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Citation:

Poku, E and Aber, A and Essat, M and Phillips, P and Buckley Woods, H and Palfreyman, S and Kaltenthaler, E and Jones, GL and Michaels, J (2017) Systematic review assessing the measurement properties of patient-reported outcomes for venous leg ulcers. *British Journal of Surgery (Open)*, 104 (14). ISSN 1365-2168 DOI: <https://doi.org/10.1002/bjs5.25>

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# Systematic review assessing the measurement properties of patient-reported outcomes for venous leg ulcers

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**Background:** A variety of instruments have been used to assess outcomes for patients with venous leg ulcers. This study sought to identify, evaluate and recommend the most appropriate patient-reported outcome measures (PROMs) for English-speaking patients with venous leg ulcers.

**Methods:** This systematic review used a two-stage search approach. Electronic searches of major databases including MEDLINE were completed in October 2015, and then updated in July 2016. Additional studies were identified from citation checking. Study selection, data extraction and quality assessment were undertaken independently by at least two reviewers. Evaluation and summary of measurement properties of identified PROMs were done using standard and adapted study-relevant criteria.

**Results:** Ten studies with data for four generic PROMS and six condition-specific measures were identified. No generic PROM showed adequate content and criterion validity; however, the EuroQoL Five Dimensions (EQ-5D<sup>TM</sup>), Nottingham Health Profile (NHP) and 12-item Short-Form Health Survey (SF-12<sup>®</sup>) had good acceptability. In general, the EQ-5D<sup>TM</sup> showed poor responsiveness in patients with venous leg ulcers. Most condition-specific PROMs demonstrated poor criterion and construct validity. Overall, there was some evidence of internal consistency for the Venous Leg Ulcer Quality of Life (VLU-QoL) and the Sheffield Preference-based Venous Ulcer questionnaire (SPVU-5D). Test-retest reliability was satisfactory for the Venous Leg Ulcer Self-Efficacy Tool (VeLUSSET).

**Conclusion:** The NHP and VLU-QoL questionnaire seemed the most suitable PROMs for use by clinicians. However, a valid condition-specific PROM is still required.

Preliminary findings presented to a meeting of the Society of Academic and Research Surgery, Dublin, Ireland, January 2017; published in abstract form as *Br J Surg* 2017; 104(Suppl 3): 14

## Funding information

National Institute for Health Research Programme Grant (Project ID: RP-PG-1210-12009).

Paper accepted 14 September 2017

Published online 13 November 2017 in Wiley Online Library (www.bjsopen.com). DOI: 10.1002/bjs.5.25

## Introduction

Venous leg ulcers (VLUs) are associated with considerable morbidity and health costs<sup>1,2</sup>. They are the most common kind of chronic leg ulcers; up to 70 per cent of such ulcers are caused solely by venous disease<sup>3,4</sup>. Open unhealed VLUs have estimated point prevalence ranging from 0.1 to 0.3 per cent in the UK<sup>5–7</sup>. They are common in the elderly but relatively rare among patients aged less than 45 years<sup>7,8</sup>.

VLUs are commonly associated with a history of venous insufficiency; they are thought to be caused by venous valve incompetence and calf muscle pump insufficiency, both of which lead to venous stasis and hypertension with resulting

localized tissue ischaemia<sup>8</sup>. The natural history of VLUs consists of a continuous cycle of healing and recurrence. Available evidence suggests that between 30 and 70 per cent of VLUs heal by 6 months, but an estimated 10–20 per cent are treated for over a year<sup>9,10</sup>. Even so, there is high risk of recurrence, with some studies reporting a recurrence rate of 45 per cent<sup>11</sup>. Treatment of VLUs is usually associated with high healthcare costs<sup>12</sup>. In the UK, estimated annual expenditure based on 2005–2006 National Health Service (NHS) data ranged between €245 and 287 million (or €2175–2610 per patient) for treatment in the primary care setting<sup>13</sup>.

Healthcare expenditure, patient-reported outcome measures (PROMs) and patient satisfaction are closely related<sup>14</sup>. Indicators such as wound healing, recurrence, readmission and adverse clinical events reveal little about the health of the majority of patients. Conversely, PROMs provide a more comprehensive and sensitive measure of patients' health<sup>15,16</sup>. These measures can be used as clinical outcomes to optimize management strategies and also examine the performance of healthcare providers.

The aim of this review was to identify, evaluate and recommend the most appropriate PROMs for use in clinical practice among English-speaking patients with VLUs.

## Methods

A systematic review was conducted based on a prespecified protocol ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015024820](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024820)) in line with recommendations of the PRISMA statement<sup>17</sup>.

## Literature searches

Electronic searches, without language or date restrictions, were undertaken systematically in MEDLINE, and MEDLINE In-Process, Embase, the Cochrane Library, CINAHL, PROQOLID PsycINFO and Web of Science. A two-stage approach was used in the MEDLINE searches and adapted for the remaining databases (*Tables S1 and S2*, supporting information). The aim of the first search (search 1) was to identify studies reporting PROMs in patients with chronic venous disease of the leg. The next stage (search 2) was designed to find studies validating the measurement properties of relevant PROMs and any studies that had not been identified previously. The strategy for stage 1 consisted of free-text words and Medical Subject Heading (MeSH) terms for venous insufficiency, varicose veins and VLUs as well as terms for known generic and condition-specific PROMs, such as EuroQol Five Dimensions (EQ-5D) and Charing Cross Venous Ulcer Questionnaire or CXVUQ. Additional terms for PROMs identified from records retrieved during search 1, and a methodological filter for finding studies on measurement properties were included in the previously developed search strategy to undertake search 2.

Electronic searches were undertaken from the date of database inception up to October 2015; an updated search in MEDLINE (including in-process and other non-indexed citations) was completed in July 2016. Supplementary searches included electronic searches in PROQOLID, the PROMs Bibliography (Oxford University) and Google Scholar; citation searching; and checking of reference lists of included studies.

## Study eligibility and selection

Studies were selected for inclusion in this review if they assessed the psychometric properties of PROMs administered as English version questionnaires to patients aged at least 18 years with VLUs. Based on current evidence regarding issues with language and cultural adaptations and translations of PROMs<sup>18</sup>, only PROMs administered as original English questionnaires were considered eligible. The following exclusion criteria were applied: studies based on non-English or translated versions of non-English PROMs; studies in patients with acute deep vein thrombosis, post-thrombotic syndrome, varicose veins, or leg ulcers with arterial, mixed or unknown aetiology; and review articles, abstracts, editorials or letters. Study selection was completed by one reviewer and checked by a second reviewer. Disagreements were resolved by discussion or referred to a third researcher if needed.

## Data extraction

Data extracted were related to general information (name of first author, year of publication, setting/country); study type (PROMs development and validation study or clinical study); population characteristics (sample size, demographics, type of VLU, treatment received); PROM-specific details (name and type, development method, psychometric evaluation and timing of assessments). Where there were multiple publications of a single study, data were extracted and presented as a single study. Data extraction was completed by one reviewer and checked by a second researcher. Discrepancies were checked, discussed and resolved by consensus.

## Methodological assessment of study quality

The methodological quality of the psychometric validation studies was assessed using criteria adopted from the COSMIN checklist<sup>19,20</sup>, University of Oxford PROMs development criteria and other studies<sup>21–28</sup>. These criteria were compatible with the US Food and Drug Administration PROMs guidelines (*Table 1*).

Study-specific criteria used to appraise reported psychometric properties in this study have been used effectively in related reviews<sup>29,30</sup>. Psychometric properties were summarized using the following ratings: 0, not reported; –, evidence not in favour; +/-, conflicting evidence; and +, evidence in favour. Disagreements in psychometric evaluations and analysis were resolved by discussion, and referred to a third researcher when necessary.

**Table 1** Appraisal criteria for assessing the psychometric properties of patient-reported outcome measures

Psychometric property domains	Subdomain	Thresholds
Reliability	Test–retest reliability	Intraclass correlation/weighted $\kappa \geq 0.70$ for group comparisons Intraclass correlation/weighted $\kappa \geq 0.90$ for individual scores Evidence of mean difference between time point 1 and time point 2, reported with 95 per cent c.i. (using paired <i>t</i> test or Wilcoxon signed-rank test) <sup>21</sup>
	Internal consistency	Cronbach's $\alpha$ score of $\geq 0.70$ indicates good evidence, but the score should not exceed $\geq 0.92$ for group comparison Item total correlations should be $\geq 0.20$ <sup>23</sup>
Validity	Content validity	Evidence that the instrument has been developed by undertaking a literature review, consulting patients, clinicians and other experts <sup>19,21,23,26,28</sup>
	Construct validity	Correlation coefficient of $\geq 0.60$ indicates strong evidence This should be supported by specific directional hypotheses and a previous estimation of strength of correlation <sup>19,21–23,26,28</sup>
	Criterion validity	Justification for selection of standard should be adequate Correlation between PROM and standard $\geq 0.70$ <sup>22</sup>
Responsiveness	Responsiveness	Statistically significant changes in score of an expected magnitude based on methods including <i>t</i> tests, effect size, standardized response means, Guyatt's responsiveness index or responsiveness statistics <sup>19,21,26,27</sup>
Acceptability	Floor/ceiling effects	Evidence of floor effect: 15 per cent of respondents are achieving the lowest score on the instrument <sup>19,22</sup> Evidence of ceiling effect: 15 per cent of respondents are achieving the highest score on the instrument <sup>19,22</sup>
	Acceptability	Completeness of data supplied $\geq 80$ per cent <sup>24,27,28</sup>

PROM, patient-reported outcome measure.

## Results

### Identified studies

A total of 3870 records were retrieved from searches (Fig. 1). Ten studies<sup>31–40</sup> (reporting on 4 generic and 6 condition-specific PROMs) were included in the review after detailed examination of 37 full-text articles.

### Study characteristics

Characteristics of the included studies are presented in Table 2. With the exception of one study from New Zealand<sup>36</sup>, all were conducted in the UK. Studies were published between 1999 and 2015. The mean or median age of participants ranged from 66.6 to 76 years. Participants included in the selected studies differed in terms of clinical presentation and ongoing ulcer treatments. Patients with a history of VLUs, chronic ulceration and active disease were included in three studies<sup>33,37,39</sup>. Timing of the PROMs administration also varied across studies. One study<sup>37</sup> reported PROMs data collection at baseline only, whereas the majority reported data collection at baseline and 3 months<sup>33,35,36,39,40</sup>; fewer studies collected PROMs data at 12 months<sup>35,40</sup>.

Four studies<sup>32,34,38,39</sup> described the development and validation of the Sheffield Preference-based Venous Ulcer-5D questionnaire (SPVU-5D)<sup>38</sup>, CXVUQ<sup>39</sup>, Venous Leg Ulcer Self-Efficacy Tool (VeLUSSET)<sup>32</sup>

and Venous Leg Ulcer Quality of Life (VLU-QoL) questionnaire<sup>34</sup>. The remaining studies assessed existing measures: the Nottingham Health Profile (NHP)<sup>33</sup>, EuroQol Five Dimensions (EQ-5D<sup>TM</sup>; EuroQol Group, Rotterdam, The Netherlands)<sup>35,36,40</sup>, Medical Outcomes Study 36-item Short Form Health Survey (SF-36<sup>®</sup>; Optum, Eden Prairie, Minnesota, USA)<sup>33,36,39,40</sup>, Medical Outcomes Study 12-item Short Form Health Survey (SF-12<sup>®</sup>; Optum)<sup>35</sup>, Hyland leg and ulcer questionnaire<sup>35</sup>, Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms (VEINES QoL/Sym)<sup>31</sup> and CXVUQ<sup>36</sup>. The focus of PROMs differed across a number of condition-specific measures. The Hyland questionnaire<sup>35</sup> provides estimates of health-related quality of life (HRQoL) in patients with open ulcers only, whereas the VeLUSSET is a self-efficacy questionnaire designed for use by patients aged 60 years and over. Palfreyman<sup>37</sup> also validated the newly developed SPVU-5D<sup>38</sup>, which is currently the only existing condition-specific PROM with preference weights based on the EQ-5D<sup>TM</sup> algorithm.

A summary of psychometric properties (Table 3) revealed that none of the PROMs identified fulfilled all the psychometric criteria. Existing condition-specific instruments showed limitations in their applicability, either owing to flaws in their validation or development. Furthermore, the responsiveness of the generic instruments such as

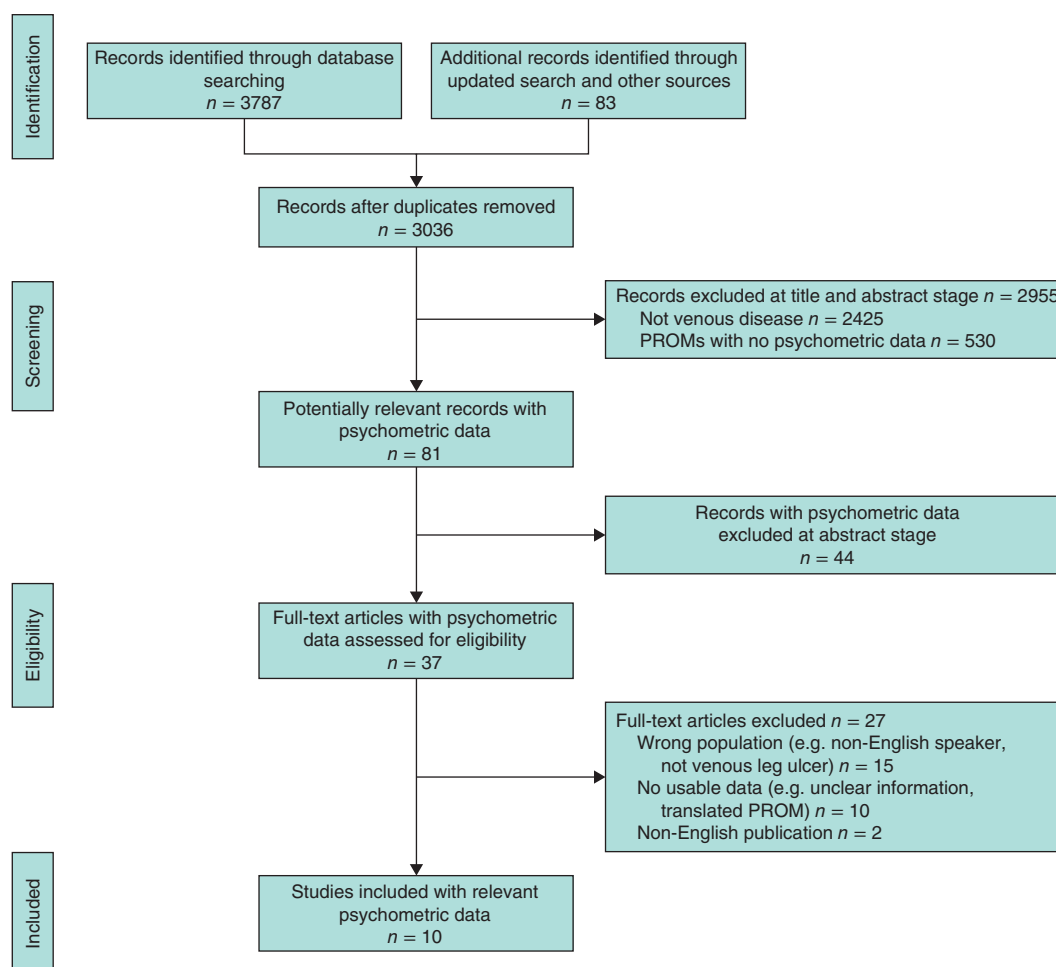


Fig. 1 PRISMA diagram selection of studies for review. PROM, patient-reported outcome measure

EQ-5D™ and SF-36® was either weak or did not support their use in patients with VLUs.

### Psychometric evidence for generic instruments used in patients with venous leg ulcers

#### *EuroQol Five Dimensions questionnaire*

EQ-5D™ is a generic measure of HRQoL that consists of five dimensions (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression) and a visual analogue scale, derived from interviews with a sample of 3395 members of the UK public<sup>41</sup>. The responsiveness and acceptability of this instrument were examined as part of the HALT (Honey as Adjuvant Leg Ulcer Therapy) trial<sup>36</sup>, VenUS I (Venous Ulcer Study I) study<sup>35</sup> and also by Walters and colleagues<sup>40</sup>. All three studies<sup>35,36,40</sup> described lack of responsiveness to change over specified follow-up periods but reported acceptability (80 per cent completed

data). All evaluations were conducted within RCTs. Walters and colleagues<sup>40</sup> also reported a good floor/ceiling effect for this instrument.

#### *Thirty-six-item Short Form Health Survey*

The SF-36® questionnaire covers 36 questions divided across eight dimensions: physical functioning, role limitations because of physical health, social functioning, vitality or energy, bodily pain, mental health, role limitations because of emotional problems and general health. The acceptability, internal consistency and construct validity of this instrument were assessed as part of a multicentre RCT<sup>40</sup> comparing the effectiveness of four-layer compression therapy *versus* usual care. The instrument demonstrated good acceptability, with 86 per cent of participants completing questionnaires. The Cronbach's  $\alpha$  value for internal consistency was less than 0.7, based on four of its dimensions. Overall, the instrument failed to show a statistically significant effect size



**Table 2** Characteristics of included studies reporting validation of patient-reported outcome measures in patients with venous leg ulcers

Reference	Type of study	PROMs	No. of participants	Age (years)*	Men (%)	Treatment	Timing of PROMs assessment
Bland <i>et al.</i> <sup>31</sup>	RCT	VEINES QOL/Sym	Chronic venous leg ulcers (451)	68.6	50.7	Four-layer bandage versus two-layer hosiery	Baseline, 2 weeks and 4 months
Brown <i>et al.</i> <sup>32</sup>	PDVS	VeLUSSET	Healed or recurrent ulcer of venous or mixed aetiology (205)	74.1	47.8	Usual care	Baseline and 4 weeks
Franks and Moffatt <sup>33</sup>	Non-RCT	NHP SF-36®	Chronic venous leg ulcers (383)	74†	36.6	Compression bandaging	Baseline and 12 weeks
Hareendran <i>et al.</i> <sup>34</sup>	PDVS	VLU-QoL	Active venous leg ulcers (160)	72	31	Compression bandaging	Baseline and 8 weeks
Iglesias <i>et al.</i> <sup>35</sup>	RCT	Hyland questionnaire SF-12® EQ-5D™	Chronic venous leg ulcers (387)	71.6	41	Four-layer bandage versus short stretch bandage	Baseline, 3, 6, 9 and 12 months
Jull <i>et al.</i> <sup>36‡</sup>	RCT	SF-36® EQ-5D™ CXVUQ	Active venous leg ulcers (368)	67.7	48.9	MHICAD with compression bandaging versus usual care	Baseline and 12 weeks
Palfreyman <sup>37</sup>	PDVS	SPVU-5D	Active and chronic venous leg ulcers (152)	66.6	n.r.	Usual care	Baseline
Palfreyman <i>et al.</i> <sup>38</sup>	PDVS	SPVU-5D	Active and chronic venous leg ulcers (19)	n.r.	n.r.	Usual care	n.r.
Smith <i>et al.</i> <sup>39</sup>	PDVS	SF-36® CXVUQ	Active venous leg ulcers (98)	76†	34	Usual care	Baseline, 6 and 12 weeks
Walters <i>et al.</i> <sup>40</sup>	RCT	EQ-5D™ SF-36®	Active and chronic venous leg ulcers (233)	75†	33.5	Four-layer compression versus usual care	Baseline, 12 weeks and 12 months

\*Values are mean, except †median. ‡Study from New Zealand; all other studies were carried out in the UK. PROM, patient-reported outcome measure; VEINES-QOL/Sym, Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms; PDVS, PROMs development and validation study; VeLUSSET, Venous Leg Ulcer Self-Efficacy Tool; NHP, Nottingham Health Profile; SF-36®, 36-item Short Form Health Survey; VLU-QoL, Venous Leg Ulcer Quality of Life questionnaire; SF-12®, 12-item Short Form Health Survey; EQ-5D™, EuroQol Five Dimensions questionnaire; CXVUQ, Charing Cross Venous Ulcer Questionnaire, MHICAD, manuka honey-impregnated calcium alginate dressings; SPVU-5D, Sheffield Preference-based Venous Ulcer-5D questionnaire; n.r., not reported.

in relation to the size of the VLU. As a result, the construct validity of SF-36® was poor. Comparisons between healed and non-healed VLUs at baseline and 12 months' follow-up did not show statistically significant differences in responsiveness for all dimensions of the questionnaire<sup>40</sup>.

The psychometric properties of this instrument were also examined as part of the HALT trial<sup>36</sup> in New Zealand, which compared the effectiveness of an active dressing in addition to compression bandage compared with usual care. SF-36® showed good acceptability (with 98 per cent complete data) and adequate responsiveness in seven of the eight dimensions at 12 weeks' follow-up.

#### Twelve-item Short-Form Health Survey

The suitability of this generic item for measurement of HRQoL in patients with VLUs was examined in a large multicentre pragmatic RCT (VenUS I)<sup>35</sup> assessing the effectiveness of two types of bandages. SF-12® questionnaires were completed by 88 per cent of the 387

participants, representing good acceptability. The responsiveness of the SF-12® was examined by comparing scores of the physical component summary (PCS) and mental component summary (MCS) of this questionnaire at baseline and up to 12 months of follow-up. The effect size was found to be statistically significant at 6 and 12 months for the MCS only; the change in PCS scores was not significant regardless of whether VLUs healed or not<sup>35</sup>.

#### Nottingham Health Profile

The NHP is a 38-item questionnaire with binary answers (yes or no) to questions grouped into six domains, namely energy, bodily pain, emotional status, sleep, social isolation and physical mobility. The NHP was validated in 383 patients with VLU, and administered at baseline and 12 weeks<sup>33</sup>. More than one-third of the patients experienced healing of ulcers by 12 weeks. Responsiveness was examined by comparing mean score changes after 12 weeks of treatment, and considered the patients' perceived change in health which was rated as improved, worse

**Table 3** Summary of the psychometric properties of patient-reported outcome measures in patients with venous leg ulcers

	Internal consistency	Test-retest reliability	Content validity	Criterion validity	Construct validity	Responsiveness	Floor/ ceiling effect	Acceptability
Generic PROMS								
NHP								
Franks and Moffatt <sup>33</sup>	+/-	0	0	0	+	+	-	+
SF-12 <sup>®</sup>								
Iglesias <i>et al.</i> <sup>35</sup>	0	0	0	0	0	+/-	0	+
SF-36 <sup>®</sup>								
Walters <i>et al.</i> <sup>40</sup>	-	0	0	0	-	-		+
Jull <i>et al.</i> <sup>36</sup>	0	0	0	0	0	+/-	0	+
EQ-5D <sup>™</sup>								
Walters <i>et al.</i> <sup>40</sup>	0	0	0	0	0	-	+	+
Iglesias <i>et al.</i> <sup>35</sup>	0	0	0	0	0	-	0	+
Jull <i>et al.</i> <sup>36</sup>	0	0	0	0	0	-	0	+
Condition-specific PROMS								
VeLUSET								
Brown <i>et al.</i> <sup>32</sup>	+/-	+	+	0	0	0	0	-
VLU-QoL <sup>34</sup>								
Hareendran <i>et al.</i> <sup>34</sup>	+	+	+	+	+	+/-	+	+/-
Hyland questionnaire								
Iglesias <i>et al.</i> <sup>35</sup>	0	0	0	0	+/-	+/-	0	-
SPVU-5D								
Palfreyman <i>et al.</i> <sup>38</sup>	0	0	+	0	0	0	0	0
Palfreyman <sup>37</sup>	+/-	0	+	0	0	0	0	0
VEINES-QOL/Sym								
Bland <i>et al.</i> <sup>31</sup>	+	+/-	0	+/-	+	+	-	+
CXVUQ								
Smith <i>et al.</i> <sup>39</sup>	+/-	+/-	+	+	0	+	-	-
Jull <i>et al.</i> <sup>36</sup>	0	0	0	0	0	+	0	+

Psychometric and operational criteria: 0, not reported (no evaluation completed); +/-, weak evidence; +, evidence in favour; -, evidence not in favour. PROM, patient-reported outcome measure; NHP, Nottingham Health Profile; SF-12<sup>®</sup>, 12-item Short Form Health Survey; SF-36<sup>®</sup>, 36-item Short Form Health Survey; EQ-5D<sup>™</sup>, EuroQol Five Dimensions questionnaire; VeLUSET, Venous Leg Ulcer Self-Efficacy Tool; VLU-QoL, Venous Leg Ulcer Quality of Life questionnaire; SPVU-5D, Sheffield Preference-based Venous Ulcer-5D questionnaire; VEINES-QOL/Sym, Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms; CXVUQ, Charing Cross Venous Ulcer Questionnaire.

or the same. NHP scores were analysed for patients with or without healed ulcers over the study period. A paired *t* test provided strong evidence that compression therapy led to significant improvement in all dimensions of the NHP, especially in patients with healed ulcers (mean difference 9.4;  $P = 0.004$ ). The study reported evidence in support of the acceptability of this instrument, with completion rates for all domains ranging from 94 to 99 per cent. The Cronbach's  $\alpha$  value was less than 0.7 when all items were considered. However, most items in individual domains had an  $\alpha$  value of more than 0.7, with the exception of energy and social isolation. The study<sup>33</sup> provided evidence in favour of construct validity of the NHP, showing a direct relationship between larger ulcer sizes and longer ulcer duration on the domain scores of the instrument. A high floor effect (best health) was reported in the social isolation, energy and emotional status domains, as the majority of patients reported best possible health at baseline.

### Psychometric evidence for the venous leg ulcer-specific PROMS

#### *Charing Cross Venous Ulcer Questionnaire*

This 20-item questionnaire<sup>39</sup> was developed by involving patients and clinicians. The authors were able to reduce the items that did not provide discriminatory value by performing factor analysis and floor/ceiling effect analysis, after administering the preliminary version. In total, 12 items were removed from the initial 32. The remaining items demonstrated modest internal consistency with a Cronbach's  $\alpha$  of 0.93, indicating the need for further item reduction. The scores of the eight dimensions of SF-36<sup>®</sup> were used to examine the criterion validity of this PROM. The reported analysis showed strong correlation between SF-36<sup>®</sup> scores and those of the CXVUQ ( $r^2 > 0.84$ ,  $P < 0.001$ ), indicating good criterion validity<sup>39</sup>. The instrument's responsiveness was further demonstrated by good correlation between scores and clinical outcomes in two studies<sup>36,39</sup>. Responsiveness of the CXVUQ was

reported to be adequate in patients with healed ulcers at 6 weeks ( $P = 0.022$ ) and 12 weeks ( $P = 0.005$ )<sup>39</sup>.

#### *Hyland questionnaire*

The 34-item Hyland leg ulcer questionnaire<sup>35</sup> was developed for patients with any type of leg ulcer, and provides estimates of HRQoL in patients with open ulcers only. It is divided into three sets of evaluations: a visual scale relating to the current progress of the leg ulcer; four single items (leg ulcer pain, sleep discomfort caused by the leg ulcer, time spent thinking about the ulcer and time spent helping the ulcer heal); and 29 items about HRQoL related to the presence of an open leg ulcer. This instrument was evaluated psychometrically in an English-speaking population as part of the VenUS I trial<sup>35</sup>. Evidence was weak for its responsiveness and criterion validity. The acceptability for the PROMS was poor (64 per cent complete data).

#### *Sheffield Preference-based Venous Ulcer-5D questionnaire*

This is the only condition-specific preference-based measure of HRQoL for patients with VLUs. It has five dimensions (pain, mobility, mood, smell and social activities) and each dimension has three to five levels<sup>37,38</sup>. The dimensions were developed based on in-depth patient interviews, focus groups and input from clinicians. Preference weights were obtained from a UK population survey, which generated values for 720 health states. The completed instrument consisted of 16 questions about the impact of living with VLUs, combined with two generic questionnaires (EQ-5D<sup>TM42</sup> and SF-6D<sup>®43</sup>). Validation data for the SPVU-5D (152 patients, mean age 66.6 years; 32 per cent with recently active ulcers, 36 per cent with ulcer duration exceeding 12 months, 80 per cent with previous history of ulcer) provided evidence for modest internal consistency (Cronbach's  $\alpha > 0.93$ )<sup>37</sup>. However, there was little evidence about its performance in terms of responsiveness and test-retest reliability.

#### *Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms*

This 26-item questionnaire addresses the following dimensions related to chronic venous disease of the leg: symptoms (12 items), limitations in daily activity (9 items) and psychological impact (5 items)<sup>31</sup>. A summary score, VEINES-QOL, is obtained by summarizing scores across 25 items. The remaining item is not scored, but provides information about when leg pain is worst during the day. The VEINES-Sym is derived from a subset of the VEINES-QOL<sup>25</sup>. The VEINES-QOL/Sym was validated as part of the VenUS IV trial<sup>31</sup>, which compared two-layer hosiery and a four-layer bandage system<sup>44</sup>. The VEINES-QOL/Sym demonstrated good acceptability

with 82.4 per cent of the questionnaires complete at baseline. Good internal consistency was observed in favour of this instrument, with a Cronbach's  $\alpha$  of 0.88 and 0.81 for the VEINES-QOL and VEINES-Sym respectively. Acceptable construct and criterion validity, based on comparisons with the pain subscale of the SF-12<sup>®</sup> and clinical measures, were also reported. It also showed moderate responsiveness when outcomes were examined at 4 months in patients with healed ulcers<sup>31</sup>. However, test-retest reliability evidence was weak ( $\kappa$  score 0.42–0.73).

#### *Venous Leg Ulcer Quality of Life*

Item generation for the VLU-QoL was based on focus group and in-depth interviews with patients with VLUs (36 patients, 24 women; age 46–91 years)<sup>34</sup>. Some 48 questions were generated and administered to 124 patients with at least one chronic VLU. The 48-item VLU-QoL was retested in a subgroup ( $n = 78$ , 62.9 per cent) of previous respondents after 48–72 h. The  $t$  test and Mann-Whitney test showed statistically significant correlation. Afterwards, 14 of the 48 questions were excluded because they either showed a poor floor/ceiling effect (more than 60 per cent of respondents choosing never or all the time) or had high interitem correlation. The final version of the instrument consisted of 34 items with three domains (activity limitations, 12 items; psychological effects, 12 items; and symptom distress, 10 items). The internal consistency of all the domains was high (Cronbach's  $\alpha > 0.8$ )<sup>34</sup>. The study also reported strong correlation with the SF-36<sup>®</sup> MCS and PCS scores, as well as a strong correlation with clinical and reported ulcer symptoms. This provided satisfactory criterion and construct validity evidence for the questionnaire. On the other hand, there was weak evidence of the responsiveness and acceptability. The interval between these instrument tests was, however, short (baseline and 8 weeks)<sup>34</sup>.

#### *Venous Leg Ulcer Self-Efficacy Tool*

The VeLUSET is a self-efficacy questionnaire designed for patients aged 60 years and over<sup>32</sup>. A focus group study was conducted to identify themes relevant to patients with VLU. Six main themes related to 111 items were found. Following further qualitative research with patients and experts, items were further reduced to 60. The acceptability of the instrument in the validation phase was poor, with only 41 per cent of the data complete<sup>32</sup>. The evidence for internal consistency (Cronbach's  $\alpha = 0.93$ ) indicated that some of the items in the questionnaire could be made redundant. The test-retest reliability showed a strong positive relationship between test and retest scores ( $r = 0.92$ ,  $P < 0.001$ ) at baseline and 4 weeks<sup>32</sup>.



## Discussion

With high recurrence rates and complex management pathways<sup>6,45</sup>, the use of outcomes that can capture the impact of chronic venous leg ulceration on the patient's quality of life is vital. PROMs can help achieve this goal by examining the effectiveness of interventions, assessing the progress of conditions, as well as contributing to shared decision-making between patients and carers.

The appropriateness of a PROM is closely related to its acceptability or practicality (linked to respondent and investigator burden in data collection), reliability and validity. It is also important that valid PROMs are developed and assessed in a specific population and context that represents the settings in which they will be used. The scope of the present review was to identify relevant PROMS for health evaluation and decision-making within the UK NHS. As a result, stricter eligibility criteria were applied in the present study than in earlier reviews<sup>46–49</sup>.

In general, generic PROMs did not demonstrate satisfactory responsiveness, including changes in clinical condition, for patients with VLUs. Of particular note was the lack of responsiveness of the EQ-5D<sup>TM</sup> and its inability to detect change over time. This raises the question of whether it is an appropriate tool when economic evaluations are incorporated into clinical trials of interventions for patients with VLU in the UK<sup>31,35,36,40</sup>. Despite recommending use of the EQ-5D<sup>TM</sup> for health technology evaluation, the National Institute for Health and Care Excellence (NICE)<sup>50</sup> recognizes that it may not be appropriate for all conditions, and this review suggests caution in relation to VLUs.

On the basis of the criteria applied, the most appropriate generic and condition-specific PROMs were the NHP and the VLU-QoL. The NHP was found to be responsive to change over time. Although it did not have evidence of test–retest reliability, it exhibited good construct validity. It seems to be the most appropriate generic tool for use in this population. One limitation of the NHP is that it is not suitable for obtaining utility estimates for economic evaluations because there is currently no existing algorithm for mapping its scores to preference weights. The most suitable condition-specific tool identified was the VLU-QoL. This instrument had good content validity, construct validity and criterion validity, as well as internal consistency. Evidence for its responsiveness, however, was weak, probably reflecting the short interval between baseline assessment and follow-up (only 8 weeks) in a population with long-term chronic VLUs<sup>34</sup>.

All studies were conducted in the UK with the exception of one originating from New Zealand<sup>36</sup>. The psychometric criteria applied in the appraisal of PROMs were based on

internationally accepted guidelines<sup>20,21,23,24</sup>. This was necessary because of the absence of an agreed assessment tool, and also owing to the limitations of using a single checklist to assess the psychometric properties of PROMs<sup>51,52</sup>.

The review aimed to identify the most suitable PROMs for use by clinicians in patients with VLUs. Therefore, only studies reporting on the development and validation of a relevant PROM were considered. To assess the clinical effectiveness of PROMs and their impact on patient management, the selection criteria may have covered clinical studies that were not specifically designed to assess measurement properties. This could lead to ambiguous findings because, without *a priori* hypothesis testing, lack of responsiveness of a PROM may stem from a poor choice of PROM tool or may be due to lack of effectiveness. Therefore, there was a trade-off between achieving robustness of the review of measurement properties and limited evidence about how the PROMs were tested in the clinical setting.

The narrow eligibility criteria applied in this review were considered appropriate. However, this led to the exclusion of potentially relevant validation studies, for example the Turkish version<sup>53</sup> and Norwegian version<sup>54</sup> of the VEINES-QOL/Sym in patients with chronic venous insufficiency. Another limitation relates to the date of the last literature search; it is possible that more recent studies may not be included in this review. The heterogeneity in the study methodology, patient population and treatment pathway could have potentially influenced the results. There was also no explanation provided of how missing data were dealt with in any of the included studies.

Requirements for a PROM for routine clinical practice may differ from the requirements of outcome measures to generate utility values for cost-effectiveness calculations. The VLU-QoL<sup>34</sup> needs further evaluation to assess its responsiveness. Further research to validate the SPVU-5D<sup>38</sup>, the only preference-based condition-specific questionnaire, is needed. This instrument seems a promising alternative to current generic preference-based PROMs and can provide meaningful utility measures for economic evaluations. Standardization in the conduct and reporting of validation studies to facilitate meaningful interpretation, comparison and analysis of data is still needed.

## Acknowledgements

The authors are grateful to R. Duncan for double-checking the psychometric analysis; and E. Wilson and K. Wilson for providing administrative support while designing and undertaking the study. This research and publication were funded by the National Institute for Health Research Programme Grant (project ID: RP-PG-1210-12009). The

funder had no role in the study design, data collection, data analysis, data interpretation or writing of this article.

*Disclosure:* The authors declare no conflict of interest.

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