4)	1.0 (–0.9 to 3.0)
SF-36 social functioning score, mean (SD)				
Early ablation	42.6 (12.4)	44.8 (11.6)	46.9 (10.7)	47.1 (11.0)
Deferred ablation	42.4 (13.5)	43.8 (12.1)	44.9 (12.4)	46.7 (11.7)
Difference (95% CI)[a]	–0.1 (–2.2 to 2.1)	0.6 (–1.7 to 2.9)	1.6 (–0.9 to 4.1)	0.1 (–2.1 to 2.4)

continued

TABLE 16 Summary of quality-of-life outcomes with multiple imputation of missing values (*continued*)

Variable	Baseline	6 weeks	6 months	12 months
SF-36 role-emotional score, mean (SD)				
Early ablation	42.7 (13.7)	46.1 (12.8)	47.0 (12.5)	45.6 (13.4)
Deferred ablation	43.7 (13.6)	45.8 (13.3)	45.1 (13.1)	47.1 (12.7)
Difference (95% CI)[a]	–1.4 (–3.8 to 1.0)	0 (–2.7 to 2.7)	1.4 (–1.3 to 4.1)	–1.9 (–4.5 to 0.8)
SF-36 mental health score, mean (SD)				
Early ablation	49.2 (10.3)	50.4 (10.5)	51.2 (10.1)	50.5 (10.2)
Deferred ablation	49.3 (10.7)	49.0 (10.8)	49.4 (10.5)	50.2 (10.6)
Difference (95% CI)[a]	–0.2 (–2.1 to 1.8)	1.4 (–0.7 to 3.4)	1.6 (–0.7 to 4.0)	0.1 (–1.9 to 2.2)
SF-36 physical component summary score, mean (SD)				
Early ablation	38.5 (10.0)	40.4 (10.4)	41.8 (11.4)	42.6 (11.8)
Deferred ablation	38.8 (10.7)	39.6 (11.5)	40.8 (12.1)	41.2 (12.2)
Difference (95% CI)[a]	–0.8 (–2.7 to 1.2)	0.2 (–1.8 to 2.2)	0.4 (–1.9 to 2.7)	1.0 (–1.1 to 3.1)
SF-36 mental component summary score, mean (SD)				
Early ablation	49.2 (10.8)	51 (10.4)	51.7 (10.2)	50.9 (10.2)
Deferred ablation	49.4 (11.5)	50 (11.1)	50.1 (10.4)	51.5 (10.4)
Difference (95% CI)[a]	–0.2 (–2.2 to 1.7)	0.9 (–1.2 to 3.1)	1.5 (–0.8 to 3.8)	–0.7 (–2.8 to 1.4)

a Difference between two groups estimated by mixed model, adjusting for time, age, ulcer size and duration as a fixed effect and trial centre and participant as a random effect. Deferred-ablation group as reference. The 95% CIs have not been adjusted for multiplicity.
b EQ-5D index calculated using the value set for England.[57]

Notes
Data presented as mean (SD). Widths of the CIs have not been adjusted for multiplicity and should not be used for formal inference. Missing scores were imputed using chained equation.
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

Clinical and technical success

Table 17 and *Figure 11* show the clinical success at 6 weeks. The number of participants with improvement of clinical grade is 72 (31.9%) and 106 (47.3%) in deferred and early ablation groups, respectively.

The VCSS evaluates changes in condition over time, with lower scores indicating better condition. *Figure 11* clearly shows that early ablation was associated with a lower VCSS at week 6 than deferred ablation, whereas the VCSS at baseline was similar in both groups.

On assessment of post-ablation duplex ultrasound scans at 6 weeks, treated segments were completely ablated in 179 (83.3%) of 215 scanned participants and 74.8% of legs had no evidence of residual reflux.

TABLE 17 Summary of clinical success at 6 weeks after randomisation

Variable	Treatment group		*p*-value
	Early (*N* = 224)	Deferred (*N* = 226)	
VCSS total score, mean (SD)			
Baseline	15.8 (3.3), *n* = 223	15.7 (3.1), *n* = 226	
Week 6	10.5 (4.7), *n* = 218	12.6 (4.4), *n* = 210	< 0.001[a]
Clinical classification downgrade (C6 to C5), *n* (%)			
Yes	106 (47.3)	72 (31.9)	0.001[b]
No	112 (50.0)	139 (61.5)	
Missing	6 (2.7)	15 (6.6)	

a *p*-value for *t*-test.
b *p*-value for Pearson's chi-squared test.
Reproduced from *The New England Journal of Medicine*, Gohel *et al.*[57] A randomized trial of early endovenous ablation in venous ulceration, vol. 378, pp. 2105–14. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission.

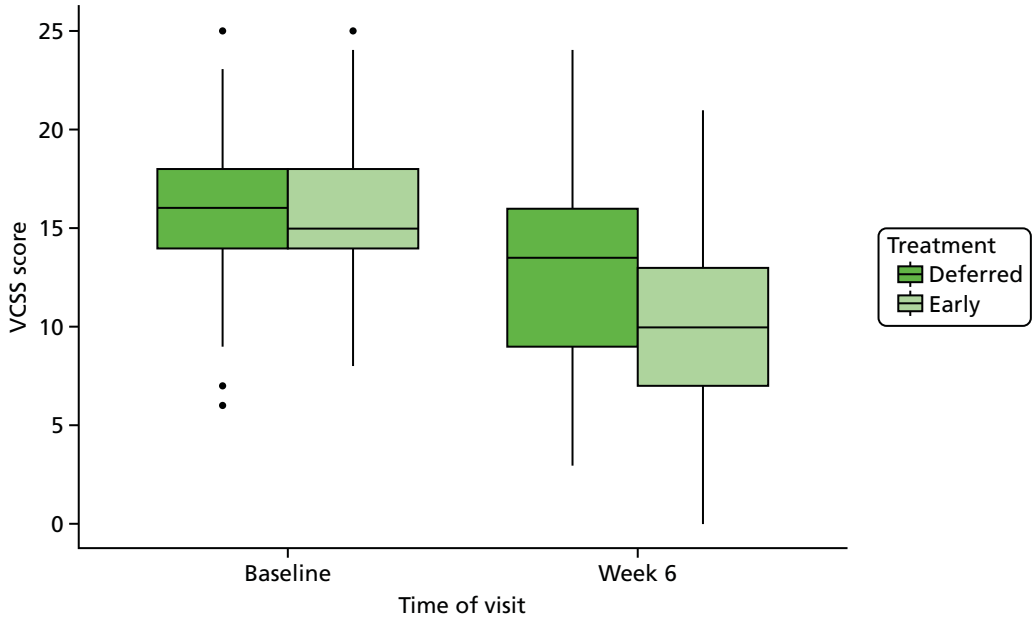


FIGURE 11 Summary of VCSS score in early- and deferred-ablation groups: VCSS score at baseline and 6 weeks after randomisation.

Safety data

Table 18 summarises the ablation procedures received by trial participants in the early and deferred groups during 1 year of follow-up (AEs are shown). In the early-ablation group, 218 participants underwent at least one ablation treatment (97.3%), whereas in the deferred group 171 participants did so (75.7%).

Table 19 summarises the procedural complications after endovenous ablation. The most common complications were DVT and pain post ablation. The vast majority of DVTs were in crural veins and were asymptomatic.

Table 20 shows the summary of SAEs. The number of SAEs possibly, probably or definitely related to the ablation procedures was three in the deferred-ablation group and four in the early-ablation group, and all were expected. SAEs assessed as being related are categorised in *Table 21*.

TABLE 18 Summary of AEs

Variable	Early (*N* = 224)	Deferred (*N* = 226)
Total number of procedures	269	203
Total number (%) of participants having a procedure	218 (97.3)	171 (75.7)
Number (%) of surgical procedures		
One	173 (79.4)	147 (86.0)
Two	39 (17.9)	17 (9.9)
Three	6 (2.8)	6 (3.5)
Four	0 (0)	1 (0.6)
Total number of AEs	117	130
Total number (%) of participants with an AE	67 (29.9)	83 (36.7)
Description of AE, *n* (%)		
Systemic	7 (6.0)	6 (4.6)
Local	110 (94.2)	124 (95.4)
Outcome, *n* (%)		
Recovered	111 (94.9)	111 (85.4)
Not yet recovered	6 (5.1)	19 (14.6)
Death	0 (0)	0 (0)
Unknown	0 (0)	0 (0)
Missing	0 (0)	0 (0)

TABLE 19 Summary of complications after endovenous ablation

Complication	Early (*N* = 28)	Deferred (*N* = 24)
Allergic reaction requiring local or no treatment	5	3
Bleeding requiring intervention	2	1
Cough/chest tightness	0	1
DVT	9[a]	3[b]
Infection[c]	3	5
Oedema	1	0
Pain	6[d]	6
Participant-reported paraesthesia	1	1
Superficial thrombophlebitis	1	4

a Post-ablation DVT in the early-ablation group: calf vein thrombosis occurred in six participants, in four of whom the thrombosis was identified on routine post-UGFS duplex ultrasonography scanning performed 7 days post UGFS (as this was the local scanning regimen in one of the recruiting centres); endothermal heat induced thrombosis (non-occlusive) occurred in three paraticipants.
b Post-ablation DVT: calf vein thrombosis (*n* = 3).
c Occurred in the perioperative period.
d Deemed severe in one participant.

TABLE 20 Summary of SAEs

Variable	Early (*N* = 224)	Deferred (*N* = 226)
Number (%) of participants undergoing an ablation procedure	218 (97.3)	171 (75.7)
Total number of procedures	269	203
Total number of SAEs	43	55
Number (%) of participants with SAE	30 (13.4)	35 (15.5)
Serious reason, *n* (%)		
Death	3 (7.0)	4 (7.3)
Life-threatening	0 (0)	0 (0)
Persistently disabling	0 (0)	0 (0)
Hospitalisation required	38 (88.4)	50 (90.9)
Congenital abnormality	0 (0)	0 (0)
Other	2 (4.7)	1 (1.8)
Frequency, *n* (%)		
Single episode	32 (74.4)	49 (89.1)
Intermittent	1 (2.3)	1 (1.8)
Frequent	1 (2.3)	0 (0)
Continuous	7 (16.3)	5 (9.1)
Unknown	2 (4.7)	0 (0)
Severity, *n* (%)		
Mild	3 (7.0)	4 (7.3)
Moderate	17 (39.5)	23 (41.8)
Severe	18 (41.9)	20 (36.4)
Life-threatening or disabling	5 (11.6)	8 (14.6)
Relation to procedure, *n* (%)		
Not related	38 (88.4)	51 (92.7)
Unlikely	1 (2.3)	1 (1.8)
Possibly	1 (2.3)	3 (5.5)
Probably	1 (2.3)	0 (0)
Definite	2 (4.7)	0 (0)
Outcome, *n* (%)		
Recovered	36 (83.7)	46 (83.6)
Not yet recovered	1 (2.3)	1 (1.8)
Death	6 (14.0)	8 (14.6)
Unknown	0 (0)	0 (0)
Expectedness, *n* (%)[a]		
Expected	4 (100)	3 (100)

a Expectedness is reported for all SAEs that are possibly, probably or definitely related to procedure (*n* = 7).

TABLE 21 Medical Dictionary for Regulatory Activities (version 20.0) coding of the expected and related SAEs

Treatment allocation	System organ classes term	Preferred term	Lowest-level term
Early	Musculoskeletal and connective tissue disorders	Pain in extremity	Leg pain
Early	Surgical and medical procedures	Vascular compression therapy	Compression dressing application
Early	General disorders and administration site conditions	Peripheral swelling	Swelling of legs
Early	Skin and subcutaneous tissue disorders	Skin ulcer	Leg ulcer
Deferred	Injury, poisoning and procedural complications	Laceration	Laceration of head
Deferred	Infections and infestations	Urinary tract infection	Urinary tract infection
Deferred	Infections and infestations	Infected skin ulcer	Infected skin ulcer

Protocol deviations

There were 89 and 74 protocol deviations in early- and deferred-ablation groups, respectively. *Table 22* shows the summary of the protocol deviations. The number of protocol deviations related to trial treatment was 38 (involving 32 participants) in the early-ablation group and 32 (involving 31 participants) in the deferred-ablation group. Participants with protocol deviations related to treatment were excluded from the per-protocol analysis.

Sensitivity analysis

The per-protocol analyses included 387 participants after excluding those with protocol deviation related to treatment. *Figure 12* shows the KM curve based on the per-protocol analysis. The difference between the two groups is less pronounced than in the ITT analysis as the participants with protocol deviations in the deferred group experienced particularly poor healing (*Figure 13*). The smaller difference between the

TABLE 22 Summary of protocol deviations

Variable	Early ($N = 89$[a])	Deferred ($N = 74$[a])
Number of participants with a protocol deviation	59	58
Deferred ablation in early group, *n* (%)	17 (19.1)	0 (0)
Non-concordance with bandaging, *n* (%)	9 (10.1)	12 (16.0)
Early ablation in deferred group, *n* (%)	0 (0)	16 (21.3)
Other, *n* (%)	63 (70.8)	46 (62.2)
Follow-up visit missing/late	40 (63.5)	34 (73.9)
Photograph/tracing not taken	4 (6.4)	4 (8.7)
Incorrect consent initially completed	3 (4.8)	4 (8.7)
Ineligible	2 (3.2)	4 (8.7)
Other	14[b] (22.2)	0 (0)

a Number of protocol deviations; a participant may have more than one protocol deviation.
b Abnormal scan ($n = 1$); deferred reporting of healing ($n = 1$); ablation not completed for technical reason ($n = 1$); one ablation outside 2 weeks ($n = 4$); no ablation ($n = 5$); other ($n = 2$).

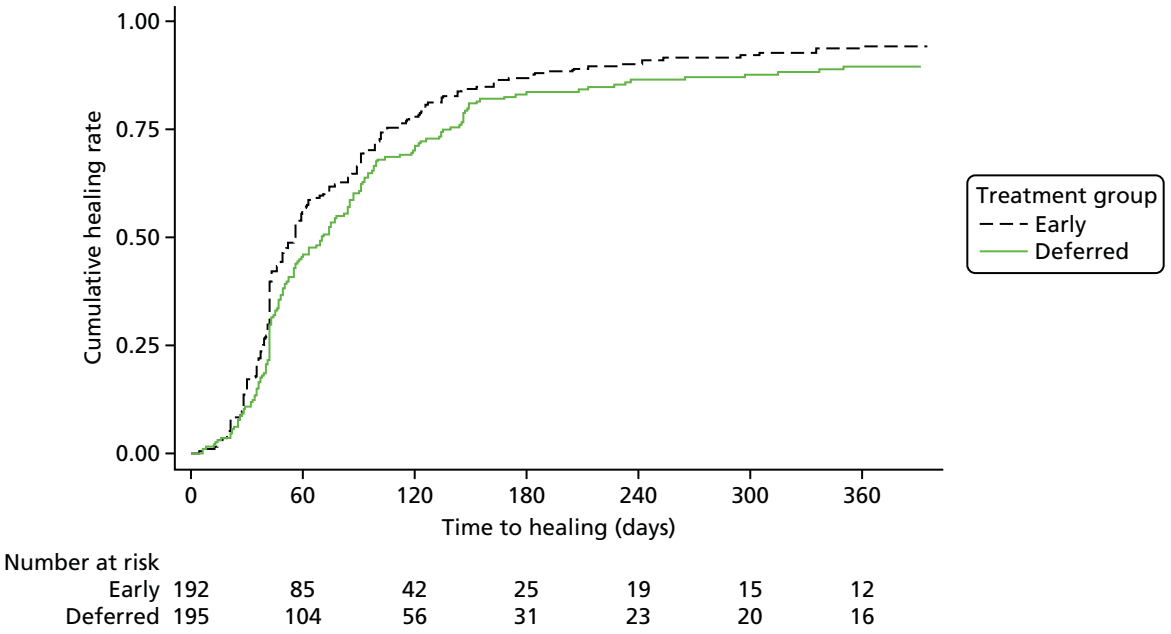


FIGURE 12 Per-protocol analysis (excluding participants with a protocol deviation) KM curve showing ulcer healing in the early and deferred (standard) ablation groups ($p = 0.04$).

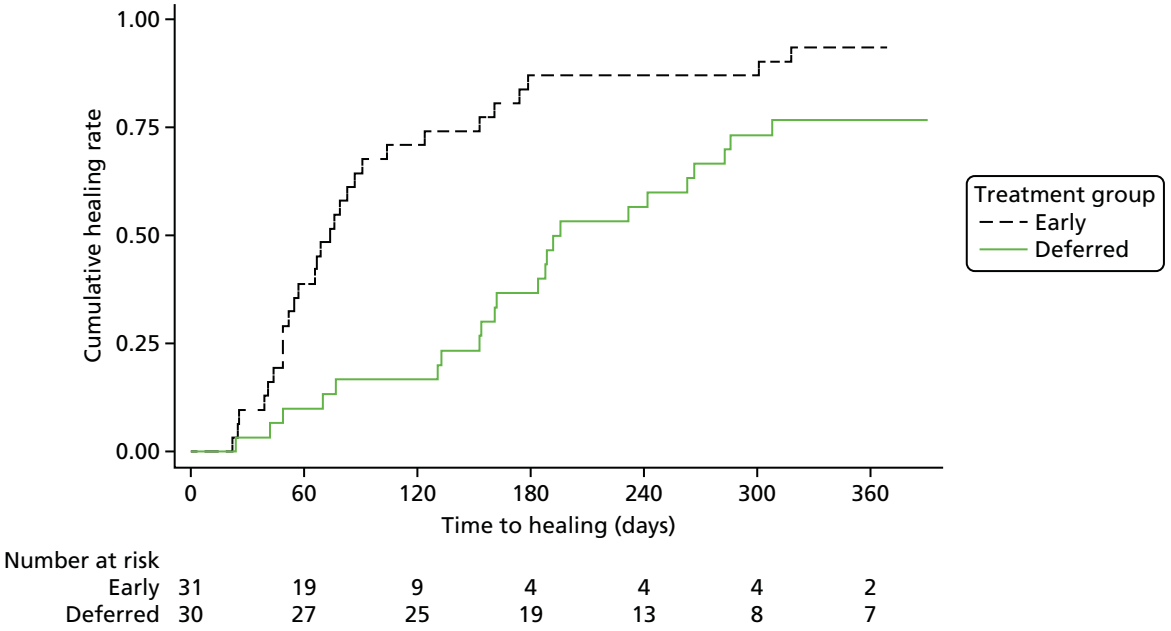


FIGURE 13 Kaplan–Meier curve showing ulcer healing time in the early- and deferred-ablation groups among participants with protocol deviations ($p < 0.001$).

treatment groups in *Table 23* also illustrates that the participants in the deferred group who did not have a protocol deviation had less severe ulcers. The 24-week ulcer healing rate in the deferred group was 76.3% in the ITT analysis and 82.6% in the per-protocol analysis. After adjusting for covariates in the Cox regression, in the per-protocol analysis the HR for time to healing associated with early compared with deferred ablation is 1.31 (95% CI 1.06 to 1.63; $p = 0.01$) (*Table 24*). In summary, although the deferred-intervention participants in the per-protocol analysis had less severe ulcers, it was still observed that early ablation led to more rapid ulcer healing in the per-protocol analysis.

TABLE 23 Per-protocol analysis for 12- and 24-week ulcer healing rate and ulcer-free time

Variable	Early (*N* = 192)	Deferred (*N* = 195)
Ulcer healing rate (95% CI) (%)[a]		
12 weeks	63.9% (57.1% to 70.6%)	57.0% (50.2% to 64.1%)
24 weeks	86.4% (81.1% to 90.8%)	82.6% (76.8% to 87.6%)
Number (%) of participants with healed ulcer at 1 year	180 (93.8)	170 (87.2)
Number (%) of participants with recurrent ulcer[b]	23 (12.8)	28 (16.5)
Ulcer-free time (days), median (IQR)	309 (240–329), *n* = 177	286 (213–325), *n* = 176

a Data presented as estimation by KM curve (95% CI).
b The proportion reported among participants with ulcer healed at 12 months.

TABLE 24 Per-protocol analysis for time to ulcer healing (Cox regression model)

			Univariable model[b]		Multivariable model[c]	
Variable	*N*[a]	*n*[a]	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treatment group						
Deferred	195	170	Reference		Reference	
Early	192	180	1.25 (1.01 to 1.55)	0.04	1.31 (1.06 to 1.63)	0.01
Age (years)	387	350	0.99 (0.98 to 1.00)	0.02	1.00 (0.99 to 1.01)	0.56
Ulcer duration (months)						
First quartile (0.9–2.2)	101	91	Reference		Reference	
Second quartile (2.3–3.1)	101	92	1.02 (0.76 to 1.37)	0.88	1.03 (0.77 to 1.39)	0.83
Third quartile (3.1–4.2)	96	91	1.09 (0.81 to 1.46)	0.56	1.14 (0.85 to 1.53)	0.38
Fourth quartile (4.2–8.4)	89	76	0.74 (0.54 to 1.00)	0.05	0.84 (0.61 to 1.15)	0.27
Ulcer size (cm^2)						
First quartile (0.4–1.5)	98	94	Reference		Reference	
Second quartile (1.6–2.9)	96	93	0.80 (0.60 to 1.07)	0.13	0.76 (0.57 to 1.03)	0.07
Third quartile (3–7.5)	98	88	0.50 (0.37 to 0.67)	< 0.001	0.50 (0.37 to 0.67)	< 0.001
Fourth quartile (8–235)	95	75	0.30 (0.22 to 0.40)	< 0.001	0.29 (0.21 to 0.41)	< 0.001

a *N*, total number of participants; *n*, number of participants with healing ulcer.
b Adjusted by centre as fixed effects.
c Adjusted by centre, age, ulcer size and duration as fixed effects.

Chapter 4 Economic evaluation results

Resource use and total cost analysis

Figure 14 and *Appendix 9* show initial ablation procedures and overall subsequent resource use in the 450 randomised participants. Total mean cost per patient was calculated over 1 year. Participants who withdrew from the trial before 12 months were not included in the cost analysis. Participants who died during the year were included in the cost analysis, with costs set to £0 after the date of death. Hence, for the purposes of the total cost analysis, 211 participants in the deferred-ablation group (226 randomised minus 15 withdrawals, i.e. lost to follow-up or protocol deviations) and 208 participants in the early-ablation group (224 randomised minus 16 withdrawals, i.e. lost to follow-up or protocol deviations) completed 12 months of the trial or died (see *Figure 3*).

The total mean cost over 1 year was very similar in the two trial groups: £2514 (SD £2770) in participants randomised to early ablation and £2516 (SD £3242) in the deferred-ablation group.

The early-ablation group incurred a greater initial cost due to the allocated ablation procedure, even though the trial protocol suggested that participants in the deferred group should have an ablation procedure once the ulcer was healed. Reasons for non-ablation in participants randomised to deferred ablation are 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 for by the lower costs of district nurse visits and consumables to quicker wound healing. Other resource use was similar in the two groups.

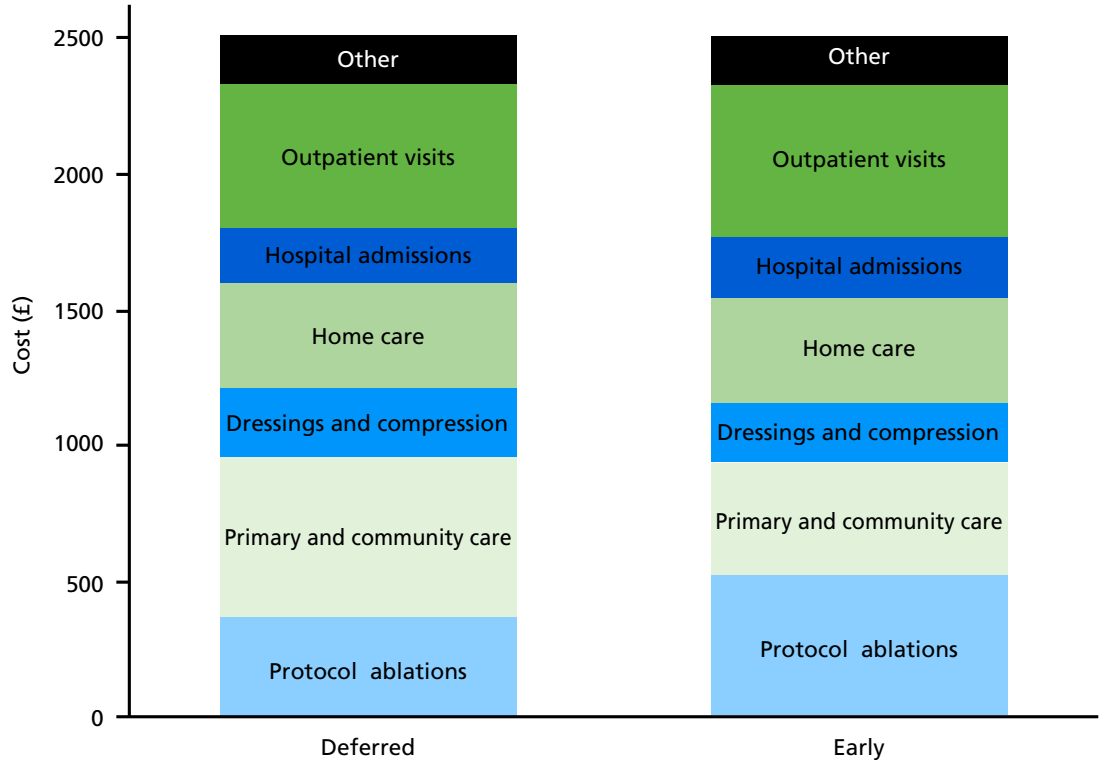


FIGURE 14 NHS and Personal Social Services costs (£) of early vs. deferred strategies over 1 year, $n = 208$ (early-ablation group) and $n = 211$ (deferred-ablation group). Reproduced with permission from Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. Epstein *et al.*[71] *British Journal of Surgery*, vol. 106, © 2019 BJS Society Ltd Published by John Wiley & Sons Ltd.

Table 10 shows the number of index endovenous ablation procedures performed. The trial also recorded further interventions in the treatment visit CRF and in the monthly telephone follow-up. These may include, for example, reinterventions for return of symptoms. Some of these may be non-protocol ablations (e.g. ablation in the non-trial leg), but there is insufficient information to be certain.

Table 25 shows the total number of vein procedures recorded in the trial, including those reported in the monthly telephone follow-up. To avoid double-counting, a record was assumed to be duplicated if a participant reported a vein procedure in the same month both on the CRF and during the telephone follow-up.

Cost-effectiveness analysis

The cost-effectiveness analysis uses data on both total costs and QALYs over 1 year. A total of 344 (76%) of 450 participants were included in the complete-case cost-effectiveness analysis. *Table 26* summarises the pattern of missing data. Thirty-one (7%) participants had missing data for costs (because either they withdrew from the trial or there was a protocol deviation). A greater proportion (16%) had some missing data at 12 months for EQ-5D-5L. This arose because of withdrawal and because not all participants fully completed all the questions in the HRQoL questionnaires at each follow-up. Overall, 24% had some missing EQ-5D or cost data over the year.

TABLE 25 All varicose vein ablation procedures recorded in the trial[a]

Number of ablation procedures per patient	Early ($N = 224$)	Deferred ($N = 226$)
No procedure	6	55
1	150	120
2	30	30
3	32	14
4	6	6
5	0	1

a Includes index interventions and reinterventions. Some procedures may include interventions on the non-trial leg.

TABLE 26 Pattern of missing data

Variable	Early	Deferred	Total
Randomised, *n*	224	226	450
Any missing cost data over the year, *n* (%)	16 (7)	15 (7)	31 (7)
Missing EQ-5D-5L at baseline, *n* (%)	2 (< 1)	0 (0)	2 (< 1)
Missing EQ-5D-5L at 6 weeks, *n* (%)	13 (6)	18 (8)	31 (7)
Missing EQ-5D-5L at 6 months, *n* (%)	36 (16)	31 (14)	67 (14)
Missing EQ-5D-5L at 12 months, *n* (%)	36 (16)	36 (16)	72 (16)
Any missing data over the year, *n* (%)	51 (23)	55 (24)	106 (24)
Complete cases, *n*	173	171	344

Table 27 shows the results of the cost and QALY regressions for the cost-effectiveness analysis.

In the complete-case analysis (model 1), the difference in cost was £163 (SE £318), the difference in QALYs gained at 1 year was 0.041 (SE 0.017) and the ICER was £3976 per QALY. There was an 89% probability that early venous surgery is cost-effective at the current willingness-to-pay (WTP) threshold of £20,000 per QALY (*Figure 15*). Assuming bivariate normality to estimate SEs gave very similar results (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 health-care costs (correlation –0.294; $p < 0.001$).

In model 3, missing data were imputed. The mean difference in total cost was –£72 (SE £290, i.e. early intervention was cheaper at 1 year), and the mean difference in QALYs gained over 1 year was 0.058 (SE 0.018). There was a 99% probability of early intervention being cost-effective at a threshold of £20,000 per QALY.

Using alternative tariff values for the EQ-5D-5L resulted in a slightly smaller difference in QALY between the treatment groups, but the ICER was similar to the base case (model 4).

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

TABLE 27 Regression results for cost-effectiveness analysis

	Model 1 (base case)	Model 2	Model 3	Model 4	Model 5
Description of model	Complete case ($n = 344$), with bootstrap SEs (1000 samples) and crosswalk EQ-5D tariff[63]	Complete case ($n = 344$), with bivariate normal SEs and crosswalk EQ-5D tariff	10 multiple imputations ($n = 450$), with bivariate normal SEs and crosswalk EQ-5D tariff	Complete case ($n = 344$) with bootstrap SEs and Devlin EQ-5D-5L tariff[57]	Per-protocol compliers ($n = 273$) with bootstrap SEs
Difference in cost: mean (SE), *p*-value	163 (318), 0.607	163 (322), 0.612	–72 (290), 0.803	163 (322), 0.612	486 (326), 0.137
Difference in QALY: mean (SE), *p*-value	0.041 (0.017), 0.017	0.041 (0.018), 0.024	0.058 (0.018), 0.002	0.033 (0.016), 0.039	0.056 (0.019), 0.003
ICER	£3976/QALY	£3976/QALY	n/c[a]	£4939/QALY	£8679/QALY

n/c, not computable.

a ICER is not computable as early intervention is estimated to cost less and deliver greater QALY gain than deferred intervention.

Note

Estimated correlation of residuals between cost and QALY in the bivariate normal model –0.294; $p < 0.001$.

Reproduced with permission from Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. Epstein *et al.*[71] British Journal of Surgery, vol. 106, © 2019 BJS Society Ltd Published by John Wiley & Sons Ltd.

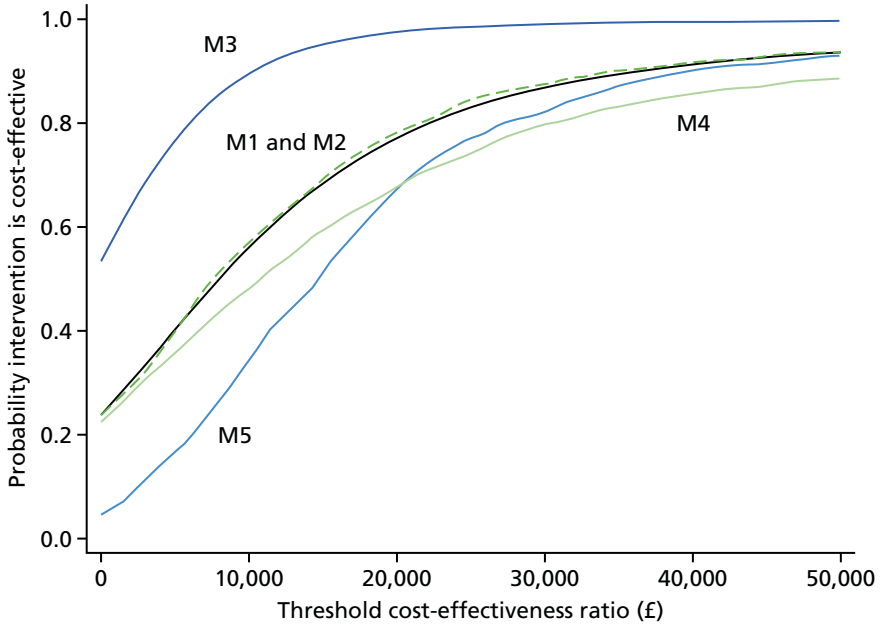


FIGURE 15 Cost-effectiveness acceptability curves for each model. Model 1: complete case (dashed line); Model 2: complete case using bivariate normal model; Model 3: multiple imputation; Model 4: alternative EQ-5D-5L tariff; Model 5: Per-protocol. Reproduced with permission from Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. Epstein *et al.*[71] *British Journal of Surgery*, vol. 106, © 2019 BJS Society Ltd Published by John Wiley & Sons Ltd.

Chapter 5 Discussion

Interpretation

The EVRA trial is the first multicentre RCT to assess the effect of early endovenous ablation for superficial venous reflux on ulcer healing in participants with venous ulceration. As standard care in the UK does not usually involve venous surgery (and, if surgery is performed, it is generally deferred until after ulcer healing with compression therapy), the results should be of interest to patients, clinicians and policy-makers.

The trial showed that early ablation of superficial reflux in addition to compression therapy significantly accelerates ulcer healing. Participants randomised to the early-ablation group also benefited from more ulcer-free time over the 12 months post randomisation.

Venous guidelines, worldwide,[40,45] recommend the ablation of superficial venous reflux based on the results of the ESCHAR trial, which demonstrated that superficial venous surgery reduced ulcer recurrence compared with compression therapy alone.[9,15] ESCHAR, however, did not show a benefit in terms of ulcer healing, which may explain why leg ulcer care pathways usually do not include provisions for early assessment and treatment of superficial reflux. The exception is the US Society for Vascular Surgery and the American Venous Forum Guidelines, which make a weak recommendation (grade 2, level C) for endovenous ablation in active ulceration based on the results of some cohort studies.[45] In addition, the lack of standardised leg ulcer pathways and the involvement of a range of specialists may contribute to the inconsistent care delivered.[8,41,44]

It is interesting to note that the healing rates at 12 and 24 weeks achieved in the deferred-ablation group (51.6% and 76.3%, respectively) are higher than those previously reported in the literature and seen in the general venous leg ulcer population.[72] This is likely to be as a result of good-quality compression applied by the specialised, highly trained research staff and not representative of usual care (which varies across regions and can suffer from lack of staffing and resource).[44,73]

Despite the excellent healing rates in the deferred-ablation group in this trial, participants randomised to early ablation still demonstrated a shorter time to healing. A widespread strategy of early ablation is likely to show an even greater benefit, as endovenous interventions are usually delivered as a single treatment episode, in contrast with compression therapy, which requires ongoing compliance for optimal outcomes. Implementation of early endovenous ablation for patients with venous leg ulceration will require considerable changes to current care pathways and treatment paradigms. The EVRA trial results reinforce the NICE recommendation that patients with leg ulceration not healed within 2 weeks should be referred promptly to a vascular service for evaluation and treatment of venous disease.

Although the results of the subgroup analysis should be interpreted with caution, there is a clear trend for a greater benefit from early ablation as ulcer duration increases. The inclusion criteria for the trial stipulated an upper limit of 6 months in duration for ulcers. This was to minimise heterogeneity within the trial population, but also because investigators expressed concerns about withholding endovenous ablation from patients with ulcers that had failed to respond to 6 months of compression therapy. Whether or not an even greater benefit would exist in those with an ulcer duration of > 6 months remains unclear.

Adverse events

The most common complications of endovenous ablation were pain and DVT. The DVT rate seen in the early-ablation group was high compared with other literature. However, in six of the participants DVT was infrapopliteal, and in four of these the thrombosis was identified on routine post-UGFS duplex ultrasonography performed 7 days post ablation (as per the local scanning regimen in one of the recruiting centres). Therefore, it is likely that this represents a very high level of detection of subclinical DVT.

Although 98 SAEs were reported over the course of the trial, as may be expected given the age of the trial population, only seven were deemed to be possibly, probably or definitely related to the ablation procedures.

Health-related quality of life

Early ablation led to significant improvements in disease-specific (AVVQ) and general HRQoL (EQ-5D index value) and body pain (SF-36 body pain), over the follow-up period. Differences were most pronounced at 6 weeks and 6 months post randomisation, which is consistent with more rapid healing.

Costs and cost-effectiveness

The complete-case analysis shows little difference in total mean cost per patient over 1 year between early and deferred ablation [mean difference £163 (SE £318); $p = 0.607$]. The greater initial mean cost of the early-ablation strategy is mostly offset by the reduced cost of treating unhealed leg ulcers. There is, however, a substantial and statistically significant QALY gain over 1 year, with a mean difference of 0.041 (SE 0.017) QALYs; $p = 0.017$. The ICER of early ablation at 1 year is, therefore, £3976 per QALY, compared with deferred ablation, with a high probability (89%) that early ablation is more cost-effective at conventional UK WTP thresholds (£20,000 per QALY). Sensitivity analyses using alternative statistical models give qualitatively similar results.

The difference in HRQoL appears to narrow at 1 year. Further follow-up is required to understand whether or not the gains from early ablation are maintained in the longer term. If early ablation results in lower recurrence risk in addition to reducing the time to healing, then even greater cost-effectiveness may be present over the lifetime of the patient.[74]

The economic analysis protocol envisaged a within-trial cost-effectiveness analysis at 1 year and a decision model [for details, see the health economic plan on the project web page: www.journalslibrary.nihr.ac.uk/programmes/hta/11129197/#/ (accessed 18 April 2019)]. The purpose of the decision model was to extrapolate recurrence rates in order to assess whether or not early ablation might be cost-effective over a patient's lifetime. At 1 year, there were insufficient recurrence events to reliably compare early with delayed ablation. Hence, the decision model results based on EVRA trial data will be reported when the trial extension results become available in late 2019.

As it was not possible to construct an economic model incorporating recurrence rates based on EVRA trial data at 1 year, an interim analysis was undertaken based on recurrence and healing rates obtained from the literature.[31] These studies compared early ablation (with surgery or endothermal techniques) plus compression versus compression only. None of these studies compared early ablation with delayed ablation; hence, they are not directly comparable with the strategies under comparison in the EVRA trial and are therefore not described in detail in this report. Nevertheless, the analysis showed that even if early ablation reduced the rate of recurrence only, and did not have an impact on healing, this strategy would be very cost-effective over a patient's lifetime.[74]

Generalisability

The trial was designed to be as pragmatic as possible, with broad inclusion criteria and interventional strategies guided by the treating clinicians. Participants were recruited from 20 centres across England and, although the trial had only a 7% inclusion rate and screened > 6500 patients to randomise 450, the baseline characteristics of the trial participants appear representative of the target population, when compared with other leg ulcer studies.[46,75,76] Of those screened but not randomised, who were excluded for not meeting the eligibility criteria, the two largest groups were those who had their ulcer for > 6 months (1772/6105, 29%) and those whose ulcer had healed by the time of randomisation (610/6105, 10%), largely as a result of delays in referral from primary to secondary care. Those with ulcers already healed have been shown in the ESCHAR trial to benefit from superficial venous intervention. Findings from the pre-planned subgroup analyses suggest that those with an ulcer duration of > 6 months may also benefit from early endovenous ablation. The results from the EVRA trial may therefore be more generalisable than initially apparent. Furthermore, as > 90% of those in the early-ablation group were treated within 2 weeks and 79.4% of these participants required only one procedure, implementation in a NHS setting seems highly feasible. Patient concordance is also likely to be higher with early ablation than with compression alone, as treatment success is less dependent on ongoing patient compliance.

Strengths of the EVRA trial

Sample size and loss to follow-up

The EVRA trial is the largest and only RCT, to our knowledge, to evaluate the effect of early endovenous ablation of superficial venous reflux, and target sample size of 450 participants was achieved. An adequate number of healing events occurred. Loss to follow-ups, withdrawals and deaths did not exceed our estimated 10% of the total recruitment; therefore, the trial was powered effectively.

Missing data

Only 31 (7%) participants were lost to follow-up, withdrew or violated protocol during the 12 months of the trial and we were able to ascertain the primary and secondary clinical end points for the majority of participants. Missing data were mainly confined to patient-reported outcomes such as AVVQ and SF-36, for which there was marked attrition over time. This was addressed in the analysis by performing sensitivity analyses using imputed values. Findings based on multiple imputation were the same as for the complete-case analysis.

For the cost-effectiveness analysis, 24% of participants had some missing data (for EQ-5D or costs over 12 months). The base case used only participants with complete data and sensitivity analyses used multiple imputation of missing data. Both methods gave qualitatively similar results, showing that the difference in cost was not significantly different from zero, whereas early ablation was associated with a substantial and significantly greater QALY gain.

Verification visit and blinded outcome assessment

Although the treatment allocation could not be blinded, it is believed that the blinded outcome assessment is a key strength of the trial.

Limitations of the EVRA trial

Centre variation

Despite each centre having an established leg ulcer care pathway, variations of practice existed between centres, most importantly in the choice of endovenous modality. In order to minimise these variations, we stratified by centre and stipulated standardised ablation principles. Similarly, compression regimens varied

across participants and for the same participant, who may have received multiple different compression therapies. In general, a pragmatic approach was adopted.

Superficial venous reflux patterns

The patterns of superficial venous reflux and presence and extent of deep venous incompetence varied. However, the results support previous studies that show clear benefits of treating superficial venous reflux, even in the presence of concomitant deep-venous incompetence.[46,77,78]

Post-ablation duplex

The 6-week follow-up duplex ultrasonography was stipulated only in the early-ablation group, whereas the deferred group strategy was as per standard care. This may have led to more repeat procedures and a higher procedure success rate than in the deferred-ablation group; however, this is not relevant to the primary outcome of time to ulcer healing.

Ulcer recurrence

The trial follow-up period was only to 1 year and hence was too short to give meaningful recurrence data, as there is a potential bias against the early-ablation group. With ongoing follow-up and longer-term recurrence data, we anticipate that this bias will diminish. The follow-up period for the extension is now complete (as of 31 March 2019) and, at the time of publication, we are cleaning and locking the database prior to data analysis. No new data available to date.

Endovenous modality

The clinicians were permitted to use modalities of their choice subject to some core stipulations of ablation. Despite the trial showing an overall benefit for early ablation, there is no clear distinction of benefit between the various endovenous modalities. The common modality used in this trial was ultrasonography-guided sclerotherapy, most likely reflecting its low cost and versatility, although some large RCTs have shown that complete venous occlusion may be lower with UGFS than with endovenous ablation.[37,55] Longer-term follow-up is ongoing and should help determine whether or not this will affect longer-term clinical outcomes and recurrence rates.

Chapter 6 Conclusion

Overall conclusions

Early endovenous ablation of superficial truncal reflux in addition to compression therapy accelerates the healing of venous leg ulcers compared with deferred ablation.

Although there is little difference between early and deferred ablation for endovenous superficial venous ablation in terms of the total mean cost per patient over 1 year, early ablation results in a significant gain in QALYs compared with deferred ablation. Therefore, early ablation has a high probability of being cost-effective at NICE WTP thresholds.

Implications for health care

Findings from this trial suggest that, for people with venous leg ulcers, early assessment and ablation of superficial venous reflux, in addition to compression therapy, accelerates healing and produces health economic benefits. Implementation of early assessment and endovenous ablation of superficial venous reflux will require further development of care pathways between primary and secondary care.

Recommendations for research (numbered in order of priority)

1. Follow up patients for longer to determine if early endovenous ablation influences ulcer recurrence rates in the medium and long term.
2. Evaluate the benefit of early ablation for superficial venous reflux in patients with venous leg ulceration of > 6 months' duration.
3. Determine the implications of deep-venous incompetence and occlusive, and the potential role of deep-venous stenting to improve venous outflow of the limb.
4. Evaluate the optimal technique and the extent of eradication of superficial venous incompetence in patients with venous ulceration.

Acknowledgements

Trial applicants

Alun H Davies, Manjit S Gohel, Jane Warwick, David M Epstein, Andrew Bradbury, Keith R Poskitt, Richard Bulbulia and Nicky Cullum.

Trial Management Group

Alun H Davies (chief investigator), Francine Heatley (trial manager), Xinxue Liu (statistician) and Jane Warwick (senior statistician).

Imperial Clinical Trials Unit

The following members were part of the wider ICTU trial team: Claire Smith, Hilda Tsang, Hema Collappen and Natalia Klimowska-Nassar (operation managers); Amanda Bravery, Sandra Griffiths, Joseph Fryer, Kayode Disu, Nayan Das, Ayse Depsen, Dinesh Sivakumar, Fiona Persaud (InForm database team); Ginny Picot (quality assurance).

Department of Surgery and Cancer, Imperial College London

The following members were part of the wider EVRA trial team: Rebecca Lawton (trial manager); Becky Ward (sponsor); Matt Ryan (research manager); and Kirti Patel and Zara Collard (contracts).

Trial Steering Committee

We would like to thank Professor Julie Brittenden (chairperson); Miss Rebecca Jane Winterborn (Consultant Vascular Surgeon); Professor Andrea Nelson (Head of School and Professor of Wound Healing); Dr Richard Haynes (Research Fellow and Honorary Consultant Nephrologist); and Mr Bruce Ley-Greaves (lay member), who all provided invaluable input and advice as an independent TSC member over the course of the trial.

Data Monitoring Committee

The team would also like to thank the independent DMC members: Professor Gerard Stansby (chairperson, Professor of Vascular Surgery), Professor Frank Smith (Professor of Vascular Surgery and Surgical Education), Professor Marcus Flather (Professor of Medicine, Clinical Trials) and Dr Ian Nunney (Medical Statistician).

Patient and public involvement

Bruce Ley-Greaves was involved in the original design during the grant application stages and was an active member of the TSC throughout the trial. Bruce's involvement is detailed in *Appendix 1*.

Core laboratory

We are thankful to Chen Liu and Rahul Velineni for core laboratory review and data activity.

Health economics

David Epstein (Health Economist) conducted the analysis of economic models for the trial.

Data cleaning

We are thankful to Yujin Lee for assistance with data cleaning and validation.

Local vascular research teams

The EVRA team would like to thank the NHS trusts, the 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): Mr Kevin Mercer, Fazah Gill, Alan Liu, Wendy Jepson, Amy Wormwell and Helen Rafferty (Bradford Royal Infirmary); Mr Manjit Gohel, Debbie Read, Simone Hargreaves, Karen Dhillon, Muzaffar Anwar, Ailsa Liddle and Helen Brown (Addenbrooke's Hospital); Alun Davies, Karen Dhillon, Raman Kaur, Emma Solomon, Kaji Sritharan, Rahul Velineni, Chung Sim Lim, Andrew Busuttil and Roshan Bootun (Charing Cross Hospital); Keith Poskitt, Richard Bulbulia, Jo Waldron, Gina Wolfrey, Fiona Slim, Colin Davies, Lorraine Emerson, Marianne Grasty, Mark Whyman, Clare Wakley, Andrew Cooper, Jo Clapp, Nicola Hogg, Julia Howard, Jackie Dyer, Sheri Lyes, Danita Teemul, Kate Harvey, Mandy Pride, Andrew Kindon, Hannah Price, Laura Flemming, Gemma Birch, Helen Holmes and Jodie Weston (Cheltenham General Hospital); Thomas Joseph, Ron Eiffel, Theo Ojimba, Toni Wilson, Adrian Hodgson, Lesley Robinson, Jane Todhunter, Dean Heagarty, Anna Mckeane and Rachel McCarthy (Cumberland Infirmary); Jamie Barwell, Clare Northcott, Alan Elstone and Clare West (Derriford Hospital); Patrick Chong, David Gerrard, Andrea Croucher, Stephanie Levy, Claire Martin and Tracey Craig (Frimley Park Hospital); Daniel Carradice, Anna Firth, Emma Clarke, Angie Oswald, Judith Sinclair, Ian Chetter, Joseph El-Sheikha, Sandip Nandhra and Clement Leung (Hull Royal Infirmary); Julian Scott, Nikki Dewhirst, Janet Woods, David Russell, Rosie Darwood, Max Troxler, Julie Thackeray, Deborah Bell, David Watson and Louise Williamson (Leeds General Infirmary); James Coulston, Paul Eyers, Katy Darvall, Ian Hunter, Andrew Stewart, Alison Moss, Jane Rewbury, Claire Adams, Louise Vickery, Leanne Foote, Helen Durman, Frances Venn, Paula Hill, Kate James, Fliss Luxton, Denise Greenwell. Karen Roberts, Suzette Mitchell, Moira Tate and Helen Mills (Musgrove Park Hospital); Andrew Garnham, Simon Hobbs, Donna Mcintosh, Marie Green, Kate Collins, Jayne Rankin, Paula Poulton and Val Isgar (New Cross Hospital); Sophie Renton, Karen Dhillon, Manoj Trivedi, Marina Kafeza, Shadeh Parsapour, Hayley Moore, Mojahid Najem, Sean Connarty, Hazel Albon, Chris Lloyd and Jackie Trant (Northwick Park Hospital); Rajiv Vohra, Jo McCormack, Jeanette Marshall, Victoria Hardy, Radu Rogoveanu and Will Goff (Queen Elizabeth Hospital Birmingham); Andrew Garnham, Ranjit Gidda, Sue Merotra, Sandy Shiralkar, Agantha Jayatunga, Rajiv Pathak, Atiq Rehman, Kiran Randhawa, Joy Lewis, Sarah Fullwood, Stacey Jennings, Sharon Cole and Michael Wall (Russells Hall Hospital); Charles Ranaboldo, Sarah Hulin, Caroline Clarke, Ruth Fennelly, Robin Cooper, Ruth Boyes, Charlotte Draper, Linda Harris and Dee Mead (Salisbury District Hospital); Andrew Bradbury, Lisa Kelly, Gareth Bate, Huw Davies, Matt Popplewell, Martin Claridge, Mark Gannon, Harmeet Khaira, Mark Scriven, Teun Wilmink, Donald Adam and Hosaam Nasr (Solihull Hospital); Colin Bicknell, Mike Jenkins, Tristan Lane and Emily Serjeant (St Mary's Hospital, London); Dominic Dodd, Shah Nawaz, John Humpreys, Mathew Barnes, Julie Sorrell, Diane Swift, Patrick Phillips, Hazel Trender and Nikki Fenwick (Northern General Hospital); Dynesh Rittoo, Sara Baker, Rebecca Mitchell, Sarah Andrews, Steve Williams and Jane Stephenson (Royal Bournemouth General Hospital); Isaac Nyamekye, Sarah Holloway, Wendy Hayes, Julie Day, Claire Clayton and Daniel Harding (Worcestershire Royal Hospital); Andrew Thompson, Andy Gibson, Zoe Murphy and Thomas Smith (York Hospital).

National Institute for Health Research Clinical Research Networks

We would like to thank the following Clinical Research Networks for their help and support throughout the study (in particular helping facilitate the set-up of patient identification centres): Clinical Research Network North West London (lead site); East Midlands; Eastern; Greater Manchester, Kent, Surrey and Sussex; North East and North Cumbria; North Thames; South London; South West Peninsular; Thames Valley and South Midlands; Wessex; West Midlands (in particular Shahnaz Khan); West of England; and Yorkshire and the Humber.

Patient identification centres

The EVRA team would like to thank the following NHS trusts for allowing some of their general practices to display posters and leaflets to help promote the trial and enhance recruitment: Lincolnshire Community Health Services NHS Trust, Lincolnshire Clinical Commissioning Groups (CCGs); Nottingham CityCare Partnership and County Health Partnerships within Nottinghamshire Healthcare NHS Foundation Trust, Nottingham City CCG and Nottinghamshire County CCGs; Derbyshire County and Derby City PCT; Derbyshire Community Health Services; Northamptonshire Healthcare NHS Foundation Trust; Leicestershire Partnership NHS Trust; Cambridgeshire Community Services NHS Trust; Cambridgeshire and Peterborough CCG; Hertfordshire Community NHS Trust; Hertfordshire Partnership NHS Foundation Trust; North Essex Partnership University NHS Foundation Trust; NHS South Norfolk CCG; Ashton Leigh and Wigan PCT; Bolton PCT; Bury PCT; Heywood, Middleton and Rochdale PCT; Manchester PCT; Oldham PCT; Salford PCT; Stockport PCT; Trafford PCT; Crawley CCG; Coastal West Sussex; Horsham & Mid Sussex; Eastbourne, Hailsham and Seaford CCG (formerly NHS East Sussex Downs and Weald); High Weald Lewes Havens CCG (formerly NHS East Sussex Downs and Weald); Hastings and Rother CCG (formerly NHS Hastings and Rother); East Surrey CCG (formerly NHS Surrey); Guildford and Waverley CCG (formerly NHS Surrey); North East Hampshire and Farnham CCG (formerly NHS Surrey); North West Surrey CCG (formerly NHS Surrey); Surrey Downs CCG (formerly NHS Surrey); Surrey Heath CCG (formerly NHS Surrey); Brighton and Hove CCG (formerly NHS Brighton and Hove); Ken and Medway CCGs; Medway Community Healthcare; North of England Commissioning CCGs; Central and North West London NHS Foundation Trust; Brent CCG; Central London Community Healthcare NHS Trust; Chelsea and Westminster Hospital NHS Foundation Trust; Hounslow and Richmond Community Healthcare NHS Trust; Bexley CCG; Lewisham CCG; Royal Devon and Exeter NHS Foundation Trust; Somerset CCG; Dorset CCG; Fareham and Gosport CCG; Isle of Wight CCG; North Hampshire CCG; North East Hampshire; Portsmouth CCG; Southampton CCG; South Eastern Hampshire CCG; Wilshire CCG; Birmingham Community Healthcare NHS Trust; Black Country Partnership NHS Foundation Trust; Worcestershire Health and Care NHS Trust; Worcestershire PCT; Walsall Healthcare NHS Trust; Royal Wolverhampton NHS Trust; Coventry and Warwickshire Partnership Trust; Bristol PCT; North Somerset and South Gloucestershire PCT; Banes CCG; NHS Swindon CCG; City Health Care Partnership; Humber NHS Foundation Trust; NHS Doncaster CCG; Airedale, Wharfedale and Craven CCG; Bradford City CCG; Bradford District CCG; Calderdale CCG; Leeds North CCG; Leeds South and East CCG; Leeds West CCG; Wakefield CCG; Vale of York CCG; Scarborough and Rydale CCG; Hambleton, Richmondshire and Whitby CCGs; Harrogate Rural and District CCG; Hull CCG; East Riding of Yorkshire CCG; and North Lincolnshire CCG.

Contributions of authors

Manjit S Gohel (Consultant Vascular Surgeon and co-applicant) was responsible for the design, conduct, supervision of the trial, acquisition of the data, interpretation of analysis and dissemination, drafting relevant chapters and final approval.

Francine Heatley (Trial Manager) managed and monitored the trial as trial manager, assisted with acquisition of the data, drafted relevant chapters and approved the final version of the report.

Xinxue Liu (Trial Statistician) was responsible for the conduct of the statistical analysis.

Andrew Bradbury (Consultant Vascular Surgeon and co-applicant) was responsible for the design of the trial, acquisition of the data and review of the final draft.

Richard Bulbulia (Consultant Vascular Surgeon and co-applicant) was responsible for the design of the trial and review of the final draft.

Nicky Cullum (Professor of Nursing, Head of the Division of Nursing, Midwifery & Social Work and co-applicant) was responsible for the design of the trial and review of the final draft.

David M Epstein (Lecturer, Applied Economics) was responsible for the design, conduct, analysis, dissemination and drafting of the cost-effectiveness chapter and review of the final draft.

Isaac Nyamekye (Consultant Vascular Surgeon) assisted with acquisition of the data and review of the final draft.

Keith R Poskitt (Consultant Vascular Surgeon and co-applicant) was responsible for the design of the trial, acquisition of the data and review of the final draft.

Sophie Renton (Consultant Vascular Surgeon) assisted with acquisition of the data and review of the final draft.

Jane Warwick (Senior Statistician and co-applicant) was involved in the design of both the trial and the statistical analysis plan, conduct of the statistical analysis and drafting of relevant chapters.

Alun H Davies (Professor of Vascular Surgery) was the chief investigator and was responsible for the design, conduct and supervision of the trial; interpretation of analysis and dissemination; drafting relevant chapters; and co-ordination of the report including final approval.

Francine Heatley, **Alun H Davies**, **Manjit S Gohel**, **Jane Warwick** and **David M Epstein** were responsible for drafting this report, although all authors provided comments on drafts and approved the final version.

Publications

Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, *et al.* A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med* 2018;**378**:2105–114.

Epstein DM, Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, *et al.* Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. *Br J Surg* 2019;**106**:555–62.

Data-sharing statement

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

References

1. Obermayer A, Garzon K. Identifying the source of superficial reflux in venous leg ulcers using duplex ultrasound. *J Vasc Surg* 2010;**52**:1255–61. https://doi.org/10.1016/j.jvs.2010.06.073
2. Posnett J, Gottrup F, Lundgren H, Saal G. The resource impact of wounds on health-care providers in Europe. *J Wound Care* 2009;**18**:154–61. https://doi.org/10.12968/jowc.2009.18.4.41607
3. 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. *Programme Grants Appl Res* 2016;**4**(13). https://doi.org/10.3310/pgfar04130
4. Graham ID, Harrison MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. *Adv Skin Wound Care* 2003;**16**:305–16. https://doi.org/10.1097/00129334-200311000-00013
5. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. *Br Med J* 1987;**294**:1389–91. https://doi.org/10.1136/bmj.294.6584.1389
6. NHS Digital. *Statistics on Obesity, Physical Activity and Diet – England, 2012*. Leeds: NHS Digital; 2012. URL: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2012 (accessed 18 March 2019).
7. Laing W. *Chronic Venous Diseases of the Leg*. London: Office of Health Economics; 1992. URL: www.ohe.org/publications/chronic-venous-diseases-leg (accessed 18 March 2019).
8. 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. https://doi.org/10.1136/bmjopen-2015-009283
9. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, *et al.* Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet* 2004;**363**:1854–9. https://doi.org/10.1016/S0140-6736(04)16353-8
10. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg* 2006;**44**:563–71. https://doi.org/10.1016/j.jvs.2006.04.053
11. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation* 2014;**130**:333–46. https://doi.org/10.1161/CIRCULATIONAHA.113.006898
12. Grabs AJ, Wakely MC, Nyamekye I, Ghauri AS, Poskitt KR. Colour duplex ultrasonography in the rational management of chronic venous leg ulcers. *Br J Surg* 1996;**83**:1380–2. https://doi.org/10.1002/bjs.1800831016
13. Adam DJ, Naik J, Hartshorne T, Bello M, London NJ. The diagnosis and management of 689 chronic leg ulcers in a single-visit assessment clinic. *Eur J Vasc Endovasc Surg* 2003;**25**:462–8. https://doi.org/10.1053/ejvs.2002.1906
14. Tassiopoulos AK, Golts E, Oh DS, Labropoulos N. Current concepts in chronic venous ulceration. *Eur J Vasc Endovasc Surg* 2000;**20**:227–32. https://doi.org/10.1053/ejvs.2000.1157
15. 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. https://doi.org/10.1136/bmj.39216.542442.BE

16. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982;**2**:243–5. https://doi.org/10.1016/S0140-6736(82)90325-7

17. Ibegbuna V, Delis KT, Nicolaides AN, Aina O. Effect of elastic compression stockings on venous hemodynamics during walking. *J Vas Surg* 2003;**37**:420–5. https://doi.org/10.1067/mva.2003.104

18. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2012;**11**:CD000265. https://doi.org/10.1002/14651858.CD000265.pub3

19. Labropoulos N, Leon M, Volteas N, Nicolaides AN. Acute and long-term effect of elastic stockings in patients with varicose veins. *Int Angiol* 1994;**13**:119–23.

20. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. *Cochrane Database Syst Rev* 2014;**9**:CD002303. https://doi.org/10.1002/14651858.CD002303.pub3

21. van den Bremer J, Moll FL. Historical overview of varicose vein surgery. *Ann Vasc Surg* 2010;**24**:426–32. https://doi.org/10.1016/j.avsg.2009.07.035

22. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. *J Vasc Surg* 2004;**40**:634–9. https://doi.org/10.1016/j.jvs.2004.07.003

23. O'Hare JL, Earnshaw JJ. Randomised clinical trial of foam sclerotherapy for patients with a venous leg ulcer. *Eur J Vasc Endovasc Surg* 2010;**39**:495–9. https://doi.org/10.1016/j.ejvs.2009.11.025

24. Darwood RJ, Gough MJ. Endovenous laser treatment for uncomplicated varicose veins. *Phlebology* 2009;**24**(Suppl. 1):50–61. https://doi.org/10.1258/phleb.2009.09s006

25. Gohel MS, Davies AH. Radiofrequency ablation for uncomplicated varicose veins. *Phlebology* 2009;**24**(Suppl. 1):42–9. https://doi.org/10.1258/phleb.2009.09s005

26. Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. Randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. *Br J Surg* 2011;**98**:501–10. https://doi.org/10.1002/bjs.7394

27. Subramonia S, Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. *Br J Surg* 2010;**97**:328–36. https://doi.org/10.1002/bjs.6867

28. van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. *J Vasc Surg* 2009;**49**:230–9. https://doi.org/10.1016/j.jvs.2008.06.030

29. Davies AH, Hawdon AJ, Greenhalgh RM, Thompson S. Failure of a trial evaluating the effect of venous surgery on healing and recurrence rates in venous ulcers? The USABLE trial: rationale, design and methodology, and reasons for failure. *Phlebology* 2004;**19**:137–42. https://doi.org/10.1258/0268355041753371

30. Samuel N, Carradice D, Wallace T, Smith GE, Chetter IC. Endovenous thermal ablation for healing venous ulcers and preventing recurrence. *Cochrane Database Syst Rev* 2013;**10**:CD009494. https://doi.org/10.1002/14651858.CD009494.pub2

31. Mauck KF, Asi N, Undavalli C, Elraiyah TA, Nabhan M, Altayar O, *et al.* Systematic review and meta-analysis of surgical interventions versus conservative therapy for venous ulcers. *J Vasc Surg* 2014;**60**(Suppl. 2):60–70.e1–2. https://doi.org/10.1016/j.jvs.2014.04.059

32. Viarengo LM, Potério-Filho J, Potério GM, Menezes FH, Meirelles GV. Endovenous laser treatment for varicose veins in patients with active ulcers: measurement of intravenous and perivenous temperatures during the procedure. *Dermatol Surg* 2007;**33**:1234–42. https://doi.org/10.1097/00042728-200710000-00014

33. Marston WA, Crowner J, Kouri A, Kalbaugh CA. Incidence of venous leg ulcer healing and recurrence after treatment with endovenous laser ablation. *J Vasc Surg Venous Lymphat Disord* 2017;**5**:525–32. https://doi.org/10.1016/j.jvsv.2017.02.007

34. Sinabulya H, Östmyren R, Blomgren L. Editor's choice – mid-term outcomes of endovenous laser ablation in patients with active and healed venous ulcers: a follow-up study. *Eur J Vasc Endovasc Surg* 2017;**53**:710–16. https://doi.org/10.1016/j.ejvs.2017.02.028

35. Kulkarni SR, Slim FJ, Emerson LG, Davies C, Bulbulia RA, Whyman MR, *et al.* Effect of foam sclerotherapy on healing and long-term recurrence in chronic venous leg ulcers. *Phlebology* 2013;**28**:140–6. https://doi.org/10.1258/phleb.2011.011118

36. Pang KH, Bate GR, Darvall KA, Adam DJ, Bradbury AW. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. *Eur J Vasc Endovasc Surg* 2010;**40**:790–5. https://doi.org/10.1016/j.ejvs.2010.08.011

37. Rasmussen L, Lawaetz M, Serup J, Bjoern L, Vennits B, Blemings A, *et al.* Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. *J Vasc Surg Venous Lymphat Disord* 2013;**1**:349–56. https://doi.org/10.1016/j.jvsv.2013.04.008

38. Siribumrungwong B, Noorit P, Wilasrusmee C, Attia J, Thakkinstian A. A systematic review and meta-analysis of randomised controlled trials comparing endovenous ablation and surgical intervention in patients with varicose vein. *Eur J Vasc Endovasc Surg* 2012;**44**:214–23. https://doi.org/10.1016/j.ejvs.2012.05.017

39. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Chronic Venous Leg Ulcers*. Edinburgh: SIGN; 2010.

40. National Institute for Health and Care Excellence (NICE). *Varicose Veins: Diagnosis and Management*. London: NICE; 2013. URL: www.nice.org.uk/guidance/cg168/resources/varicose-veins-diagnosis-and-management-pdf-35109698485957 (accessed 15 February 2019).

41. Davies HO, Popplewell M, Bate G, Kelly L, Darvall K, Bradbury AW. Impact of UK NICE clinical guidelines 168 on referrals to a specialist academic leg ulcer service. *Phlebology* 2018;**33**:84–8. https://doi.org/10.1177/0268355516688357

42. Onida S, Davies AH, Franklin I. Varicose veins – who should be referred? *Phlebology* 2015;**30**(Suppl. 2):4–8. https://doi.org/10.1177/0268355515589249

43. National Institute for Health and Care Excellence (NICE). *Varicose Veins in the Legs. Quality Standard [QS67]*. London: NICE; 2014. URL: www.nice.org.uk/guidance/qs67/resources/varicose-veins-in-the-legs-pdf-2098792680901 (accessed 18 March 2019).

44. Bulbulia RA, Poskitt KR. The need for a National Service Framework for leg ulcers. *Phlebology* 2010;**25**(Suppl. 1):68–72. https://doi.org/10.1258/phleb.2010.010s10

45. O'Donnell TF, Passman MA. Clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) – management of venous leg ulcers. Introduction. *J Vasc Surg* 2014;**60**(Suppl. 2):1–2. https://doi.org/10.1016/j.jvs.2014.04.058

46. Gohel MS, Barwell JR, Earnshaw JJ, Heather BP, Mitchell DC, Whyman MR, *et al.* Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study) – haemodynamic and anatomical changes. *Br J Surg* 2005;**92**:291–7. https://doi.org/10.1002/bjs.4837

47. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med* 1982;**1**:121–9. https://doi.org/10.1002/sim.4780010204

48. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods* 2012;**9**:671–5. https://doi.org/10.1038/nmeth.2089

49. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J Vasc Surg* 1995;**21**:635–45. https://doi.org/10.1016/S0741-5214(95)70195-8

50. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, *et al.* Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004;**40**:1248–52. https://doi.org/10.1016/j.jvs.2004.09.027

51. Rutherford RB, Padberg FT, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000;**31**:1307–12. https://doi.org/10.1067/mva.2000.107094

52. Marston WA, Vasquez MA, Lurie F, Wakefield TW, Rabe E, Shortell CK, *et al.* Multicenter assessment of the repeatability and reproducibility of the revised Venous Clinical Severity Score (rVCSS). *J Vasc Surg Venous Lymphat Disord* 2013;**1**:219–24. https://doi.org/10.1016/j.jvsv.2012.10.059

53. Garratt AM, Macdonald LM, Ruta DA, Russell IT, Buckingham JK, Krukowski ZH. Towards measurement of outcome for patients with varicose veins. *Qual Health Care* 1993;**2**:5–10. https://doi.org/10.1136/qshc.2.1.5

54. Brittenden J, Cotton SC, Elders A, Ramsay CR, Norrie J, Burr J, *et al.* A randomized trial comparing treatments for varicose veins. *N Engl J Med* 2014;**371**:1218–27. https://doi.org/10.1056/NEJMoa1400781

55. 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. https://doi.org/10.1002/hec.3564

56. Garratt AM, Ruta DA, Abdalla MI, Russell IT. Responsiveness of the SF-36 and a condition-specific measure of health for patients with varicose veins. *Qual Life Res* 1996;**5**:223–34. https://doi.org/10.1007/BF00434744

57. Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, *et al.* A randomized trial of early endovenous ablation in venous ulceration. *N Engl J Med* 2018;**378**:2105–14. https://doi.org/10.1056/NEJMoa1801214

58. 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**:1705–18. https://doi.org/10.1007/s11136-005-2751-9

59. Ashby RL, Gabe R, Ali S, Saramago P, Chuang LH, Adderley U, *et al.* VenUS IV (Venous leg Ulcer Study IV) – compression hosiery compared with compression bandaging in the treatment of venous leg ulcers: a randomised controlled trial, mixed-treatment comparison and decision-analytic model. *Health Technol Assess* 2014;**18**(57). https://doi.org/10.3310/hta18570

60. 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**:1157–70. https://doi.org/10.1007/s40273-014-0193-3

61. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal*. London: NICE; 2013.

62. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Int J Technol Assess Health Care* 2013;**29**:117–22. https://doi.org/10.1017/S0266462313000160

63. 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**:708–15. https://doi.org/10.1016/j.jval.2012.02.008

64. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108. https://doi.org/10.1097/00005650-199711000-00002

65. National Institute for Health and Care Excellence (NICE). *Position Statement on EQ-5D-5L 2017*. London: NICE; 2017. URL: www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf (accessed 5 February 2018).

66. ClinicalTrials.gov. *Prospective Evaluation of the ReCell® Autologous Cell Harvesting Device For Specific Compassionate Use Cases*. URL: https://clinicaltrials.gov/ct2/show/NCT02992249 (accessed 15 March 2019).

67. ClinicalTrials.gov. *REVEAL: Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL)*. URL: https://clinicaltrials.gov/ct2/show/NCT01252953 (accessed 15 March 2019).

68. Joint Formulary Committee. *British National Formulary 73*. London: BMJ Group and Pharmaceutical Press; 2017.

69. 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**:487–96. https://doi.org/10.1002/hec.944

70. Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Stat Med* 2018;**37**:2252–66. https://doi.org/10.1002/sim.7654

71. Epstein DM, Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, *et al.* Cost-effectiveness analysis of a randomized clinical trial of early versus deferred endovenous ablation of superficial venous reflux in patients with venous ulceration. *Br J Surg* 2019;**106**:555–62.

72. Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. *Int Wound J* 2018;**15**:29–37. https://doi.org/10.1111/iwj.12814

73. Chamanga E, Christie J, McKeown E. Community nurses' experiences of treating patients with leg ulcers. *J Community Nurs* 2014;**28**:27–34.

74. 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**:203–12. https://doi.org/10.1002/bjs5.56

75. Ashby RL, Gabe R, Ali S, Adderley U, Bland JM, Cullum NA, *et al.* Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. *Lancet* 2014;**383**:871–9. https://doi.org/10.1016/S0140-6736(13)62368-5

76. Guest M, Smith JJ, Tripuraneni G, Howard A, Madden P, Greenhalgh RM, *et al.* Randomized clinical trial of varicose vein surgery with compression versus compression alone for the treatment of venous ulceration. *Phlebology* 2003;**18**:130–6. https://doi.org/10.1258/026835503322381333

77. Padberg FT, Pappas PJ, Araki CT, Back TL, Hobson RW. Hemodynamic and clinical improvement after superficial vein ablation in primary combined venous insufficiency with ulceration. *J Vasc Surg* 1996;**24**:711–18. https://doi.org/10.1016/S0741-5214(96)70002-2

78. Adam DJ, Bello M, Hartshorne T, London NJ. Role of superficial venous surgery in patients with combined superficial and segmental deep venous reflux. *Eur J Vasc Endovasc Surg* 2003;**25**:469–72. https://doi.org/10.1053/ejvs.2002.1894

79. de Wit M, Abma T, Koelewijn-van Loon M, Collins S, Kirwan J. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences. *BMJ Open* 2013;**3**:e002241. https://doi.org/10.1136/bmjopen-2012-002241

80. Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K, *et al.* A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials – a work in progress. *Res Involv Engagem* 2016;**2**:15. https://doi.org/10.1186/s40900-016-0029-8

81. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, *et al.* Patient engagement in research: a systematic review. *BMC Health Serv Res* 2014;**14**:89. https://doi.org/10.1186/1472-6963-14-89

82. Shippee ND, Domecq Garces JP, Prutsky Lopez GJ, Wang Z, Elraiyah TA, Nabhan M, *et al.* Patient and service user engagement in research: a systematic review and synthesized framework. *Health Expect* 2015;**18**:1151–66. https://doi.org/10.1111/hex.12090

83. National Institute for Health Research INVOLVE. *INVOLVE Briefing Notes for Researchers: Public Involvement in NHS, Public Health and Social Care Research*. 2012. URL: www.invo.org.uk/wp-content/uploads/2014/11/9938_INVOLVE_Briefing_Notes_WEB.pdf (accessed 5 October 2017).

84. National Institute for Health Research INVOLVE. *Jargon Buster*. URL: www.invo.org.uk/resource-centre/jargon-buster/ (accessed 1 July 2018).

85. Nuffield Department of Primary Care Health Sciences. *Developing a Patient and Public Involvement Intervention to Enhance Recruitment and Retention in Surgical Trials (PIRRIST)*. URL: www.phc.ox.ac.uk/research/health-experiences/research-projects/developing-a-patient-and-public-involvement-intervention-to-enhance-recruitment-and-retention-in-surgical-trials-pirrist (accessed 1 July 2018).

86. Gamble C, Dudley L, Newman J. Evidence base for patient and public involvement in clinical trials (EPIC). *Trials* 2013;**14**:O34–O. https://doi.org/10.1186/1745-6215-14-S1-O34

87. National Institute for Health Research INVOLVE. *INVOLVE Policy on Payments and Expenses for Members of the Public*. 2016. URL: www.invo.org.uk/posttypepublication/involve-policy-on-payments-and-expenses-for-members-of-the-public-including-involve-group-members-february-2016/ (accessed 5 October 2017).

88. National Institute for Health Research. *Going the Extra Mile: Improving the Nation's Health and Wellbeing Through Public Involvement in Research*. 2015. URL: www.nihr.ac.uk/patients-and-public/documents/Going-the-Extra-Mile.pdf (18 March 2019).

89. 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**(27). https://doi.org/10.3310/hta19270

90. NHS Supply Chain. *Advanced Wound Care. Dressings Price List 2017. NHS Supply Chain*. URL: www.supplychain.nhs.uk/product-news/contract-launch-briefs/price-ranking/contract-info/advanced-wound-care/ (accessed 11 April 2017).

91. Department of Health and Social Care. *NHS Reference Costs 2015 to 2016*. URL: www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 (accessed 1 September 2018).

92. Curtis L. *Unit Costs of Health and Social Care 2016*. Canterbury: PSSRU, University of Kent; 2016.

93. Curtis L. *Unit Costs of Health and Social Care 2015*. Canterbury: PSSRU, University of Kent; 2015.

94. NHS Digital. *Personal Social Services: Expenditure and Unit Costs 2014–15*. Leeds: NHS Digital; 2016.

Appendix 1 Patient and public involvement

Introduction

In addition to the ethical obligation of researchers to include patients and the public in research, the NIHR grant application process requires an element of public consultation from the outset. The benefits of public involvement have been shown throughout all stages of research, including identifying outcome measures.[79,80] More recent systematic reviews of patient involvement in research highlighted that active participation in research can lead to more relevant research by identifying patient-important outcomes and more credible results.[81,82]

In order to avoid a tokenistic approach to PPI, the *INVOLVE Briefing Notes for Researchers: Public Involvement in NHS, Public Health and Social Care Research* were consulted from the outset to plan PPI involvement in the trial.[83] The notes reinforce the importance of early engagement of lay members to enhance inclusivity, ownership of the study and a sense of purpose.

How patient and public involvement influenced the research design

Patient consultation

The 2004 ESCHAR trial suffered from a high crossover rate, as 19% of patients randomised to surgery refused an operation and this weakened the power of the trial.[15] It was assumed that the less invasive interventional modalities employed in the EVRA trial would not have the same rate of refusal. To corroborate this assumption, a small group of patients with active leg ulceration were consulted with the proposed trial design to see if they would be willing to undergo early intervention. Almost all the patients agreed that they would have been willing to participate in the trial, as they all wished to undergo intervention to heal their ulcer, and the trial offers the possibility of being treated sooner than standard care coupled with a less invasive strategy than open surgery.

Patient collaboration

A patient with healed leg ulceration (Bruce Ley-Greaves) who had previously shown an interest in research was approached to join as a lay member co-applicant to assist in the design of the research trial and ensure that the research question and outcomes were relevant to those affected by venous leg ulceration. Lay member involvement at the design stage helped the EVRA trial team gain insight into the following (quotations from Bruce Ley-Greaves):

- patients' fears and lack of knowledge about procedure and options
- thoughts on early referral and intervention ('my ulcer would have healed quicker if I had been referred and treated promptly as intervention had an immediate impact')
- deciding an appropriate primary outcome measure ('time to healing is the most important outcome as the smell associated with the ulcer affected my social confidence'), as well as important secondary outcome measures, including patient quality of life and ulcer-free time
- the frequency of follow-ups ('most patients would benefit from a 6-week clinic visit and monthly telephone calls to give them reassurance that they were not lost in the system as most patients are discharged out into the community post procedure').

Role description and expectations

In line with INVOLVE guidance, a role description was drafted to detail the expectations, commitment levels of the post, details of reimbursement for travel/time and some training and support resource links, including a link to the INVOLVE jargon buster (see *Appendix 10*).[84]

The lay member co-applicant agreed to act as our trial-specific PPI representative for the duration of the trial and join the TSC that met on an annual basis at a minimum. The trial manager and PPI representative met several times on an informal basis throughout the trial. All out-of-pocket expenses were covered for travel to the meeting and refreshments were provided at each meeting.

Trial set-up phase

As part of the set-up phase, the PPI representative reviewed all the patient-facing documents, including, but not limited to, the patient information sheet, consent form and patient diaries prior to Research Ethics Committee submission, to ensure that the language was appropriate and easily understood and that jargon was eliminated. Feedback from sites during the recruiting phase indicated that this was a successful exercise as patients needed little clarification after reading the patient information sheet.

Recruitment phase

The PPI representative attended the first TSC meeting and contributed and co-approved the charter. During the recruitment phase, he was an active member of the committee and attended all the TSC meetings, either in person or via teleconference, depending on availability.

To aid recruitment, he suggested that recruitment posters and leaflets were placed in GP surgeries to help recruit patients from primary care and contributed to the design of these. The impact of the recruitment posters and leaflets was difficult to evaluate; however, several patients who saw the posters requested referral to the recruiting hospitals and subsequently participated in the trial.

The trial manager kept in regular contact with the PPI representative in between TSC meetings to keep him engaged and informed of trial progress, particularly recruitment numbers. A shopping voucher was offered as recognition for his time.

Follow-up phase

Trial participants were e-mailed a newsletter during the follow-up phase to keep them updated on trial progress and timelines, and when they could expect to find out the results of the trial. The PPI representative helped design this newsletter, which also included a one-page article on the PPI involvement within the trial.

Results

The PPI representative attended the TSC/DMC results meeting to help provide a public/patient perspective on the interpretation of trial findings.

Dissemination

The PPI representative contributed to the design of the dissemination plan to ensure that the research team will disseminate the results to trial participants, the general public and health professionals, and has contributed to and reviewed the plain English summary for this report.

Measuring the impact of the EVRA trial

As the HTA programme has granted an extension to the trial to collect recurrence data, there will be an opportunity for the PPI representative to be involved in the adoption of the trial results in clinical practice and measuring the impact of a trial's findings and informing future trial design.

The EVRA trial team eagerly await the findings from the current University of Oxford study *Patient and Public Involvement Intervention to Enhance Recruitment and Retention in Surgical Trials (PIRRIST)*,[85] which aims to determine if PPI can improve recruitment and retention in clinical trials.

Evaluating patient and public involvement

A PPI involvement feedback meeting was convened in August 2017 to obtain the PPI representative's views on his involvement to date. The results of this meeting are summarised in *Table 28*. Written consent was obtained to use direct quotations.

Interestingly, these opinions are in line with results of the 2013 *Evidence Base for Patient and Public Involvement in Clinical Trials (EPIC)* study,[86] which concluded that involvement from patients and the public is successful if the 'goals are clear, if there are well developed plans for PPI in a trial, and if models of PPI are more responsive and managerial (e.g. membership of a Trial Management Group) rather than restricted to general oversight (e.g. membership of a TSC)'.

Summary

Based on the findings of the lay member involvement feedback, when designing future studies the research team would aim to:

- involve more than one member from the outset (e.g. a patient representative, someone newly diagnosed with the condition and a member of the public)
- include the members in the Trial Management Group discussions if appropriate
- ensure that the trial manager spends time with the members before and after meetings to explain reports and debrief
- ensure that TSC meetings are always held face to face
- provide an additional study-specific 'jargon buster' dictionary
- ensure that the reimbursement schedule is clear at the outset and calculated in line with the *INVOLVE Policy on Payments and Expenses for Members of the Public*[87] advice, considering an hourly rate of payment for time.

By incorporating these findings in future trial design, the EVRA trial team hopes to aid the INVOLVE vision: by 2025 INVOLVE expect 'all people using health and social care, and increasing numbers of the public, to be aware of and choosing to contribute to research by identifying future research priorities and research questions, informing the design and development of innovations, participating in research studies, advocating for the adoption and implementation of research in the NHS'.[88]

TABLE 28 Lay member involvement feedback (August 2017)

What he enjoyed the most	What he would do differently
Education about leg ulcers: *Learning more about leg ulcers and their treatment . . .* And: *. . . the chance to see better ways of doing something*	More specific jargon buster, in addition to the INVOLVE dictionary: *Some form of dictionary would help, as sometimes I sat there thinking 'what does this mean?' but didn't necessarily want to jump in and say 'sorry I don't know what you're talking about'* *. . . the jargon buster is more helpful than the PPI videos as I did lose interest easily as they seemed to go on a bit*
Repaying health-care providers: *Being able to [provide] feedback [on] treatment and say thank you for previous care*	Clearer reimbursement schedule, payment for time: *For the number of meetings payment was not necessary as I was learning and I was paying back and giving back to the system but if I was coming more often, though, there should be some sort of payment, for example £30 to £50*
Being able to offer insights into personal treatment experiences, referral problems, social concerns of having an leg ulcer: *Sitting at GP getting frustrated and down about the whole thing, wondered what was going to happen. I'm rotting away here*	Include another representative for support and understanding: *Include a second person to gain a better understanding on the basis that the two reps got together outside the meeting to debrief with the Trial Manager. That would be the advantage of having a second person*
Seeing that his input made a difference: *I was pleased to contribute to the study design and that my ideas, such as posters in the GP surgeries, ideas [sic] were listened to* *Participant documents were interesting to read and I was pleased to help make items more user friendly*	Pre-TSC meeting to talk through the trial manager's report and an after-meeting debrief: *I had no problems with confidence speaking up but I usually only say something when I think I have some to contribute. I didn't like to interrupt as I thought there was a job to be done and everyone is on short timescales and things did become clear late but a chance to speak before and after the meeting to go over detail I did not understand would be useful*
Reimbursement for time and contribution: *. . . the thank you voucher was a lovely touch and reinforced the collaboration*	Ensure that all participants always attend in person as easier to engage: *Better to have face-to-face meetings preference. Did not feel like a burden to attend meetings and combine with other things I wanted to do, like meet friends* *. . . much hard to understand items when discussed over a teleconference than in person*

Appendix 2 Trial committees' meeting dates

Data Monitoring and Ethics Committee

- 21 October 2013.
- 30 June 2014.
- 22 April 2015.
- 15 January 2016.
- 26 July 2016.
- 17 January 2018.

Trial Steering Committee

- 12 December 2013.
- 24 April 2014.
- 5 November 2014.
- 19 October 2015.
- 23 June 2016.
- 4 May 2017.
- 17 January 2018.

Investigator meetings

- 25 April 2013.
- 20 June 2013.
- 27 November 2013.
- 24 April 2014.
- 28 November 2014.
- 25 May 2015.
- 11 November 2015.
- 8 July 2016.
- 11 July 2017.
- 28 February 2018.

Appendix 3 Digital photograph protocol

Ulcer tracing

The ulcer size was determined at the baseline and 6-week clinic visit via manual tracing:

- Place planimetry (with 1 cm^2 markers) grids over the wound.
- Trace around end of ulcer with an indelible pen.
- Count the square descriptive units (cm^2) and enter into InForm.
- Scan tracing and save as PtTrialnumber_Baseline_tracing_dd/mm/yy.
- E-mail to EVRAtrial@imperial.ac.uk via the Imperial College FileExchange: https://icseclzt.cc.ic.ac.uk/.

Digital photograph of the ulcer

The ulcer size was determined at the baseline and 6-week clinic visit via digital photograph:

- A digital camera (minimum 8 megapixel) should be used (recommended trial camera is the Sony Cyber-shot DSC-WX60 16.2 Megapixel Digital Camera).
- Write the patient trial ID on the 3-cm calibration strip (red and white strips found in the site file) and place in the field of vision of camera on the leg but not obscuring wound edge.
- Enable flash (all other camera macros should be disabled, i.e. general mode).
- Position camera 15 cm from wound perpendicular to mid-point.
- Capture two images to ensure one suitable image for analysis.
- If wound cannot be captured in one single image, divide wound into two or more segments and summate images.
- Save photo as PtTrialnumber_Baseline_Photo_dd/mm/yy.
- E-mail to EVRAtrial@imperial.ac.uk via the Imperial College FileExchange: https://icseclzt.cc.ic.ac.uk/.

Appendix 4 The EVRA flow diagram

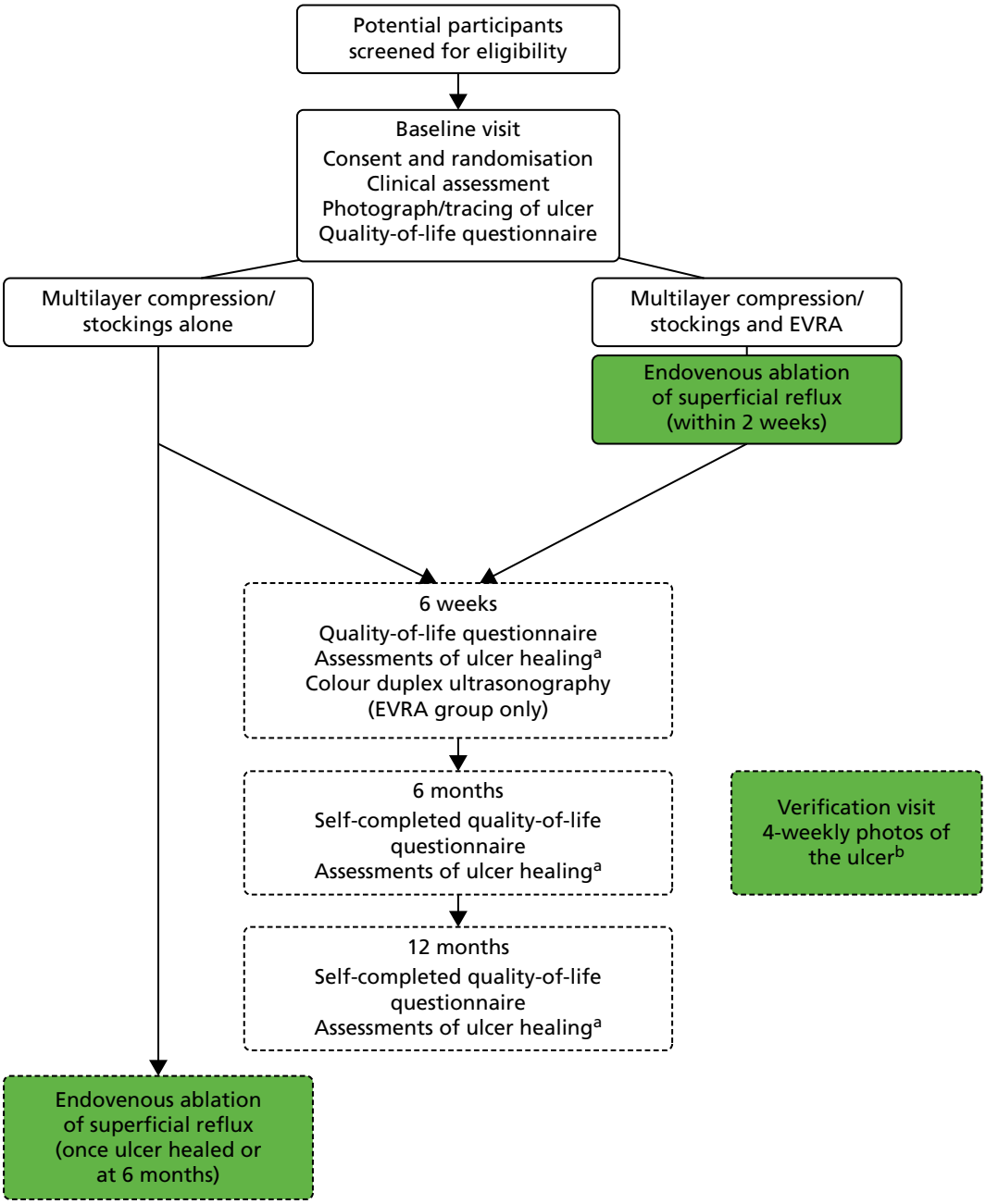


FIGURE 16 Early Venous Reflux Ablation flow diagram. a, Assessments of ulcer healing will be ongoing throughout the trial follow-up period and will be performed by community nursing teams and research staff (at least every month); b, once the research team has been informed by the patient that the ulcer has healed (can occur any time during the 12 months).

Appendix 5 Decision rules for verification of the primary outcome measure

Verification of ulcer healing will be by clinical assessment and digital photography, to be repeated weekly for 4 weeks. The digital images will be evaluated by two blinded expert assessors in order to ascertain the date of healing, which will be considered the primary healing end point. Disagreements will be resolved with involvement of a third blinded expert reviewer if necessary.

If the two blinded assessors agree that the reference ulcer has healed at the first photograph, the date of healing notification (by patient or community nurse) will be taken as the date of ulcer healing. If the two blinded assessors agree that the reference ulcer has healed at subsequent photographs, the date of those photographs will be used as the date of healing. If the two blinded assessors agree that the reference ulcer has healed at the first photograph, but the ulcer reoccurs at subsequent photographs, the date of healing from the first photograph will be used and the reoccurrence will be noted in the electronic CRF. Patients may undergo intervention for venous reflux after the first point the ulcer is confirmed healed (they do not have to wait until all four photographs are verified).

If the two assessors say 'unsure', then the ulcer has not healed at that point and the next photograph will be assessed.

If the two blinded assessors disagree on whether or not the reference ulcer has healed, there will be the following combinations with regard to healing:

- Yes/unsure.
  If the two assessors state 'yes/unsure' then the ulcer has healed, using the date provided by the assessor who said 'yes' or if the first photograph, the date of healing notification will be used.
- No/unsure.
  If the two assessors state 'no/unsure' then the ulcer has not healed.
- Yes/no.
  If the two assessors state 'yes/no' a third assessor will be consulted and will decide if the ulcer is healed or not. The third assessor's decision will be final. If they are unsure whether or not the ulcer has healed, the ulcer will be considered unhealed.

If no photographs of the reference ulcer are available, the unblinded date and the treating nurse/GP recorded will be used if available.

If the (treating) nurses state that the wound is healed and stop taking photographs but blinded assessors say that the wound is not healed, then the wound is considered healed.

If photographs are taken of a participant for > 12 months and the date of healing occurs beyond 12 months post randomisation, then the participant will be regarded as unhealed at 12 months.

Photographs taken after a large interval of time has elapsed (i.e. $\geq$ 1 month) since the due date of the last healed photograph (post-healed photograph 4), will not be included in the blinded outcome assessment.

Appendix 6 Health economic unit costs

Resource	Unit cost (£)	Assumption	Source
Index procedure			
Staff procedure costs			
EVLA	5.49/minute	Assumed same cost/minute for RFA	Brittenden *et al.* 2015[89]
UGFS	4.67/minute	Assumed same cost/minute for MOCA	Brittenden *et al.* 2015[89]
Disposable kit or catheter prices			
EVLA	238.60		Angiodynamics (Caley Kitchen, 14 February 2018, personal communication). List price catheter £200. Generator £22,000 (assuming 2-year life, 600 procedures in total, cost of capital 3.5% per year). This gives an annuitised cost per procedure of £38.60
RFA	543		Harriet Ellis, Imperial College Healthcare NHS Trust, 16 November 2017, personal communication. Includes generator rental
MOCA	375		Harriet Ellis, personal communication
Other theatre consumables and anaesthetic			
EVLA	66		Brittenden *et al.* 2015[89]
RFA	66		Assumed same cost as EVLA
UGFS	50		Brittenden *et al.* 2015[89]
MOCA	50		Assumed same cost as UGFS
Other costs of vein ablations (pre-procedure and recovery)			
EVLA	72		Brittenden *et al.* 2015[89]
RFA	72		Assumed same cost as EVLA
UGFS	42		Brittenden *et al.* 2015[89]
MOCA	42		Assumed same cost as UGFS
Consumables ulcer healing			
KTwo compression bandages	7.84	Assumed changed two times per week until healing	NHS supply chain[90]
VenoTrain® ulcertec compression stockings (Bauerfeind, London UK)	27.10	Assumed two pairs changed every 3 months until healing	NHS Supply Chain[90]
Ulcer dressing		Assumed changed two times per week until healing	
NA dressing	11.20 (for 40)		NHS Supply Chain[90]
Inadine 9.5 × 9.5 cm	15 (for 25)		NHS Supply Chain[90]
Atrauman® dressing (Paul Hartmann Ltd., Heywood, UK)	10.89 (for 30)	Assumed used if no other information provided	NHS Supply Chain[90]

Resource	Unit cost (£)	Assumption	Source
Consumables after healing to prevent recurrence			
Class 2 compression stocking	31.27	Assumed changed every 3 months	NHS Supply Chain[90]
Admissions to hospital (other than vein procedures)			
Overnight stay without procedure	265/night		*NHR Reference Costs 2015 to 2016*.[91] Excess bed-day: peripheral vascular disorders with CC score 2–4
Spinal surgery	4142	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Shoulder replacement	5110	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient[91]
Ankle surgery	2667	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Hip replacement	5877	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Knee replacement	5745	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Cataract	917	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Hernia repair	1726	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Pacemaker	2063	Not ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Elective inpatient
Angiography and stent	1449	Ulcer related	*NHR Reference Costs 2015 to 2016*.[91] Day case
Follow-up outpatient visit			
Without procedure	140/visit		*NHR Reference Costs 2015 to 2016*.[91] Vascular surgery
Office-based sclerotherapy	245/visit		Brittenden *et al.* 2015[89]
Primary care			
Visit to district nurse/general practice nurse/vein clinic	38/visit	Assume 15.5 minutes	*NHR Reference Costs 2015 to 2016*[91]
District nurse home visit	72/visit	Includes travel time	*NHR Reference Costs 2015 to 2016*[91]
Visit to GP	36/visit		PSSRU 2016[92]
GP home visit	88/visit	Includes travel time	PSSRU 2015.[93] Expenditure and unit costs
Other health care use			
Occupational therapist	79/visit		*NHR Reference Costs 2015 to 2016*[91]
Physiotherapist	49/visit		*NHR Reference Costs 2015 to 2016*[91]
Home carer visit	38/visit	Nursing care	Assume same as district nurse
Home help visit	29/visit	Personal care	NHS Digital.[94] Expenditure and unit costs
Medicines[68]			
Apixiban 2.5 mg	4.40/day		5 mg BD every day
Aspirin 75 mg	0.03/day		75 mg OD every day
Clopidogrel 75 mg	0.06/day		75 mg OD every day

Resource	Unit cost (£)	Assumption	Source
Dalteparin 12,500 units/ml	20.32/day	Males	For average weight 96 kg, 18,000 units/day
	14.12/day	Females	For average weight 80 kg, 12,500 units/day
Warfarin	0.04/day		
Rivaroxaban 10 mg	3.60/day		20 mg OD
Clexane (Enoxaparin)	11.02/day	Male	1.5 mg/kg OD
	7.84/day	Female	
Dabigatran 150 mg	1.70/day		150 mg BD

BD, twice daily; NA, non-adherent; OD, once daily; PSSRU, Personal Social Services Research Unit.

Appendix 7 Recruitment per centre

EVRA site	Participants recruited, *n*
Imperial College Healthcare NHS Trust	45
Cambridge University Hospitals NHS Foundation Trust	27
Worcestershire Acute Hospitals NHS Trust	20
North West London Hospitals NHS Trust	29
Gloucestershire Hospitals NHS Foundation Trust	124
Heart of England NHS Foundation Trust	51
University Hospitals Birmingham NHS Foundation Trust	9
North Cumbria University Hospitals NHS Trust	32
The Dudley Group NHS Foundation Trust	8
Royal Wolverhampton NHS Trust	3
York Teaching Hospital NHS Foundation Trust	2
Hull and East Yorkshire Hospitals NHS Trust	7
Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust	22
Frimley Health NHS Foundation Trust	6
University Hospitals Plymouth NHS Trust	23
Bradford Teaching Hospitals NHS Foundation Trust	6
Salisbury NHS Foundation Trust	5
Leeds Teaching Hospitals NHS Trust	4
Sheffield Teaching Hospitals NHS Foundation Trust	6
Taunton and Somerset NHS Foundation Trust	21

Appendix 8 Recruitment graph

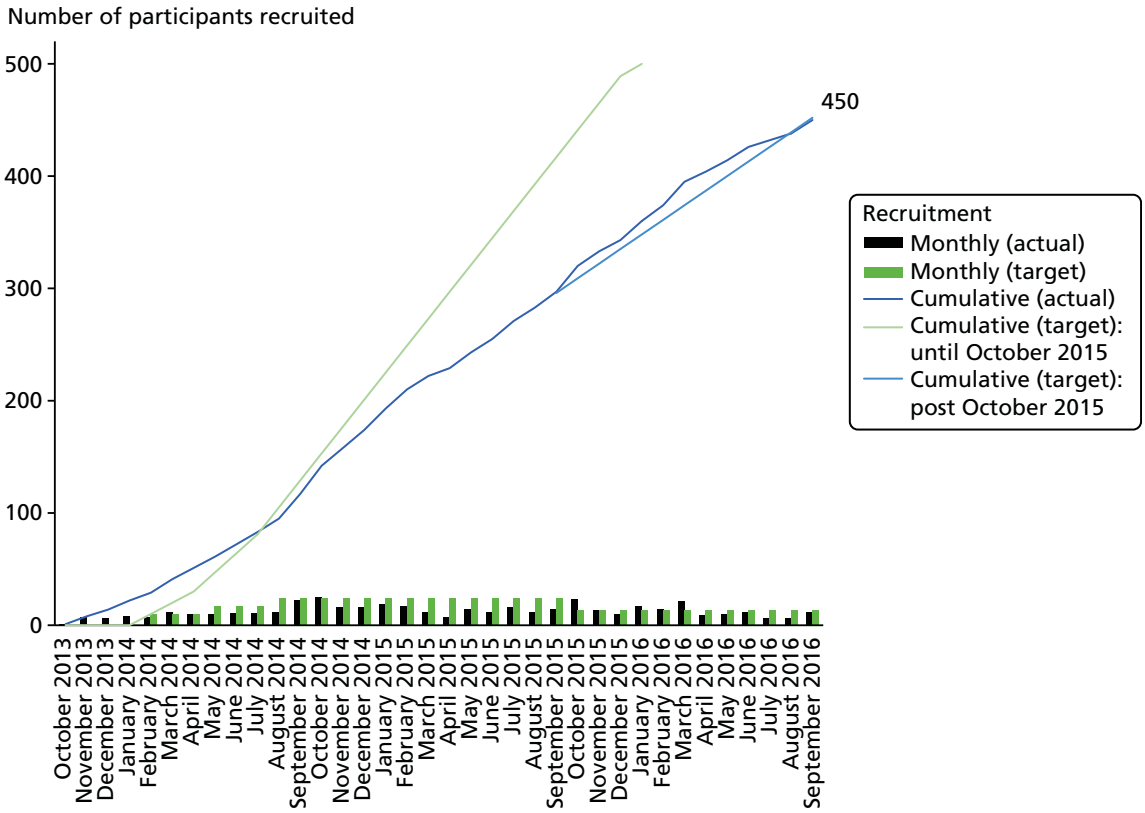


FIGURE 17 The EVRA trial recruitment graph (target vs. actual recruitment). Initial target recruitment was 24 participants a month, which was revised to 13 participants a month in October 2015. The target of 450 participants was achieved in September 2016.

Appendix 9 Total resource use

The following table shows the total resource use reported during the trial ($n = 450$), and mean (SD) cost per participant with 1 year of follow-up ($n = 419$). Analyses without imputation.

Resource type	Resource use (total)		Early ($N = 208$), mean cost (£)	SD (£)	Deferred ($N = 211$), mean cost (£)	SD (£)
	Early ($N = 224$)	Deferred ($N = 226$)				
Treatment visits in the trial leg			523	368	370	369
Number of procedures	7	55				
One or more procedure	217	171				
Two or more procedures	45	24				
Three or more procedures	6	7				
Four procedures	0	1				
Compression and dressings until healing (cost)			229	230	255	242
Compression stockings after healing (cost)			87	33	77	39
Hospital inpatient and day case admissions, not recorded as trial procedures	27	16	227	693	207	1526
Of which further ablation procedures, not recorded as trial procedures	12	5				
Visits to district nurse	1947	2196	102	148	112	169
Visits from district nurse	624	1025	220	804	366	1263
Visits to GP	528	546	89	84	91	92
Visits from GP	23	49	9	28	20	56
Outpatient consultations and procedures, not recorded as trial procedures	807	731	588	851	527	952
Of which further ablation procedures, not recorded as trial procedures	73	69				
Occupational therapy (visits)	6	14	2	17	5	24
Warfarin			1	4	2	4
Rivarox			16	106	24	159
Apixaban			13	114	1	9
Dalteparin			2	29	10	65
Dabigatran			0	4	2	36
Enoxaparin			0	0	2	23
Clopidogrel			1	3	1	3
Aspirin			2	4	2	4

Resource type	Resource use (total)		Early ($N = 208$), mean cost (£)	SD (£)	Deferred ($N = 211$), mean cost (£)	SD (£)
	Early ($N = 224$)	Deferred ($N = 226$)				
Physiotherapy	106	247	25	109	57	285
Home care	1413	1573	257	1593	262	1207
Home help	875	882	121	799	121	646
Total cost			2514	2770	2516	3242
Hospital admissions unrelated to venous leg ulcer	59	31	342	1435	192	1340
Outpatient visits unrelated to venous leg ulcer	151	156	98	207	103	414
Out-of-pocket expenses	87	122				
Unpaid carer (days)	4673	5132				
Off-work days	921	1458				
Normal days lost	4068	4947				

Appendix 10 Lay member role description

Role description of lay panel member for the EVRA Trial Steering Committee (TSC)

For further details about this project – please contact the Trial Manager, Francine Heatley [redacted]

Role Description for:

Bruce Ley-Greaves, lay member on Steering Group for the EVRA Research Project

EVRA Study Summary:

The EVRA study is for participants who have leg ulcers. A venous leg ulcer is a longstanding (chronic) wound on the leg or foot. These ulcers may either not heal or take a long time to heal and are usually caused by your leg veins not working very well. This problem with the veins is sometimes called varicose veins.

The usual care for venous ulcers is compression bandaging, followed by treatment of the varicose veins once the ulcer has healed. This study is being done to find out whether early treatment (within 2 weeks) of the varicose veins by modern keyhole (endovenous) procedures, in addition to compression bandaging, will help the leg ulcer heal quicker compared to the treatment with compression bandaging alone. Studies have shown that treating varicose veins can reduce the chance of an ulcer coming back, but we do not know if treating the veins early (within 2 weeks) will help your ulcer heal quicker.

Purpose of steering group:

The role of the TSC is to provide advice, through its Chair, to research team on all appropriate aspects of the trial and in particular that the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.

Other roles include:

- monitoring the progress of the trial, adherence to the protocol, participant safety and the consideration of new information of relevance to the research question
- to ensure appropriate ethical and other approvals are obtained in line with the project plan
- to agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- to provide advice to the investigators on all aspects of the trial

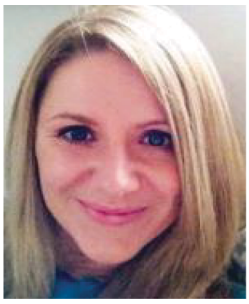
The Imperial Research Team:

The EVRA Chief Investigator is Professor Alun Davies. The trial manager is Francine Heatley.

Professor Alun Davies:

Professor Alun Davies Professor of Vascular Surgery at Imperial College London and a Consultant Surgeon whose NHS practice is based at Charing Cross and St Mary's Hospital, London. Professor Davies trained in Cambridge, Oxford, Plymouth, Boston (USA) and Bristol, prior to taking up a Consultant appointment in Charing Cross in 1994. Professor Davies is regarded as a world expert in the management of venous disorder. He has also written extensively on many aspects of vascular disease, writing over 370 peer reviewed manuscripts and runs a large research group.

Francine Heatley, Trial Manager:



Francine Heatley is a Trial Manager at the UKCRC registered Imperial Clinical Trials Unit (ICTU) in the School of Public Health within the Faculty of Medicine at Imperial College. She is a Biology graduate from the University of Nottingham and has over 10 years' experience of conducting clinical research in therapeutic areas such as vascular surgery, cardiovascular and oncology. She spent 3 years working for an academic research organisation in Canada and is familiar in both Health Canada and FDA clinical trial regulations.

Why involve you in the steering committee?

We are inviting you to be a member of the EVRA as we believe public involvement is an essential part of the development of modern health and social care services. Research that reflects the needs and views of the public is more likely to produce results that can be used to improve health and social care.

The TSC Committee Members:

The TSC chair:

- Professor Julie Brittenden, Chair in Surgery (Clinical)

Other committee members:

- Miss Rebecca Jane Winterborn, Consultant Vascular Surgeon
- Professor Andrea Nelson, Head of School and Professor of Wound Healing
- Dr Richard Haynes, Research Fellow and Honorary Consultant Nephrologist
- Dr Jane Warwick, Statistician, University of Warwick

Other members who may attend the meetings:

- Professor Alun Davies, Chief investigator
- Francine Heatley, Trial Manager
- ICTU Member, Operations Manager
- Sponsor or HTA (funding) representative if requested

Confidentiality:

As a representative of the EVRA trial TSC you are asked not to share confidential information you may have received as a result of your position.

Roles and responsibilities of user representative:

We would like you to:

- To attend the TSC meetings in person or by phone as per your preference
- To represent the patient/lay user views of the EVRA Research Project at other meetings you are asked to attend.
- To contribute to the discussion within the steering group and help us solve any problems we are facing with the study from your perspective.

Essential Criteria:

- Understanding or experience of the issues relating to chronic venous leg ulcers
- Be able to maintain confidentiality
- Have the time to attend meetings

Desirable Criteria:

It would be helpful if you have access to a computer and e-mail and have an understanding of the NHS and research processes

Remuneration:

Travel expenses and out-of-pocket expenses will be reimbursed and refreshments will be provided where appropriate.

Support:

You are able to access support and advice from the Trial manager (contact emails at the top of this document). Please do not hesitate to ask you don't understand something, research is full of acronyms and sometimes we forget to say the terms in full. Further information on Public involvement can be found here:

NIHR HTA Information on lay member reps: *http://www.nets.nihr.ac.uk/ppi*

INVOLVE Information on public involvement in research*:* *http://www.invo.org.uk/wp-content/uploads/2011/12/PIP1whatisitallabout.pdf* and a helpful jargon buster *http://www.invo.org.uk/wp-content/uploads/2011/12/PIP44jargonbuster.pdf*

Many thanks for contributing to the EVRA research trial we really do appreciate your involvement to help us improve the quality of

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library