VenUS 6 EVIDENCE SYNTHESIS ANALYSIS PLAN

Version: 1.0 19.03.2024

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Content

1 INTRODUCTION

This document aims to provide an analysis plan for the evidence synthesis of the effectiveness evidence to be carried out for VenUS 6. The synthesis will include effectiveness evidence from VenUS 6, a multi-centred, pragmatic, parallel group, randomised, controlled, three arm trial comparing evidence-based treatment (choice of four-layer bandage or two-layer compression hosiery), two-layer bandage (2LB) and compression wraps in the treatment of venous leg ulcers. Further details of VenUS 6 can be found in the trial protocol.[1]

To make judgement on clinical and cost-effectiveness, decision makers within the UK NHS ideally need to have robust relative effectiveness data for all relevant comparators. VenUS 6 will provide relative data on the three trial treatments; to expand the relevance of our analyses for decision makers we need to encompass relevant effectiveness evidence for all suitable compression therapies in this decision space. To do this we will conduct a systematic review and synthesise evidence using a network meta-analysis (NMA).

Network meta-analysis is a commonly used statistical tool that enables the use of all the evidence and the simultaneous comparison of all treatments within a single synthesis model. In addition to individual-patient data (IPD) from VenUS 6, this synthesis model will consider all relevant data from the VenUS IV NMA [2] and evidence from studies that will be identified in a systematic literature review, the search date of which will extend, up to the last year of VenUS 6. The evidence synthesis analysis plan here being presented may be considered as an extension to the previous NMA performed in the VenUS IV.[2]

2 OBJECTIVES

The key evidence synthesis aim for VenUS 6 is to i) estimate the relative effectiveness of full compression treatments for healing venous leg ulcers using all available RCT evidence and ii) evaluate how the inclusion of evidence from VenUS 6 informs the estimation of treatment effectiveness, treatment recommendations and the uncertainty regarding these.

3 METHODS

3.1 Identification of relevant evidence

3.1.1 Review methodology

We will conduct an update review from the previous review we did within the VenUS IV economic analyses, which was based on the current Cochrane review at the time. Further details on this review can be found elsewhere.[3]

3.1.2 Data extraction

If required, study extraction conducted for VenUS IV will be revisited to obtain information on baseline characteristics deemed relevant for the VenUS 6 model (e.g., age, BMI) in addition to ulcer area, ulcer duration and patient mobility, which were extracted previously for VenUS IV.

For new studies identified in the updated review as eligible for inclusion, we will extract covariates in line with variables that were used in the VenUS IV NMA model: intervention, maximum follow up (weeks), number of participants in each arm, mean ulcer duration (months), mean ulcer size (cm^2), number of healing at follow-up, evidence format (IPD or aggregated/summary data (AD)). New covariates which are defined and validated to be clinically relevant (such as BMI and age) will also be extracted for potential inclusion in the modelling.

As with the previous Cochrane review, in studies for which Kaplan-Meier curves of ulcer healing time are reported, those curves will be digitised.

3.2 Data quality assessment

Cochrane risk-of-bias tool for randomised trial (RoB 2) will be used to assess each of the studies extracted.[4] The CiNeMA (Confidence in Network Meta-Analysis) tool will be used describe the confidence in the results of the implemented network meta-analyses.[5] The CiNeMA method will consider the risk of within-study bias, the risk of selective outcome measure, reporting bias, indirect evidence, inaccuracy, heterogeneity and incoherence/ inconsistency.

3.3 Classification of compression treatments

In VenUS IV, a thorough process of treatment classification was carried out (see Chapter 10, Ashby et al., 2014).[2] Using a similar classification system, treatments evaluated within the set of newly identified studies will be categorised into relevant treatment groups. This classification update will be performed by the project principal investigator, in consultation with trialists and nurse specialists, if necessary.

3.4 Individual patient-level data

Incorporating IPD in an NMA may enable an appropriate exploration of the within and between study heterogeneity for the relevant contrasts in the evidence network. It may also enable studying the effectiveness of treatments within population subgroups. When the outcome of interest is time to event, incorporating IPD will also enable a correct exploration of the hazard of the event over time. In this work, we will use IPD that are available to us, in addition to the data from VenUS 6. These will include:

- VenUS IV 2014 RCT**:** This study enrolled 454 patients with venous leg ulcers into two treatment arms: four-layer bandage and compression hosiery. Full detail of this trial can be sought elsewhere.[2]
- VenUS I 2004 RCT**:** This study enrolled 387 patients with venous leg ulcers into two treatment arms: four-layer bandages and short stretch bandage. Full detail of this trial can be sought elsewhere.[6]

3.5 Methods of analysis

3.5.1 Network of evidence

The structure of the evidence available will be presented using a network diagram, which will identify the number of studies available for each contrast, under the classification of treatments. The treatment that is at the "centre" of the network will be chosen as the reference treatment (e.g., 4LB in the VenUS IV synthesis model). This treatment usually has the highest number of pairwise comparisons vs other treatments. This choice of reference treatment is to reduce the potential correlations between mean treatment effects of treatment pairs which may impede convergence and result in ineffective sampling from posterior distribution.[7]

3.5.2 Statistical modelling

Upon the completion of the tasks described above we may be able to present a complete statistical model for the adequate quantitative synthesis of the relevant time to ulcer healing data for all alternative treatments. The plan presented below is primarily based on the methods that were employed in the VenUS IV base case mode which will consider several data formats, comprising:

- three studies with full IPD: VenUS I [6], VenUS IV [2], VenUS 6;
- AD for the studies included in VenUS IV and from the newly identified studies resulting from the updated Cochrane review conducted for the VenUS 6;
- in exploratory analyses, we will also consider including pseudo-IPD reconstructed from published Kaplan-Meier curves from larger, more recent (i.e., more likely to be representative of the current clinical practice), and higher quality studies.

The NMA model for IPD will include baseline covariate adjustments considering the mean duration of ulcer, mean size of ulcer, mobility and centre frailty effect. An assessment over the usefulness of adjusting for other potentially relevant prognostic variables (e.g., age and BMI) will be performed.

3.5.2.1 Data preparation

AD will be tabulated in line with the data format in the VenUS IV NMA model.[2] The IPD of VenUS 6 will be transformed/adapted to fit the data requirements of the software where the (Bayesian) statistical inference will be performed.

Where relevant and possible, published Kaplan-Meier curves will be digitised using a free web-based tool (https://automeris.io/WebPlotDigitizer/) and pseudo-IPD will then be reconstructed using Guyot algorithm.[8]

3.5.2.2 Model selection – choosing a parametric model to facilitate use of aggregated data

Similarly, to the VenUS IV synthesis model, the model of current assessment will bring together all available IPD and AD into a same synthesis model where both formats of evidence contribute to the estimation of key model parameters. In order to achieve this, we will assume that the time to healing of venous leg ulcers follows a similar pattern (i.e., parametric distribution) for both AD and IPD. It is thus necessary to examine the behaviour of the covariate-adjusted time to healing hazard observed in all available IPD (and pseudo-IPD in the exploratory analysis). To do this, we will examine which parametric distributions commonly used in survival analysis (exponential, Gompertz, Weibull, lognormal, loglogistic, generalised gamma) best fit the Kaplan-Meier curves presented in each IPD. Visual inspection and goodness of fit (AIC and BIC statistics) will be used to rank the best fit distribution for each set of IPD (and pseudo-IPD if applicable). [9] The parametric distribution that consistently ranks higher across datasets and is clinically validated, will be considered the best fit. The model will incorporate relevant covariates such as the ones relating to ulcer area and duration, patient mobility, and centre effects.

3.5.2.3 Model selection – choosing a model for NMA

Fixed- and random-effects models will be assessed, with final model selection being determined by the smallest posterior mean of the deviance information criterion (DIC).

Our analysis will examine the impact of each of the patient baseline characteristics, as well as the inclusion of a centre effect into the model. We will also assess the inclusion of the treatment-by-covariate interaction terms, similar to the VenUS IV synthesis model. A statistically significant coefficient for the interaction together with model fit statistics (via DIC) will determine judgements around the presence/absence of treatment effect modification for which relative effects will be used for the economic evaluation of subgroup populations (see section 3.1, health economics analysis plan).

3.5.2.4 Synthesis model

We here present the provisional evidence synthesis models which are subject to the data availability and the aforementioned assessment of the behaviour of the hazards observed in the IPD. The models'

codes are specified using WinBUGS/ OpenBUGS softwares for Bayesian inference, which are commonly used in quantitative evidence synthesis involving NMA. The synthesis model will potentially comprise three sub-models, one for AD, one for IPD and one for pseudo-IPD (only considered for exploratory analysis) and one to bring all pooled relative effects together:

Model of AD studies

$$r_{jk} \sim Bin(p_{jk}, n_{jk})$$

$$p_{jk} = 1 - S(t; s, \lambda_{jk}^{AD})$$

$$log\lambda_{jk}^{AD} = \begin{cases} \mu_{jb}^{AD} \; if \; k = b \\ \mu_{jb}^{AD} + d_{bk} + \beta \overline{X}_j \; if \; k > b \end{cases}$$

where

r_{jk} is the observed number of participants with a healed ulcer within each study out of the total number of participants receiving the k^{th} treatment in the j^{th} trial (n_{jk}), assumed to be Binomially distributed;

p_{jk} is the underlying probabilities of an event for arm *k* in the j^{th} trial;

$S(t; s, \lambda_{jk}^{AD})$ is the closed form of survivor function of the parametric distribution that is selected in section 3.5.2.2; s is the common shape parameter and λ_{jk}^{AD} is the varying scale parameter;

μ_{jb}^{AD} is the log hazard of an event for treatment *b* in study *j;*

d_{bk} is the log hazard ratio of treatment *k* vs the baseline treatment *b*;

$\beta \overline{X}_j$ is the treatment-by-covariate interaction regression term, where β is the association effect and is assumed common across studies and treatments, $\overline{X}_j$ is the mean (or median, subject to data availability) of covariate.

Model of IPD studies

$$t_{ijk} \sim Distribution; (s, \lambda_{jk}^{IPD}) I(t_{ijk}^{c})$$

$$log\lambda_{ijk}^{IPD} = \begin{cases} \mu_{b}^{IPD} + \gamma_{j}^{c} + \beta_{0j} x_{ijk} \; if \; k = b \\ \mu_{b}^{IPD} + \gamma_{j}^{c} + \beta_{0j} x_{ijk} + d_{bk} + \beta x_{ijk} \; if \; k > b \end{cases}$$

where

t_{ijk} / t^c_{ijk} are the time to ulcer healing/ censoring of participant *i* in the j^{th} study and in the k^{th} treatment arm, assumed to be in form a parametric distribution that is selected in section 3.5.2.2;

γ^c_j is the centre frailty effect and is defined for each centre;

β_{0j} exemplifies a covariate effect, i.e., the difference in the log hazard ratio per unit increase in the patient-level covariate x_{ijk};

Model of pseudo − IPD studies (exploratory analysis)

$$t_{ijk} \sim Distribution; (s, \lambda^{IPD}_{jk}) I(t^c_{ijk})$$

$$log\lambda^{pseudo-IPD}_{ijk} = \begin{cases} \mu^{pseudo-IPD}_b + \beta_{0j} x_{ijk} \; if \; k = b \\ \mu^{pseudo-IPD}_b + \beta_{0j} x_{ijk} + d_{bk} + \beta x_{ijk} \; if \; k > b \end{cases}$$

Although the model for pseudo-IPD is presented similarly to that for full IPD, patient-level characteristics and study centres may not be available for pseudo-IPD. The software will treat those variables as missing values. Nonetheless, if the mean (or median) and measure of uncertainty at study level are reported for the relevant covariates, it is possible to assign informative prior distributions to those covariates, which will inform the patient-level covariate imputation.

3.5.2.5 Implementation

Three separate chains of non-informative initial values were used for both fixed and random effects models. The NMA analyses will thus be undertaken in the chosen inference software, linked to the statistical software R.[10] The MCMC sampler will run for 10000 iterations as 'burn-in' and then run for further 20000 iterations, on which inferences will be based. Chain convergence and absence of autocorrelation will be assessed by running different chains, and by inspecting density, history, and Gelman-Rubin graphic outputs for each model. Non-informative prior distributions will be used to inform estimated parameters.

3.5.2.6 Tests for inconsistency

We will investigate and attempt to explain between-study heterogeneity in scenario analyses, using meta-regression and assessing how exchangeable treatment effects are, through consistency checks and verifying if there are discrepancies between direct and indirect evidence via an inconsistency model.[9]

3.6 Sensitivity analysis

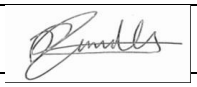
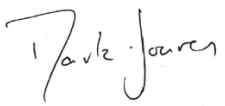
Table 1 list a series of proposed sensitivity analyses to assess the robustness of pooled effect estimates obtained from the base case NMA model.

Table 1 Proposed sensitivity analyses

Step	Analysis	Detail
Network of evidence	Network of evidence	We will explore alternative network of evidence that comprise: - Core network that includes only treatments that are of policy interest (i.e., commercialised in the UK and available in clinical practice) - Core network plus ad hoc high compression treatments
	EBC	In VenUS 6, evidence-based treatment reflects the pragmatic use of four-layer bandage or two-layer compression hosiery and is the reference treatment arm. In base-case analysis, EBC is treated as a new group of treatment. We will consider allocation to 4LB and HH in the EBC arm as being conducted totally at random (equivalent to randomisation).
	With and without VenUS 6 IPD	We will examine the outcomes estimated from the synthesis models including and excluding IPD from VenUS 6 to explore the added value of this trial to the network of evidence.
Statistical model	Parametric distribution	In the main analyses, a single parametric distribution will be used to describe the hazard of healing across time and for all treatments. Where time to healing hazard may follow a different pattern, we will explore the impact of assuming a different parametric distribution (according to aforementioned software implementation constraints).
	Shape parameter	For multi-parametric distributions (e.g., Weibull, Log-logistic, Gompertz), we will explore the impact of using different values of the nuisance parameter(s) estimated from available IPD.

4 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		20.03.2024

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