VenUS 6
Health economics analysis plan (HEAP)

Version: v1.0 19.03.2024

Authors: Han Phung, Pedro Saramago, Marta Soares

Content

This document presents the economic analysis plan for a randomised controlled trial (RCT) examining compression therapies for the treatment of venous leg ulcers (VenUS 6). This study's protocol is available elsewhere.[1] An analysis plan for the synthesis of the clinical effectiveness evidence is provided in a separate document. The health economics analysis plan, together with the evidence synthesis plan, is designed to supplement the protocol and associated statistical analysis plan (SAP), adding detail where required and ensuring no unnecessary duplication or conflicting activities or analysis and it should be read in conjunction with them.

In accordance with the trial protocol, a trial-based (or within-trial) cost-effectiveness analysis will not be considered for this study. Within-trial cost-effectiveness analyses compare the value for money between treatment alternatives being evaluated within a single experimental study (i.e., evidence-based compressions - EBC, two-layer bandages – 2LB, compression wraps – CWs in VenUS 6). The internal validity of such analyses is widely acknowledged, but a single trial may provide limited information for decision making as it may not examine: all relevant treatments that decision-makers are interested in evaluating; all the existing relevant evidence that could inform the decision problem at stake; or the relevant time horizon to account for the long-term costs and health consequences.

The economic evaluation for VenUS 6 will use a decision-analytic modelling (DAM) framework. This approach allows simultaneous consideration of all relevant evidence, from multiple sources across a full range of possible alternative comparators. In VenUS 6 we will build on the DAM developed in VenUS IV, which compared all relevant high-compression treatments for venous leg ulcers.[2] The DAM used VenUS IV data, other effectiveness results identified via systematic review and pooled via meta-analyses and other required published data obtained from additional systematic review.

In this economic analysis plan, we aim to update the VenUS IV DAM (henceforth referred to as VenUS IV model) using:

- trial data from VenUS 6;
- pooled effectiveness data from an updated evidence synthesis model (for which the analysis plan is presented in a separate document);
- additional newly available data from updated structured literature reviews with the aim of informing model parameters relating to ulcer recurrence, resource use and costs, utilities and mortality.

This updated decision model will consider all relevant up-to-date evidence on all comparators.

1 DECISION PROBLEM

Venous leg ulcers are one of the most prevalent complex wound types in the UK with a point prevalence of 0.29 per 1000 people.[3] The estimated annual cost attributable to leg ulcer specific care for someone with an active venous leg ulcer is £4787.7.[4] Whilst endovenous ablation is an effective surgical treatment for venous ulceration, most patients remain in compression for several weeks before undergoing surgery, if they do at all. Therefore, optimising compression use remains vital to maximising ulcer-free days and ensuring cost effectiveness for patients and the NHS.

VenUS 6 is a multi-centred, pragmatic, parallel, randomised controlled trial evaluating four compression treatments relevant to UK clinical practice which are:

- four-layer bandage (4LB);
- two-layer bandage (2LB);
- two-layer compression hosiery (HH);
- adjustable hook-and-loop fastened compression systems (referred to as compression wraps (CW)).

The choice of interventions is guided in part by existing evidence, with 4LB and HH known to be clinically and cost-effective compression therapies.[2] Inclusion of 2LB is motivated by the fact this is a widely used compression system in the NHS despite its limited evidence base. The use of CW, which have not been evaluated in a large and well conducted RCT was requested as part of the commissioning process for this study. A full description of those compression treatments can be found in the trial protocol.[1]

The VenUS 6 cost effectiveness analysis aims to determine which full compression treatment(s) for venous leg ulcers are the most cost-effective for use within the UK NHS. The study population is people over the age of 18 years with at least one venous leg ulcer who are able and willing to tolerate high compression therapy. The primary health outcome measure for this economic assessment will be Quality-Adjusted Life Years (QALYs) derived from utility scores, obtained using the EQ-5D-5L health-related quality of life instrument which will be then mapped to EQ-5D-3L.[5] The analysis will take the perspective of the NHS and Personal Social Services (PSS), consistent with the recommendations produced by the National Institute for Health and Care Excellence (NICE). The findings are expected to inform decision-makers about which treatment or treatments, from a set of alternatives, are most cost effective for use in the NHS. The time horizon will be extended to include the entire lifetime of the relevant population, subject to data availability, in compliance with current NICE guidance.[6]

2 IDENTIFICATION OF THE TREATMENTS OF INTEREST

This cost-effectiveness analysis will focus on policy-relevant full compression treatments commercialised in the UK and available in clinical practice. These treatments aimed to achieve full compression, defined as a sub-bandage pressure of 35-40 mmHg at the ankle. Impact of treatments consider to not be currently used in UK clinical practice will be assessed in sensitivity analyses.

Since VenUS IV was published in 2014, it is possible that new relevant data for full compression treatments are available. Relevant studies will be identified via systematic review, with full compression treatments and any relevant corresponding data categorised into relevant treatment groups (see sections 3.1 and 3.3 of evidence synthesis plan).

3 DECISION MODEL

We will conduct a systematic literature review that replicates, but updates, the search performed in VenUS IV to help ensure the VenUS 6 DAM structure remains contemporaneous and relevant. The database and search term are presented in the Appendix 1. Two reviewers will independently screen the abstracts against the eligibility criteria (i.e., full cost-effectiveness studies that employed decision analytic models to evaluate full compression treatments which are of policy interest used for the healing of venous leg ulcers) with ambiguous studies to be discussed with a senior researcher (PS). Full papers of selected studies will be obtained. Data regarding model structure and study specifications will be extracted and summarised.

The current VenUS IV model is shown in Figure 1. Where required, we will adapt the VenUS IV model structure to reflect any major developments identified found in the literature. We will consult with clinical colleagues as required. This current model (Figure 1) is characterised by two key events: ulcer healing and ulcer recurrence. It is assumed that all people begin in the unhealed state and that ulcer healing occurs over time. It is possible for ulcers to recur after they have been healed. There is a risk of death from any cause for both healed and unhealed people. To estimate the total costs and QALYs from the model, utility scores, resource use and costs varying according to treatment types will be assigned to the duration of stay in different health states.

Figure 1 Decision model structure of VenUS IV model (Figure 16, Ashby et al., 2014) [2]

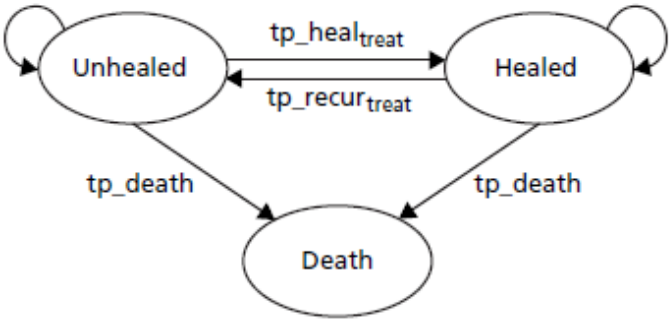


Table 1 shows the key parameters that were used in the VenUS IV model. Given that we aim to utilise and adapt this model, these parameters will be considered in the updated VenUS 6 model.

Table 1 Description of decision model parameters (Table 48, Ashby et al., 2014) [2]

Parameter	**Parameter description**	**Potential data source**
Specification of patient population		
Ulcer duration	Duration in months of reference ulcer at trial baseline	VenUS 6 data for the base case; pooled data across IPD for the scenario analysis
Ulcer area	Size of the reference ulcer at start of treatment	VenUS 6 data for the base case; pooled data across IPD for the scenario analysis
Participant mobility	Patient mobility categorised: 'walks freely', 'walks with difficulty' and 'immobile'	VenUS 6 data for the base case; pooled data across IPD for the scenario analysis
Age	Age of the patient at start of trial treatment (years)	VenUS 6 data for the base case; pooled data across IPD for the scenario analysis
Transitions (see Figure 1)		
tp_heal_{treat}	Transition probability from unhealed to healed	The results of the synthesis model performed in the VenUS 6
tp_recur_{treat}	Transition probability of having a recurrent ulcer, i.e. from healed to unhealed	VenUS 6 data for the base case; pooled data across IPD and VULCAN [7] for the scenario analysis
tp_death	Transition probability of dying (health state dependency will be defined based on the structured literature review)	Data from the structured literature review
Costs and resource use		
Costs while unhealed, not related to treatment		
Hospv	Average number of monthly ulcer-related hospital outpatients visits	VenUS IV [2], VenUS 6, studies identified from the structured literature search
Clinv	Number of ulcer-related doctor consultations per month	VenUS IV [2], VenUS 6, studies identified from the structured literature search
c_hospv	Cost of hospital visits	Most recent PSSRU [8]/ NHS reference cost[9]
c_clinv	Cost of ulcer-related doctor consultations	Most recent PSSRU [8]/ NHS reference cost[9]
Costs while unhealed, related to treatment		
T_durtreat	Duration of compression treatment (treatment dependent)	VenUS IV [2], VenUS 6, studies identified from the structured literature search
nursevtreat	Average monthly number of ulcer-related nurse consultations while receiving treatment (treatment dependent)	VenUS I [10], VenUS IV [2], VenUS 6, studies identified from the structured literature search

c_nursev	Cost of a nurse consultation excluding costs of treatments (treatment independent)	Most recent PSSRU [8] / NHS reference cost [9]
c_bandtreat	Cost of compression treatment, per consultation (treatment independent)	Most recent PSSRU [8] / NHS reference cost [9]
nursev_after	Average monthly number of ulcer-related nurse consultations while patient receives standard care (treatment dependent)	VenUS I [10], VenUS IV [2] and VenUS 6, studies identified from the structured literature search
c_band_after	Cost of standard care (bandages and stockings) per consultation (treatment independent)	Most recent PSSRU/ NHS reference cost
Quality-of-life score		
u_decunh	EQ-5D scores for unhealed leg ulcer patients	Pooled utility decrement across VULCAN [7], VenUS I [10] - IV [2] and 6, and relevant data identified in the structured literature review
u_pop	EQ-5D scores for healed leg ulcer patients	UK population norms adjusted for baseline utility values from pooled data across VenUS IV [2] and VenUS 6

IPD, individual patient data; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

Possible extensions to the model structure

Any potential extensions to the model structure will be considered based on findings from the aforementioned review of relevant models and the clinical events observed in VenUS 6 (e.g., amputation, surgical treatment).

As described above, a variety of model parameters will be considered, including treatment effectiveness, utility, costs, and health resource consumption. In the section below, we describe how we plan to identify, collect and potentially quantitatively synthesise that data.

3.1 Evidence synthesis on effectiveness

Data from an updated review of randomised controlled trials of compression therapies for the treatment of venous leg ulcers [11] will be combined with data from studies for which IPD is available to us (at this time these are VenUS I [10], VenUS IV [2] and VenUS 6). Additionally, we aim to include (rather than exclude) trials reporting different measures of complete healing, such as proportion of people healed at a specific timepoint or time to healing. We will maximally include all relevant complete healing outcome data by modelling them appropriately in a network meta-analysis (NMA) framework. Bayesian methods will be used to make statistical inference. Details of the evidence synthesis analysis plan are presented in a separate document. The NMA results will be incorporated into the decision model using the posterior samples or predictive distributions extracted from the Convergence Diagnostic and Output Analysis output (CODA).

Using the outputs from the NMA model, we will estimate the probability of transition from unhealed to healed for the reference treatment (section 3.5.1 in the evidence synthesis analysis plan) and its alternatives. We will assume that the transition probability from unhealed to healed will follow the same fully parametric survival distribution across all compression treatments with a common shape parameter *s* (also referred to as ancillary or location parameter) and a varying scale parameter λ. The scale parameter of the reference treatment on log scale will be generated by linearly combining the mean values (see Table 1) and the regression coefficients (obtained from the VenUS 6 evidence synthesis model) of a set of patient characteristics including ulcer size, ulcer duration, mobility with the absolute treatment effect μ, using the following formula:

$$log\lambda_{reference\_treatment}^{VenUS\ 6} = \mu_{reference\_treatment}^{VenUS\ 6} + \beta_{ulcer\_size}\,\bar{x}_{ulcer\_size} + \beta_{ulcer\_duration}\bar{y}_{ulcer\_duration} + \beta_{mobility\_difficulty}\bar{z}_{mobility\_difficulty} + \beta_{mobility\_immobile}\bar{z}_{mobility\_immobile}$$

The transition probability of reference treatment will then be calculated as:

$$tp_{heal}^{reference\_treatment}(t) = 1 - exp\{H(t-1) - H(t)\}$$

where H(t;λ, s) is the cumulative hazard at time *t* in a closed form of a parametric survival distribution defined by shape parameter *s* and scale parameter λ. The relative effects of the remaining treatments over the reference treatment will then be:

$$tp_{heal}^{treatment\ i}(t) = 1 - exp\left\{HR^{treatment\ i} \times (H(t-1) - H(t))\right\}$$

where $HR^{treatment\ i}$ is the hazard ratio of treatment *i* over the reference treatment, obtained from the synthesis model.

The set of covariates included in the above formulas (i.e., ulcer size, ulcer duration, mobility, and potentially other covariates such as age, BMI) will be determined based on its clinical relevance and assessment performed in the NMA model selection (see section 3.5.2.3, evidence synthesis analysis plan).

Subgroup analysis (exploratory)

The evidence synthesis model also aims to examine whether any covariate is an effect modifier by introducing treatment-by-covariate interaction terms (see section 3.5.2.3, evidence synthesis analysis plan). Where treatment-by-covariate regression coefficient appears to be statistically significant, a covariate is considered a treatment modifier for which the relative treatment effects vary across

subgroups. This will enable the economic evaluation on subgroups, thus exploring potential heterogeneity in the cost-effectiveness results.

3.2 Other model parameters

Following on from the VenUS IV model, we will perform structured literature review aimed at identifying evidence on HRQoL and utilities, costs and resource use, ulcer recurrence and mortality. Detailed research methods, data extraction, and results are presented in Chapter 15 of Ashby et al., 2014.[2] The aims of searches for each parameter are in line with the methods presented in the VenUS IV model and are replicated in Table 2.

Table 2 Aims of searches for each parameter type (Table 49, Ashby et al., 2014) [2]

Parameter type	Aim to identify evidence on	Inclusion criteria
Health-related quality of life/utility	Health-related quality-of-life scores of patients with venous leg ulcers both healed and unhealed	Studies were included if they: • included or related to people with, or who had previously had, venous leg ulcers • presented quantitative health-related quality-of-life/utility data for people with venous leg ulcers or a history of venous leg ulcers
Costs and resource use	Cost/resource use by patients with healed and unhealed venous leg ulcers	Studies were included if they: • included or related to people with venous leg ulcers • presented costs/resource-use data regarding venous leg ulcers in the UK
Recurrence	Recurrence rates of patients with venous leg ulcer	Studies were included if: • they included or related to study populations with, or who have previously had, venous leg ulcers • participants were treated with a relevant form of compression • details regarding prevention treatments were reported/ considered standard practice • they measured (or may have measured) recurrence
Mortality	Whether having a venous leg ulcer affects the patient's mortality	Studies were included if they: • included or related to people with, or who had previously had, venous leg ulcers • reported mortality data

3.2.1 Health-related Quality of life/ utility

In the VenUS IV model, patients in the healed state were assigned a utility score based on the UK population adjusted for age and baseline values from the VenUS IV trial. Patients with an unhealed ulcer had a utility decrement attached, with the decrement value obtained from pooling data from the VULCAN trial, VenUS I trial and VenUS IV trial.

Similarly to the VenUS IV model, the utility of patients with healed ulcers in the VenUS 6 model will be obtained from the most recent UK population statistics being adjusted for age and baseline characteristics from VenUS 6.[12]

The EQ-5D-5L states which can be obtained from participant self-report in VenUS 6 will be converted to index value using the UK tariff.[5] Those index values then will be pooled with the utility data in the VenUS IV model to derive the utility decrement for unhealed health state. The inverse variance-weighted average method will be used to aggregate utility evidence across data sources.

3.2.2 Unit costs

The unit cost of compression treatment will be based on the most recent UK-published data source for medical treatment prices (i.e., BNF).[13] The cost will be expressed in pounds sterling. The last year of the project will be used as the year of pricing. Costs will be inflated to the pricing year using the NHS Cost Inflation Index. [9]

The unit cost of health and social care resources (e.g., nurse visit) will be derived from the most recent UK-published source (e.g., NHS reference costs and the Unit Cost of Health and Social Care).[8,9] We will use VenUS 6 data to assist with the calculation of such unit costs (e.g., by providing the average nurse visit duration).

3.2.3 Resource use and cost

Resource use of the compression treatments (i.e., number, type, and duration of compression treatments used) in VenUS 6 will be collected through the treatment logs completed by nurses. Resource use of other compression treatments which are not evaluated in VenUS 6 trial will be obtained from literature.

In VenUS 6 the use of wider NHS resources, such as use of community, primary and secondary care staff time are collected using participant self-report questionnaires in which participants are asked to provide details of any care received from the NHS within the past 3 months, recording the number of consultations the participants had with health professionals. This will inform the resource use regarding the number of consultations with health care professional for compression treatments in VenUS 6 trial whilst those resource use for the other compression treatments will be obtained from literature.

In the VenUS IV model, two main cost components were defined:

- costs dependent on health state (healed and unhealed): the model considered only ulcer-related costs, so once a person's ulcer had healed then no costs were incurred in the model (in the VenUS 6 model, however, we will explore the feasibility of including the costs of

compression used for secondary prevention once the ulcer is healed). When a person had an open ulcer, i.e., was in the unhealed health state within the model, clinician and hospital consultations were considered (assumed to be not treatment dependent); and

- costs dependent on treatment: costs were a function of the average number of nurse consultations per month for each participant, the cost of each of those nurse contacts and the cost of the treatment applied in each visit, i.e., mean number of nurse consultations x (cost of nurse visit + cost of applied treatment).

This approach will be replicated in our economic model, and where relevant, costs will be updated.

3.2.4 Recurrence

A recurrence rate is used to determine the likelihood of transitioning from a healed state to an unhealed state. In the base case analysis of VenUS IV, the hazard of recurrence was modelled using VenUS IV data. A sensitivity analysis was conducted using a constant recurrence rate which was obtained from the VULCAN trial.[7]

In VenUS 6 trial, ulcer recurrence will be monitored until participants are censored or the trial ends or the maximum follow-up period (12 months) has been reached. We will assess the hazard of time to recurrence in the same manner as we assess the time to healing (see section 3.5.2.2, evidence synthesis analysis plan) to determine the best fit parametric distribution and potentially quantitively synthesise evidence on recurrence from VenUS 6 with VenUS IV. The analysis will, however, be less extensive, meaning that a comprehensive evidence synthesis process will not be considered. In exploratory analyses, we will explore integrating the aggregated data on ulcer recurrence from the VULCAN trial.[7]

3.2.5 Mortality

Patients with venous leg ulcers are typically elderly and have, on average, more comorbidities than the general population. There may be no direct effect of venous leg ulcers on mortality in those affected, but people's characteristics may indicate that they have a higher death risk than the general population. In the VenUS IV model, UK population mortality data were adjusted for leg ulcer patients (i.e., mortality ratio was taken to be 2.36 times higher among patients with ulcers, calculated based on Brown et al., 2002 [14]). In this model, mortality was assumed to be independent of treatment and health states. Recent evidence will be examined via performing a structured literature review on mortality. Up to date general population statistics on mortality will be used to adjust data on mortality of unhealed patients.

For all the model input parameters listed above, data from IPD sources, such as the VenUS I, VenUS IV, VenUS 6 studies, may be used to inform these where relevant. Sensitivity analyses will be used to explore the implications of employing different data sources.

4 METHODS OF ANALYSIS

The outputs of the model will be the estimated mean costs, effectiveness, and QALYs associated with each alternative treatment. The estimated total costs and outcomes will be appropriately discounted in accordance with the latest guidelines for health technology appraisal.[6]

Cost effectiveness outputs

The mean QALYs and costs associated with each treatment option will be estimated, from which the Incremental Cost-Effectiveness Ratio (ICER) will be calculated as:

$ICER = \Delta C / \Delta E$

where ΔE is the incremental effect (i.e., lifetime QALYs) and ΔC is the incremental cost of the treatment of interest against the reference treatment. ICER reflects the value for money of investing additional budget on new technology (e.g., how many QALYs are gained by investing an extra budget at marginal level). In the event if $\Delta E > 0$ (i.e., new technology is clinically more effective than the reference treatment) and:

- $\Delta C < 0$ (i.e., new treatment is less expensive): the reference treatment is strongly dominated by the new technology then the introduction of such technology is cost-saving;
- $\Delta C > 0$ (i.e., new treatment is more expensive): a decision rule is required in which a cost-effectiveness threshold (λ) need to be established. An ICER below this value suggests the treatment of interest is cost-effective vs the reference treatment.

Given that we are evaluating multiple treatments, a fully incremental framework will be performed where dominated and extendedly dominated alternatives are excluded to define non-dominated treatments. In order to be considered cost-effective, the ICER of one dominant treatment vs the next best alternative must be lower than the cost-effectiveness threshold λ.

Alternatively, the mean QALYs and costs can be combined with a feasible range of values for λ to obtain distribution of net monetary benefits at different levels of λ. The incremental net monetary benefit (INMB) is defined as:

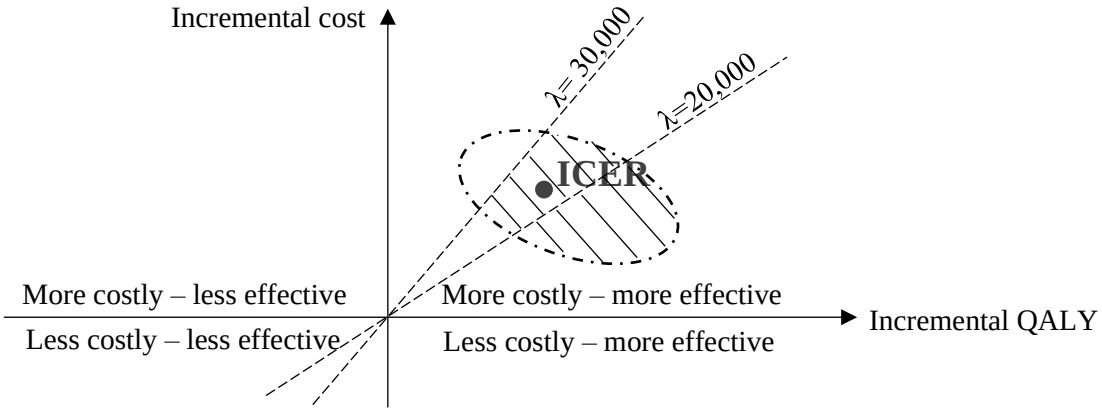
$INMB = \lambda \times \Delta E - \Delta C$

An alternative is cost effective compared to the reference treatment if its INMB > 0. For the analysis of multiple treatments, one that yields the highest INMB is the most cost-effective treatment at that specific value of λ. In England and Wales, NICE stated that λ (the cost effectiveness threshold) falls between £20,000 – £30,000 / QALY gain. [6] An empirical study using UK data, however, estimated that the threshold was £12,936 per QALY in the 2008 expenditure.[15]This threshold will be used in an exploratory analysis.

Decision uncertainty

Uncertainty in cost-effectiveness results will be evaluated using probabilistic analysis, in which inputs are defined as probability distributions reflecting their inherent uncertainty. Figure 2 presents the result of probabilistic analysis in form of a cost-effectiveness plane in which the circled field presents the uncertainty of the point estimate of ICER. The plane also shows that the probability of being cost-effective, which is the area under the threshold line and marked by the circle, depends on the threshold being used. The illustration example shows that the point estimate of ICER falls between the lower and upper bounds of the cost effectiveness threshold stated by NICE while the probability of being cost-effective at λ of £30,000 is much higher than that of £20,000.

Figure 2 Cost-effectiveness plane



Another way of illustrating how the probabilities of the alternative interventions being cost-effective vary across a range of cost-effectiveness thresholds is to use a Cost-Effectiveness Acceptability Curve (CEAC). A CEAC shows the probabilities of interventions being cost-effective (on the vertical axis) at various policy threshold levels (on the horizontal axis) relevant to the health outcome being investigated. The 95% CI of the mean ICER at the cost effectiveness thresholds will also be reported.

Scenario analyses

We plan to examine the following two scenarios:

- In the base case analysis, all of the evidence from the literature will be incorporated alongside the findings from VenUS 6.
- In a scenario analysis, all model inputs will be defined based on evidence obtained from the literature, excluding the findings from VenUS 6. We thus can determine the extent to which VenUS 6 trial contributed to the decision problem.

Sensitivity analysis

The robustness of the findings in the base case analysis will be tested by:

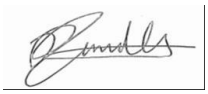
- using efficacy estimates from a set of scenarios performed in the sensitivity analysis of the evidence synthesis model;
- using alternative evidence sources for the key parameters (e.g., patient characteristics, recurrence rate, mortality rate from healed and unhealed states);
- checking alternative assumptions regarding the extrapolation beyond the observed duration of the trials.

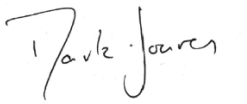
Value of further research

Under uncertainty over treatment decisions, there is a risk that the decision made under current evidence is wrong. The impact over population health of such uncertainty will be determined using Expected Value for Perfect Information (EVPI) analyses. By quantifying the impact of uncertainty, we can establish whether further research may be of value. In addition, it would be helpful to know what type of additional evidence would be most valuable. Therefore, the expected value of partially perfect information (EVPPI) for parameters is calculated to identify those parameters for which more precise estimates would be most valuable.

5 ROLES AND RESPONSIBILITIES

Sign-off of the Health Economic Analysis Plan by, as a minimum, the responsible Health Economists, Trial Manager and the Chief Investigator.

Name	**Trial Role**	**Signature**	**Date**
Prof. Jo Dumville	Chief Investigator		19th March 2024

Dr Marta Soares	Health Economist		20th March 2024
Dr Pedro Saramago	Health Economist		20th March 2024
Catherine Arundel	Trial Manager		19.03.2024

References

1. Dumville J. VenUS 6: A randomised controlled trial of compression therapies for the treatment of venous leg ulcers. Study protocol. 2023. https://nil-admin.nihr.ac.uk

2. Ashby RL, Gabe R, Ali S, 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*. Sep 2014;18(57):1-293, v-vi. doi:10.3310/hta18570

3. Hall J, Buckley HL, Lamb KA, et al. Point prevalence of complex wounds in a defined United Kingdom population. *Wound Repair Regen*. Nov-Dec 2014;22(6):694-700. doi:10.1111/wrr.12230

4. Urwin S, Dumville JC, Sutton M, Cullum N. Health service costs of treating venous leg ulcers in the UK: evidence from a cross-sectional survey based in the north west of England. *BMJ Open*. 2022;12(1):e056790. doi:10.1136/bmjopen-2021-056790

5. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics*. Feb 2023;41(2):199-207. doi:10.1007/s40273-022-01218-7

6. NICE. The National Institute of Health and Care Excellence: health technology evaluations: the manual. 2022

7. Michaels JA, Campbell WB, King BM, et al. A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial. *Health Technol Assess*. Nov 2009;13(56):1-114, iii. doi:10.3310/hta13560

8. Jones KC, Burns, Amanda. Unit Costs of Health and Social Care 2021. *Unit Costs of Health and Social Care* 2021;doi:10.22024/UniKent/01.02.92342

9. National Cost Collection for the NHS 2020/2021., https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (accessed March 27, 2023)

10. Iglesias C, Nelson EA, Cullum NA, Torgerson DJ. VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. *Health Technol Assess*. Jul 2004;8(29):iii, 1-105. doi:10.3310/hta8290

11. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev*. Nov 14 2012;11(11):Cd000265. doi:10.1002/14651858.CD000265.pub3

12. Statistics OoN. National life tables – life expectancy in the UK: 2018 to 2020. 2021;

13. BNF. British National Formulary. https://bnf.nice.org.uk/ (accessed March 27, 2023)

14. Brown A, Bums E, Chalmers L, et al. Effect of a national community intervention programme on healing rates of chronic leg ulcer: Randomised controlled trial. *Phlebology*. 10/01 2002;17:47-53. doi:10.1007/s005230200029

15. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess*. Feb 2015;19(14):1-503, v-vi. doi:10.3310/hta19140

APPENDIX

Search on cost-effectiveness decision models

Database: MEDLINE, EMBASE and the NHS Economic Evaluation Database (NHS EED).
Search strategy
1. exp Stochastic Processes/
2. exp Models, Theoretical/
3. exp Models, Statistical/
4. exp Models, Economic/
5. exp Monte Carlo Method/
6. exp Markov Chains/ ((stochastic or mathematical or statistical or theoretical or population or process or probabili* or simulat* or monte carlo or markov) adj model*).tw. ((economic* or pharmacoeconomic* or decision* or cost*) adj model*).tw.
7. exp Economics, Medical/
8. exp Health Care Costs/
9. exp "Costs and Cost Analysis"/
10. exp "Cost of Illness"/ (cost-effective* or cost effective* or cost-utility or cost utility or cost-benefit or cost benefit or cost-minimi* or cost minimi*).tw.
11. or/1-13
12. exp Leg Ulcer/ (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).tw.
13. or/15-16
14. 14 and 17

// a code line to limit search time from 2012 onwards will be added///