Compression products for treating venous leg ulcers [GID-HTE10048]:
EAG protocol

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1. INTRODUCTION AND BACKGROUND

1.1. Introduction

As described in the NICE scope for this assessment, this Late-Stage Assessment (LSA) aims to investigate the evidence base for compression products for treating venous leg ulcers to assess whether price variations between technologies are justified by the incremental differences and advancements, and which technologies represent value for money in the NHS. This assessment protocol outlines what the External Assessment Group (EAG), an independent, academic group supporting NICE with the assessment, will do during its evaluation. This protocol was produced in response to the NICE scope for this assessment.

1.2. Decision problem

Table 1 summarises the decision problem to be addressed in this assessment. Further detail on each item can be found in the published scope. The table reports the EAG's comment on each of the decision problem areas. These comments outline the EAG's interpretation of the key areas of consideration for the assessment and therefore inform the eligibility criteria for the EAG's assessment, shown in Section 2.1.

Table 1: Summary table of the decision problem

Item	Description	EAG comment
Population	People aged 18 or over with a venous leg ulcer	The EAG anticipates that the majority of evidence (and demand in the community) will be in people with diabetes. The EAG does not plan to specifically filter for diabetes vs other causes in its searches, as evidence may apply to both (but see comment on subgroups).
Subgroups	If the evidence allows, the following subgroups will be considered: • People with conditions that may impact self-care (such as issues with memory, manual dexterity, mobility and visibility) • People with low or high exudate wounds • People with very fragile skin • People with irregular leg shapes (such as an upside-down champagne bottle)	As per comment above, people with diabetes are likely to represent a large proportion of the relevant patient population. If data and resources allow, the EAG will explore subgroups amongst people with and without diabetes.
Interventions	Compression products available to the NHS on Part IX of the Drug Tariff or the NHS Supply Chain, delivering strong or full compression (defined as 40mmHg or more). Interventions will include: • 4-layer compression bandage systems and kits • 2-layer compression bandage systems and kits (these include 2-layer inelastic systems and 2-layer multi-component systems) • 2-layer compression hosiery • Compression wraps Features within and between compression products will be explored in this assessment.	Comments at the scoping workshop indicated that it might be more useful to look at bandages designed to deliver strong compression given individual differences in the compression actually delivered. The EAG understands products are sourced through different routes, prices other than those stated in Drug Tariff. EAG understands NICE will supply the EAG the prices to be used.

Item	Description	EAG comment
Comparators	A compression product or products that is considered current standard of care in the NHS (for example, based on clinical expert advice and clinical evidence)	The EAG considered the comparators broadly appropriate and will seek input from clinical experts to better understand standard of care.
Outcomes	Outcome measures for consideration may include but are not limited to: <u>Intermediate outcomes</u> • Reduction in wound size • Changes to wound bed condition (for example slough or presence of bacterial film, exudate, granulation and oedema) • Condition of peri-wound skin • Levels and reduction of oedema • Frequency of compression product changes <u>Clinical outcomes</u> • Percentage of wounds healed • Time to complete wound healing • Intervention related adverse events <u>Patient reported outcomes</u> • Health-related quality of life • Wound-related pain • Patient adherence • Ease of treatment use • Mobility <u>Costs and resource use</u> • Cost of the technology • Cost of supporting products for example a hosiery applicator, a 'boot' to protect bandages when	The EAG understands that the key outcome for the economic analysis is likely to be reduced time to healing of the ulcer. However, adverse events for which specific features are intended to reduce or avoid will also be included (comprehensive list to be supplied by NICE).

Item	Description	EAG comment

	showering, a 'shoe' or an oversized sandal to help walking with bandages, or a foot, ankle or toe piece for wraps to provide full leg compression)
	• Cost of dressings
	• Cost of other resource use including:
	  ○ Leg ulcer-related health care professional appointments or visits (primary, community and secondary care)
	  ○ Planned and unplanned leg ulcer-related hospital admission or surgery
	  ○ Staff band and time
	  ○ Staff training
	  ○ Clinical waste disposal
	
	User preference will be assessed to identify and understand features of the technologies that influence decision making when selecting which technology to use. This is done alongside the assessment of the clinical and economic evidence.	

Healthcare setting	Community (including people's homes, care homes, community hospitals, leg ulcer clinic) Primary care (GP practice)	The EAG understood these settings to be appropriate but will check with clinical expects.
Economic analysis	A health economic model will be developed, where possible, comprising a cost-comparison or cost utility analysis. Costs will be considered from an NHS and Personal Social Services perspective. Sensitivity and scenario analysis should be undertaken to address the relative effect of parameter or structural uncertainty on results. The economic modelling will also	The EAG anticipates that most of the features of specific bandages will ultimately impact time to healing, thus for the economic analysis the model will estimate the maximum economically justifiable price for a bandage that increases the rate of healing by n weeks compared with that observed in a 'basic' 4-layer compression bandage.

Item	Description	EAG comment
	consider the impact of the availability of individual bandages as well as the kits. The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The ultimate design of the model will depend on the nature, quality and quantity of evidence identified. If possible, a cost-effectiveness analysis will be conducted as well as the eJP analysis.
Other issues for consideration	• Ongoing VenUS-6 trial evaluating compression therapies for the treatment of venous leg ulcers. It is a three-arm randomised controlled trial comparing evidence-based compression (4-layer compression bandage kit or 2-layer compression hosiery) with 2-layer compression bandage kits and compression wraps. Estimated completion date of the trial is 31 August 2024. It will also include a health economic analysis. Initial results are expected before the end of 2024. • There is information on some potentially relevant economic models associated with the VenUS IV trial (2014) and in a systematic review published in 2019 (Layer et al.). • There is known variation in practice across local formularies and care pathways in the NHS. • Dressings do not play a direct role in this aspect of venous leg ulcer management. However, it is important for clinicians to select dressings that are not adversely affected by compression products and ensure that they do not interfere with the compression of the legs. • Compression should only be applied by trained healthcare professionals and in accordance with the manufacturer's instructions. Incorrect application can lead to uneven, inadequate or hazardous levels of	The EAG is in communication with the investigators of VenUS-6 and will work to ensure the results of VenUS-6 can be incorporated into the decision model as easily as possible. However, the EAG anticipates that the results of that study will not be available in time to inform this LSA.

Item	Description	EAG comment
	pressure. This in turn can lead to pain, delayed healing, trauma or even loss of the limb. • People with venous leg ulcers who are having compression therapy using 4-layer compression bandage systems may be more likely to be immobile, have co-morbidities and more severe leg ulcers than people with venous leg ulcers that have been prescribed other types of compression products. • Data from Open Prescribing suggests that sales of individual compression bandages made up over half of the sales of compression products between May 2023 and April 2024. The flexibility in the market because of the availability of individual bandages should be explored in the economic modelling. • The NHS is aiming to reduce its carbon footprint to net zero by 2040. Treating venous leg ulcers uses a lot of products and requires considerable travel as most care is delivered in the community. Using reusable compression products may improve sustainability and may also reduce waste (Morton, 2022).	

Abbreviations: EAG, External Assessment Group

1.3. Objectives

The objective of this assessment is to identify evidence for the effectiveness of compression products for treating venous leg ulcers in the NHS, to assess whether price variations are justified. The outcome of the assessment will support NHS procurement and commission decisions. Specifically, the assessment will attempt to address the following research questions:

- What evidence is available to determine the clinical and cost effectiveness of compression products for treating venous leg ulcers?
- Which features of compression products are associated with benefits for adults with venous leg ulcers and are these commensurate with the price charged by manufacturers?

The features we are focusing on are the different types of compression products described and listed in the final scope. The EAG may also describe and explore other features that came up in the evidence.

Ultimately, the findings of this assessment are intended to be used by adults with venous leg ulcers, clinicians and commissioners to inform decisions about the use of compression products in practice.

In accordance with Section 4.8 of the NICE interim methods and process statement for LSA [3], we will undertake a rapid evidence review taking a pragmatic approach. The assessment will involve a systematic search for published evidence that evaluates compression products. Evidence will also be sought from the manufacturers of compression products, who may hold data that have not been published. Evidence that is useful to the decision problem for this assessment (i.e. represents the relevant population, interventions, outcomes, settings and is of suitable quality to inform clinical decisions) will be extracted and appraised by the EAG. A tabulated overview of the evidence landscape will be constructed to represent the evidence available and where there are meaningful gaps for the decision problem. Where feasible, an economic analysis will be conducted to compare the benefits of intervention features with their price. Full details of the stages of the assessment are provided in Sections 2 and 3.

2. EVIDENCE REVIEW

During the preparation of this protocol, the EAG conducted a rapid literature search in Medline (Ovid) and Google Scholar for systematic literature reviews (SLRs), published in the last ten years, that identified and evaluated published evidence for compression products to consider whether it would be feasible to update an existing SLR for this assessment.

Thirteen SLRs were identified that were at least partially within scope (Table 2). Depending on the quality and coverage of these reviews, the EAG may use one or more of the reviews as a basis for an updated review.

Table 2: identified systematic reviews

Author	Date	Title
Ferguson and Baguley[2]	2024	Decision-making on the use of compression hosiery and compression bandaging: a systematic review
Mauck et al[3]	2024	Comparative systematic review and meta-analysis of compression modalities for the promotion of venous ulcer healing and reducing ulcer recurrence
Patton et al[4]	2024	A systematic review of the impact of compression therapy on quality of life and pain among people with a venous leg ulcer
Silva et al[5]	2024	Compression for preventing recurrence of venous ulcers (Review)
Patton et al[6]	2023	A meta-review of the impact of compression therapy on venous leg ulcer healing
Shi et al[7]	2021	Compression bandages or stockings versus no compression for treating venous leg ulcers (Review)
Tai et al[8]	2021	A dual pressure indicator, two-layer compression system for treatment of venous leg ulcers: a review
Fulcher and Gopee[9]	2020	Effect of different compression bandaging techniques on the healing rate of venous leg ulcers: a literature review
Goka et al[10]	2020	Clinical and Economic Impact of a Two-layer Compression System for the Treatment of Venous Leg Ulcers: A Systematic Review
Health Quality Ontario[11]	2019	Compression Stockings for the Prevention of Venous Leg Ulcer Recurrence: A Health Technology Assessment
Stather et al[12]	2019	Review of adjustable velcro wrap devices for venous ulceration
Carvalho et al[13]	2018	A Meta-analysis to Compare Four-layer to Short-stretch Compression Bandaging for Venous Leg Ulcer Healing
Welsh[14]	2017	What is the existing evidence supporting the efficacy of compression bandage systems containing both elastic and inelastic components (mixed-component systems)? A systematic review

Author	Date	Title
Nelson and Adderley[15]	2016	Venus Leg Ulcers

The EAG will also conduct its own evidence review to identify evidence evaluating the features of compression products. The evidence review will involve two systematic literature searches for published evidence relevant to the decision problem:

- one literature search will be conducted to identify evidence for the clinical effectiveness and safety of the features of compression products for treating venous leg ulcers.
- one literature search will be conducted to identify published economic evaluations of compression products and health-related quality of life (HRQoL) and utility studies relevant to the decision problem.

The searches will be conducted separately as the inclusion criteria vary according to each evidence type (Section 2.1).

The literature search will not specifically target studies publishing cost and resource use data associated with compression products for treating venous leg ulcers (i.e. searches will not include filters and free-text terms for cost and resource use). Cost and resource use data are rarely identified independently from economic evaluations or standard data sources (e.g. NHS reference costs, PSSRU) but require substantial additional resource to identify and screen, and so this decision was taken within the pragmatic methods recommended for use within LSAs. Further detail of the search strategy is provided in Section 0.

Searches developed for the purposes of the evidence review will be devised by an experienced information specialist and quality assured by a second information specialist. The review will employ methods used to conduct SLRs (e.g. as outlined by the Centre for Reviews and Dissemination[16] including undertaking a systematic and transparent approach to the identification and analysis of published evidence. However, consistent with methods for NICE LSAs,[17] the evidence review will also incorporate pragmatic methods to ensure the evidence review best addresses the NICE decision problem within the timeframe of the assessment. This includes the use of artificial intelligence to identify relevant studies and a tiered evidence selection process (Section 2.3). The EAG may consider potentially limiting the age of included evidence, based on input from SCMs.

Following the LSA Process and Methods Guide, the EAG will prioritise key studies if a large volume of evidence is identified. Prioritisation may be based on the hierarchy of evidence for study designs. The EAG may also ask SCMs for advice on key pieces of evidence if there is a large volume of high-quality evidence.

Further details of the review methods are provided in this section of the protocol.

2.1. Inclusion criteria

2.1.1. Clinical effectiveness

The inclusion and exclusion criteria for the clinical effectiveness and safety evidence are shown in Table 3. These criteria were informed by the NICE scope, discussion with the NICE team, and feedback from stakeholders to this assessment given in the scoping workshop and in consultation with the EAG. The criteria have also been informed by the need to capture the key evidence for the purposes of the assessment objectives. The EAG may prioritise key outcomes,[17] which will be determined with SCM advice. The EAG will only include evidence in English.

Table 3: Inclusion and exclusion criteria, clinical effectiveness

	Inclusion criteria	Exclusion criteria
Population	Adults 18 and over with a venous leg ulcer	Children and young people aged <18 years Adults without a venous leg ulcer
Intervention	Compression products available to the NHS on Part IX of the Drug Tariff or NHS Supply Chain , delivering strong or full compression (defined as 40mmHg or more). Interventions will include: • 4-layer compression bandage systems and kits • 2-layer compression bandage systems and kits (these include 2-layer inelastic systems and 2-layer multi-component systems) • 2-layer compression hosiery • Compression wraps	Treatments other than compression products Compression products not available to the NHS on Part IX of the Drug Tariff or NHS Supply Chain Compression products that do not deliver strong or full compression. Reduced compression is out of scope.
Comparators	4-layer compression bandages or other standard of care compression products s used in the NHS	All other treatments besides 4-layer compression bandages or standard of care in the NHS Mixed comparator studies
Outcomes	<u>Intermediate outcomes</u> • Reduction in wound size • Changes to wound bed condition (for example slough, exudate, granulation and oedema) • Condition of peri-wound skin • Levels and reduction of oedema • Frequency of compression product changes <u>Clinical outcomes</u> • Percentage of wounds healed	Outcomes not aligned to these categories

	Inclusion criteria	**Exclusion criteria**

	• Time to complete wound healing
	• Intervention related adverse events
	<u>Patient reported outcomes</u>
	• Health-related quality of life
	• Wound-related pain
	• Patient adherence
	• Ease of treatment use
	• Mobility
	<u>Costs and resource use</u>
	• Cost of the technology
	• Cost of supporting products (for example a hosiery applicator, a 'boot' to protect bandages when showering, a 'shoe' or an oversized sandal to help walking with bandages, or a foot, ankle or toe piece for wraps to provide full leg compression)
	• <u>Cost of other resource use including:</u>
	  ○ Leg ulcer-related health care professional appointments or visits (primary, community and secondary care)
	  ○ Planned and unplanned leg ulcer-related hospital admission, surgery
	  ○ Staff band and time
	  ○ Staff training
	  ○ Clinical waste disposal	

Study design	<u>Priority</u> Full-text studies will be prioritised where available	

	Inclusion criteria	Exclusion criteria
	• RCTs and quasi-randomised studies • Prospective observational studies <u>Secondary</u> • Retrospective observational studies <u>Tertiary</u> • Time series analyses • Single-arm studies (with a before and after comparison) The EAG may consider other study designs if a low volume of evidence is available.	
Setting	<u>Priority</u> Community (including people's homes, care homes, community hospitals, leg ulcer clinic) Primary care (GP practice) If there is no evidence or not good enough evidence in community or primary care, the EAG may consider evidence from other settings like secondary care.	
Language	English	Studies not reported in English
Date limit	A review of reviews (Patton 2023)[6] offers a comprehensive overview of the evidence base. After reviewing this, the EAG will consider whether it is able to restrict the date to studies published since the search date of this review (2021), or whether an earlier date is required.	(See left)

Abbreviations: GPs, general practitioners; HRQoL, health-related quality of life; RCT, randomised controlled trial; UK, United Kingdom

2.1.2. Economic evaluations and quality of life

Economic and HRQoL evidence will be identified using a similar set of population and intervention criteria as used in the clinical effectiveness review. The inclusion criteria are less restrictive as economic studies that do not meet the exact inclusion criteria for the effectiveness review may still yield information of value to inform the economic analysis. Identified papers will inform the economic model and the quality of life, resource use and cost impacts of complications and events where there is expected to be the potential for a difference in rates or scale of impact on the outcome for interventions featured in the decision problem. ICERs from economic evaluations will be extracted if studies provide information relevant to compression therapy.

Table 4: Inclusion and exclusion criteria, economic evaluations and quality of life

	Inclusion criteria	**Exclusion criteria**
Population	Adults 18 and over with a venous leg ulcer	Children and young people aged <18 years Adults without a venous leg ulcer
Intervention	Any compression product listed in the final scope.	
Comparators	Any comparator. No comparator.	NA
Outcomes	<u>Economic evaluations</u> • Model structure • ICERs • Cost savings (cost comparison studies only) <u>HRQoL studies and HRQoL data identified in economic evaluations</u> • HRQoL data regardless of the method of elicitation and valuation. Data expressed in the form of utilities will be prioritised <u>Cost and resource use identified in economic evaluations</u> • Resource use identified in OECD studies • Bandage costs identified in OECD studies • Other cost sources identified in UK studies • Resource use and costs of interest include frequency of re-dressing bandages, health care professional appointments or visits, management of complications, wastage, dispensation and necessary add-on supporting products	Studies not reporting an included outcome

	Inclusion criteria	**Exclusion criteria**
Study design	• Economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost comparison) • Primary studies reporting HRQoL data • Mapping studies reporting HRQoL data • Systematic reviews of economic evaluations or HRQoL • Conference abstracts will be included unless data are superseded by another conference abstract or full journal article	• Abstracts with insufficient methodological details • Editorials and commentaries
Setting	Economic evaluations must be set in the UK or countries with comparable healthcare systems. HRQoL studies can be conducted in any country.	Economic evaluations set in countries with dissimilar health care systems to the UK.
Language	English	Studies not reported in English
Date limit	Studies published in 1994 or later; 1994 was chosen as no relevant publications before this date were identified in scoping searches	Studies before 1994

Abbreviations: HRQoL, health-related quality of life; ICER, incremental cost effectiveness ratio' OECD, The Organization for Economic Cooperation and Development

2.2. Search strategy

The literature searches for the evidence review are intended to capture a broad range of sources so as to capture evidence relevant to the assessment that may or may not be indexed in traditional literature databases. This includes searching for grey literature sources.

The databases that we shall search are:

- Medline (via OVID)
- Embase (via OVID)
- Cochrane Library (trials and systematic reviews, via Wiley)
- CINAHL (via EBSCOhost)
- International HTA database (INAHTA)

In addition, we will search the following:

- Ongoing clinical trials will be searched in ICTRP and clinicaltrials.gov.

The clinical, economic and utility searches will be limited by date, based on the EAG's assessment of the identified systematic reviews. Search results, supplemental records and submitted information that meet the inclusion criteria will be added to an Endnote (v20) database for deduplication.

An example clinical search strategy (based on the search to be used in Medline) is listed in the appendices. The clinical search combines terms for compression bandages or stockings/hosiery and venous leg ulcers with published filters for 1) RCTs,[18] and 2) observational studies.[19] The observational studies filter has been modified to remove terms associated with case studies and case controls, and terms added to include interrupted time series, before and after studies, and single arm studies. The search delivered 506 hits (with no date limit).

The economics and utilities search is expected to combine similar population and intervention terms (see

Table 4) with published filters for 1) economic evaluations[20] and 2) utilities.[20] The economic evaluations filter will be modified to remove terms associated with costs and resourcing studies – it will also be combined with the NICE OECD countries studies filter. The utilities filter may further be modified by adding terms for condition-specific HRQoL scales.

These Medline searches will be fully translated into Embase. We will use shorter search strategies for other databases, however, given their smaller sizes and less comprehensive indexing.

Information sent from companies and other stakeholders to NICE will be scrutinised to identify additional relevant studies. We will not formally review manufacturer websites, given the large number of manufacturers and products potentially in scope. However, submitted documents and information from manufacturers' request for information (RFI) will be incorporated into our search results (further details provided in Section 4).

If the above search process provides insufficient evidence (see section 2.3), supplemental searching, using Scopus (Elsevier) or Google Scholar may be used.

2.3. Study selection

Three levels of screening will be used to select relevant evidence for the assessment:

Level 1: titles and abstracts of identified publications will be screened using the population, intervention, comparator, and study design criteria shown in Table 3. Machine learning-powered priority screening algorithms will be investigated to support screening.

Level 2: full texts of publications included at level 1 will be screened according to the full eligibility criteria shown in

Table 3 Reasons for exclusion will be noted. Included studies will be tagged using the following categories to aid prioritisation decisions: randomised controlled trial; single arm; UK trial.

Level 3: a final list of included studies will be prioritised for inclusion from those included at level 2. Where feasible, all studies identified at level 2 will be included, although if a large evidence base is identified, then a subset of the most relevant and influential studies will be prioritised for inclusion. Studies tagged as randomised trials and UK studies at level 2 (randomised controlled trials, UK study) will be considered first for inclusion. To guide the prioritisation of other studies included at level 2, we will use the following criteria: economic evaluations conducted using a UK NHS and PSS perspective; studies with no obvious quality concerns (e.g. selection bias, high rates of missing data); studies addressing gaps in the prioritised evidence (e.g. evidence for intervention features for which no studies have yet been prioritised for inclusion); studies including utility data; economic evaluations presenting quality of life and cost and resource use data. Reasons why studies were not prioritised for inclusion will be noted and reported in the appendix of the report.

Real world evidence sources will also be considered for inclusion in reference to the eligibility criteria outlined in Table 3 and

Table 4 and will be considered for prioritisation using the same criteria as described in Level 3 for publications.

The flow of studies through all three levels of screening will be recorded and displayed on a PRISMA diagram. The EAG shall not include in its report studies that do not meet the inclusion criteria, as set out in Tables 3 and 4. A list of prioritised studies will be shared with NICE prior to data extraction for comment.

Consistent with NICE methods for conducting LSAs,[17] a single reviewer will screen each study at each level. Studies will be marked uncertain if further discussion about inclusion is required. Studies marked as uncertain will be discussed in team meetings and a determination made. As a quality assurance step, all studies included at level 2 but not prioritised for inclusion in the review will be screened by a second reviewer and discussed in team meetings as required.

2.4. Data extraction strategy

Data from prioritised studies will be extracted into a data extraction table (DET) in Microsoft Excel. The DET will be developed *a priori* and piloted on three studies of each study type (economic evaluations; primary utility studies; clinical effectiveness studies) to inform any final changes. A separate tab in the DET will be used for each study type, including real world

evidence sources. The data extracted for each study or real-world evidence source will be aligned with the decision problem for the assessment, i.e., information about the study population, interventions, outcomes and study design that characterise its relevance for the decision problem. To guide decisions on data extraction where studies report the same outcome in multiple formats and at multiple timepoints, we will extract formats most likely to be comparable across studies.

In addition, we will prioritise the following:

- Prioritisation of HRQoL data in the form of utilities for the HRQoL review
- Prioritisation of economic evaluations most closely meeting the decision problem specification and carried out from a UK NHS and Personal Social Services (PSS) perspective.

2.5. Quality assessment strategy

Quality assessment will be in accordance with Section 3 of NICE's health technology evaluations manual. Pivotal studies will be quality assured using a standardised tool specific to the research design. More broadly, a general comment about the strengths and applicability of the studies included in the review will be provided in the report.

Economic evaluations will only be formally quality assessed if they compare compression products meeting the effectiveness review criteria in a UK setting. Quality of life studies identified will not be formally quality assessed. Quality of life studies will instead have their quality considered informally as part of the consideration for selection of utility data to be included within the decision model.

Consistent with NICE's real-world evidence framework, the Data Suitability Assessment Tool (DataSAT) will be completed to provide structured information on data suitability including provenance, quality and relevance.

The judgements made in the critical assessment of included evidence will be presented in the EAG report and considered in the evidence landscape and gap map. Where feasible and relevant, critical assessment judgements will be considered in the synthesis/analysis.

2.6. Methods of synthesis/analysis

The features the EAG will focus on in this assessment are the 4 compression product types, one of which has 2 sub-types which would be considered as subgroups if evidence is available.

Depending on available evidence , narrative synthesis, pairwise meta-analysis and/or network meta-analysis may be used for evidence synthesis.

3. ECONOMIC ANALYSIS

This section describes the EAG's plan for the economic evaluation of compression products for treating venous leg ulcers. The approach is based on the NICE methods for LSAs, scoping searches conducted by the EAG, and input from stakeholders at the NICE scoping workshop for this assessment. The approach is subject to change dependent on the evidence identified in the evidence review.

The EAG will endeavour to perform a pragmatic economic evaluation of compression products in adults with venous leg ulcers from the perspective of the UK NHS and PSS, consistent with the methods recommended in the NICE reference case and ISPOR Good Practices Report. Any deviation from the NICE reference case (see NICE Manual) will be identified and discussed as appropriate.

Scoping searches identified a number of relevant studies likely to provide useful data to inform a decision model,[21-24] including the VenUS IV trial[25] and the on-going VenUS 6 study.[26] The EAG will explore whether these are directly applicable to the decision problem. If not, a *de novo* Microsoft Excel decision model will be constructed. The model will be constructed using available evidence, including any models submitted by stakeholders, and following guidance on good practice in decision analytic modelling for HTA.

The structure of any model will be determined on the basis of evidence identified via the evidence review, company RFIs, and from clinical expert advice. This includes input on:

- Appropriate assumptions to make if there are data gaps in the information available to populate resource use or quality of life information per health state
- Which outcomes should be included in the model

All assumptions applied in the modelling framework will be clearly stated and all data inputs and their source will be clearly identified. A decision model will not be developed if no suitable data are available.

If a *de novo* model is developed, it is expected to be simple two state transition model (healed or unhealed) with a time horizon of two to five years. If relevant additional health states representing adverse events will also be included. Most existing clinical studies are of 12 months' duration, at which time point a number of people with ulcers had not healed (eg Guest et al. 2023[23]), allowing potential for there to be uncaptured differences in costs and outcomes between products after this time point. Extrapolations of observed data will be used to predict longer term costs and

outcomes where appropriate and data allow. A state transition model is considered the most expedient approach to modelling the health status of people with leg ulcers, reflecting the progressive nature of healing and resolution of any issues particular products are intended to address. A decision tree could also achieve this, although less elegantly. However, if the EAG considers a decision tree to be more appropriate (eg given data limitations), then the model will be structured as such. The transition period is anticipated to be monthly but may be modified on expert advice or nature of data available to the EAG to populate the model.

Key outcomes for the model such as time to healing will be informed by discussion with clinical experts.

The EAG will calculate the economically justifiable price (eJP), and uncertainty around that, for each of the relevant outcomes in the NICE scope. For example, the eJP of an increased time to healing of x weeks is the price of a product that yields an ICER of £20,000 taking into account the change in cost to the NHS and health gain to patients associated with the accelerated healing time. The eJP will then be compared to the additional cost currently being charged for compression products with those additional features over and above a 'basic' compression product, where possible, to identify which products provide value for money. If possible, and data are available, the EAG will calculate both incremental cost-effectiveness (ICERs) as well as the eJP.

The expected model structure is subject to change during the assessment, principally in response to the evidence identified in the evidence review. Clinical experts will be consulted to provide input to key features and assumptions of the model structure. In addition, the model structure will be reviewed once the evidence review has been completed and company RFIs have been received.

Health benefits will be calculated through disutilities attributable to leg ulcer and associated issues such as oedema. If feasible within the timeframe of the assessment, the EAG will use structured expert elicitation techniques to estimate quantitative values for model inputs where there is no published evidence. Given the requirements of this process, if used, it is likely that this will be focussed towards a small number of model inputs and conducted with experts/SCMs with support from the NICE team.

Outcomes will only be included in the model where there is an expected difference in either the rates or the scale of impact on cost and HRQoL across different types of compression products.

Costs will be considered from an NHS and Personal Social Services perspective as per the NICE manual. Costs for consideration may include:

- Costs of the technologies as identified from the Part IX drug tariff or the NHS Supply Chain, including wastage and customisation costs, where applicable
- Cost of add-on supporting products such as boots that fit over the products
- Cost of appointments in relation to care of the ulcer and redressing
- Cost of other resource use (e.g., associated with managing adverse events and complications):
    - GP appointments
    - Medication
    - Clinical nurse specialists
    - Hospital stays for more serious events

The eJP for additional features will be calculated based upon a willingness-to-pay threshold of £20,000 per QALY, in line with the NICE methods guidance for LSAs. The impact of lower thresholds may be tested in scenario analysis in line with analysis by Martin et al (2023),[27] which suggested that the marginal cost per QALY for all NHS expenditure is around £7,000, based upon the latest available data.

This eJP will then be compared to the additional cost currently being charged for products, to identify which provide value for money. The cost effectiveness of products with intervention features will therefore be estimated in terms of an incremental cost per additional QALY gained and net monetary and health benefit in comparison to the predetermined price range for a 'basic' dressing without features. Base case analyses will be probabilistic as this generates expected outcomes and costs and is in line with the NICE LSA methods. Additional scenario and one-way sensitivity and/or scenario analyses will be conducted where these add value and clarity, looking for example at individual bandages vs kits.

The EAG will consult clinical experts to assess the face validity of the final model and the results. This includes:

- the plausibility of the assumptions used
- that the model accurately reflects current care for people with venous leg ulcers within primary care and community settings
- the plausibility and interpretation of model results.

4. HANDLING INFORMATION FROM THE COMPANIES

Manufacturers of compression products have been invited by NICE to submit evidence relevant to the LSA through a request for information (RFI). It is likely that the EAG will not be able to consider any additional company RFI documents or new evidence (except where clarification has been sought by the EAG) after Wednesday 18 September 2024. Publicly available information will be used when a company RFI is not available.

RFIs received from companies will be appraised using the eligibility criteria used for the evidence review (Section 2.1). Only evidence that meets the eligibility criteria will be considered in the assessment. Evidence in RFIs will also be subject to the prioritisation criteria used in Level 3 of the study selection process (Section 2.3). Evidence from companies included in the evidence review will be extracted into its own tab on the DET for the evidence review, including a description of the characteristics of the evidence source comparable with the approach used for published studies. Evidence that is supplementary to information about a study that is reported in published literature will be considered as part of the quality assessment for that study. Quality assessment of evaluations of compression products will be conducted using the methods described in Section 2.5. Evidence submitted by companies based on surveys or qualitative data with relevant populations will be quality appraised informally. This will include a summary of any important limitations in the evidence, informed by criteria relevant for determining the quality of this evidence.[28,29]

For pivotal evidence submitted by the companies and where necessary and feasible, the EAG will seek clarification or further information from the submitting company to inform the assessment.

As part of the RFI, NICE advises companies to highlight any data that are sensitive and unable to be published in the public domain. Any ‘commercial in confidence’ data, and specified as such, will be highlighted in blue and underlined in the report. Any ‘academic in confidence’ data, and specified as such, will be highlighted in yellow and underlined in the report.

5. ADDITIONAL INFORMATION SOURCES

NICE will recruit experts and specialist committee members for this assessment who will provide input at various stages of the assessment.

6. COMPETING INTERESTS OF AUTHORS

The authors have no conflicts of interest. The EAG will not separately collect conflict of interest information from stakeholders it consults as part of its assessment. The EAG expects that this information has been collected by the NICE team and the EAG will only consult with experts recruited by NICE as stakeholders to the assessment.

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Appendix A: Example search strategy

Example search strategy (for Medline).

RCTs and observational studies

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 09, 2024
Search Strategy:

#	Searches	Results
1	compression bandages/ or stockings, compression/	2977
2	(Compression adj2 (bandag* or dressing* or wrap* or sock* or stocking* or hosiery or garment* or sleeve* or clothes or clothing or suit)).ab,ti,kw.	4202
3	(anti-embolic or antiembolic).ab,ti,kw.	87
4	or/1-3	5949
5	Varicose Ulcer/ or Leg Ulcer/	13594
6	((varicose * or venous * or leg * or crural or cruris or stasis) adj2 (ulcer* or ulcus)).ab,ti,kw.	10766
7	vlu.ab,ti,kw.	381
8	or/5-7	16643
9	4 and 8	1267
10	randomized controlled trial.pt.	618733
11	controlled clinical trial.pt.	95586
12	randomized.ab.	656099
13	placebo.ab.	250713
14	clinical trials as topic.sh.	202985
15	randomly.ab.	439581
16	trial.ti.	315288
17	or/10-16	1618685
18	Epidemiologic Methods/	31624
19	exp Epidemiologic Studies/	3325122
20	Observational Studies as Topic/	9963
21	Clinical Studies as Topic/	839
22	(Observational Study or Validation Studies or Clinical Study).pt.	165724
23	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	250807
24	cohort*.ti,ab,kf.	966904
25	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	574237
26	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	182133
27	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	377718
28	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	764076
29	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	170356
30	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	642
31	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	252889
32	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	5449
33	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	23207
34	(interrupt* time* series or (segment$2 adj3 regression) or (before adj2 after)).ti,ab,kf.	360351
35	("single-arm" or "single arm" or "non random*" or "non-random").ti,ab,kf.	43703
36	or/18-35	4768243
37	9 and (17 or 36)	507
38	exp animals/ not humans.sh.	5247600

39	37 not 38	506