Developing outcome measures for patients with vascular conditions.

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3- Aber A, Lumley E, Phillips P, Woods HB, Jones G, Michaels J. Themes that Determine Quality of Life in Patients with Peripheral Arterial Disease: A Systematic Review. Patient. 2018 Oct;11(5):489-502. PMID: 29736612
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4- Aber A, Howard A, Woods HB, Jones G, Michaels J. Impact of Carotid Artery Stenosis on Quality of Life: a systematic review. Patient. 2019 Apr;12(2):213-222. PMID: 30328068
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5- Aber A, Phillips P, Lumley E, Radley S, Thomas SM, Nawaz S, Jones G, Michaels J, UK Vascular PROMs Group. Mixed methods study to develop the content validity and the conceptual framework of the electronic patient reported outcome measure for vascular conditions. BMJ Open. 2020 Aug 11;10(8):e034154. PMID: 32784253

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Contribution: I was involved in the development of the conceptual framework of ePAQ-VAS including the design of the sections and items within this new instrument. I performed the consensus study, updated the ePAQ-VAS based on input from the face validity study and wrote the manuscript.

6- Aber A, Phillips P, Hughes J, Keetharuth AD, Rooney G, Radley S, Walters S, Nawaz S, Jones G, Michaels J. Electronic personal assessment questionnaire for vascular conditions (ePAQ-VAS): development and validity. Br J Surg. 2020 Jul;107(8):1004-1012. PMID: 32250452

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Contribution: I designed the specific statistical analysis, senior authors confirmed the analysis. I recruited patients for the survey and updated the recruitment strategy. I performed all the analyses and wrote this manuscript.

Summary

The electronic patient assessment questionnaire for vascular conditions (ePAQ-VAS) was developed by the Sheffield Vascular Research group. It consists of the following sections: generic, carotid artery disease, abdominal aortic disease, lower limb vascular disease and a second generic section that include EQ-5D.

The six papers included in this thesis present some of the work I have done to develop ePAQ-VAS, including qualitative evidence synthesis, systematic reviews, developing the conceptual work and psychometric analysis.

The first stages of developing ePAQ-VAS comprised of five systematic reviews to identify patient-reported outcome measures (PROMs) that can be directly included into ePAQ-VAS. These reviews did not identify any PROMs that fulfilled the psychometric criteria defined by the authors. Since no PROMs were identified, qualitative evidence synthesis was undertaken to develop new PROMs. This included five qualitative evidence synthesis reviews and a primary qualitative study that was completed before I joined the team.

The qualitative evidence was used to develop the primary pool of ePAQ-VAS items. I helped develop the conceptual framework of ePAQ-VAS including a clinicians' consensus study, and modifications of the instrument based on the face validity study. The last of the six papers in this PhD by publication is the paper on the validation of ePAQ-VAS. This paper presents the results of the survey in which vascular patients completed ePAQ-VAS. I used the data from this survey to perform factor analysis and reduce items from the instrument. The paper also presents the results of internal reliability, test-re-test, known-group validity and responsiveness analyses. In the additional chapters of this thesis, I have provided further insight into the methods used in developing ePAQ-VAS. ePAQ-VAS is a holistic tool for the assessment of patients with a vascular disease with acceptable validity, reliability and responsiveness. This tool can be used to measure outcomes to improve service provisions.

Abbreviations

AAA	Abdominal aortic aneurysm
ADL	Activities of daily living
AVVQ	Aberdeen Varicose Vein Questionnaire
CAD	Carotid artery disease
CASP	Critical Appraisal Skills Programme
CFA	Confirmatory factor analysis
CFI	Comparative fit index
COSMIN	Consensus-based Standards for the selection of health status Measurement instruments
CSSOM	Carotid Stenosis Specific Outcome Measure
CXVUQ	Charing Cross Venous Ulcer Questionnaire
NHS	National Health Service
DHI	Dizziness Handicap Inventory
ePAQ	electronic patient assessment questionnaire
ePAQ-VAS	electronic patient assessment questionnaire for vascular conditions
EQ-5D™	EuroQol questionnaire
HADS	Hospital Anxiety and Depression Scale
ICCs	Intra-class correlation coefficients
MI	Modification indices
NHP	Nottingham Health Profile
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
PAD	Peripheral arterial disease
PADQoL	Peripheral Artery Disease Quality of Life Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROMs	Patient-reported outcome measures
PROSPERO	International prospective register of systematic reviews
RC	Residual correlations
RMSEA	Root mean square error of approximation
SF-36®	36-item Short Form Health Survey
SPVU-5D	Sheffield Preference-based Venous Ulcer-5D questionnaire
SQOR-V	Specific Quality of life and Outcome Response–Venous
TIA	Transient Ischaemic Disease
US FDA	The United States Food and Drug Administration
VVs	Varicose veins
VLU	Venous leg ulcer

Chapter One: Introduction

One of the main aims of the National Institute of Health Research (NIHR) programme grant considering the configuration and monitoring of vascular services in the United Kingdom was to develop PROMs for routine clinical use for vascular patients. This tool was designed so that patients could complete it online, at home or in the hospital. The data gathered can help in assessing patients. The PROMs were developed to also measure and track longitudinal outcomes among vascular patients. The aggregate data generated from completing the tool routinely in clinical practice over time from different vascular departments can help decision-makers when deciding on vascular services quality improvement.

Vascular services have undergone several cycles of quality improvement and reconfigurations in the past decades. The leading quality indicators for these significant changes to the vascular services were clinical outcomes, particularly short-term mortality following elective repair of abdominal aortic aneurysm, which has been compared to other European countries **(1)**. Past changes to the provisions of vascular services led to the creation of larger vascular centres by merging smaller units together to increase the operative volume. The evidence for this policy was that higher operative volume was associated with reduced in-hospital mortality and lower incidence of adverse clinical outcomes following surgical interventions **(2-4)**.

However, future changes to vascular services may want to consider other aspects of the service that are important to the patients. The volume of cases treated is only a proxy to examine the quality of the service, and outcomes are undoubtedly influenced by a multitude of factors. Furthermore, evidence from clinical practice suggests that many vascular patients are treated with the best medical therapy or conservative non-surgical interventions **(5-6)**. This means that there are limited data on outcomes for large groups of patients.

Most vascular conditions are either chronic or require long-term follow-up. Also, new surgical and endovascular interventions may have better short-term outcomes. However, there is limited evidence of durability and cost-effectiveness **(7)**. Therefore, improved methods to measure outcomes for most patients is imperative, and it is an important consideration when considering future vascular services reconfiguration.

Health related quality of life (HRQoL) is a valuable indicator to measure outcomes in health care settings. HRQoL is a complex concept and can be measured by assessing the burden of a disease or a condition on the physical, emotional and social wellbeing of the affected individual. Patient reported

outcome measures (PROMs) are commonly used to examine HRQoL. These are developed with input of patients to examine self-perceived health as well as physical, emotional and social functioning **(8).** PROMs provide a report on a patient's condition that comes directly from the patient, without interpretation of the patient's response by anyone else. PROMs can be a valuable method of collecting information on the effectiveness of care delivered to patients **(9)**.

PROMs are classified into generic and disease-specific; the generic PROMs measure aspects of health that are potentially relevant for a wide range of patient groups and the general population. They are multidimensional and enable comparison between different health conditions and populations. The SF-36® (Short Form Questionnaire-36 items) is one of the most widely used generic PROMs **(10-13)**. The broad nature of these PROMs means that some level of detail must be sacrificed, which may limit the relevance of these instruments when used by a specific patient population. Generic PROMs also can be less responsiveness to clinically meaningful changes in health **(12-13)**.

Disease-specific PROMs address a disease area and do not contain any items or health dimensions that are not relevant to the disease. The acceptability of disease-specific PROMs to patients and clinicians is often high because it is reflecting the concerns of patients with the presenting problem. The disadvantages of using disease-specific PROMs include the difficulty of administering them to samples that do not have a relevant health problem. This means that health status scores cannot be compared across various conditions and with those for the general population. Also, the restricted focus of disease-specific PROMs may prevent them from detecting side effects or unforeseen effects of treatment **(14)**.

ePAQ-VAS was designed to include generic and disease-specific sections that can be completed by vascular patients. The generic section also had the 5 level EQ-5D to measure the utility values of the respondents. This utility measured was chosen since it is preferred measure of health-related quality of life in adults by the National Institute for Health and Care Excellence (NICE).

ePAQ-VAS was designed for routine clinical use as there are several advantages of using PROMs in routine clinical practice. Evidence suggests that data collected using PROMs may facilitate the detection of physical or psychological problems that might otherwise be overlooked **(15-16)**. Also, regular use of these instruments can monitor disease progression and provide information about the impact of treatments **(17-20).** Another benefit of using PROMs in routine clinical practice is that the data generated can facilitate patient-clinician communication and contribute to shared decision

making **(21-23)**. PROMs adopted into regular clinical care can be used to monitor outcomes as a strategy for quality improvement and/or reward presumed superior care **(21-23)**.

Despite increased research interest in PROMs and their regular use in clinical research, attempts to embed PROMs into routine practice have revealed many technical, cultural and logistical barriers **(21-23)**. Clinicians are often reluctant to use PROMs routinely because of the perception that it may increase their workload and impact efficiency and effective care. Furthermore, many clinicians argue that they already understand the patients' problems using the traditional face-to-face encounter and do not need additional information **(23)**. Some studies report that patients expressed concern about the burden of the questionnaires, especially when in paper format; others raised concern that the data generated may misdirect the focus of the clinical encounter to factors that have value to clinicians **(22-24)**. A specific disadvantage to vascular patients presenting to vascular services is that patients may present with overlapping symptoms or mixed conditions. Additionally, it is challenging to use paper-based PROMs to monitor patients with chronic, recurrent or multiple vascular conditions **(25-26)**. The evidence regarding the impact of the data collected using PROMs on patient outcomes is weak, and this can explain the infrequent use of PROMs as an outcome measure. However, the use of PROMs as a performance measure is not well investigated either. Studies suggest that the healthcare organisations planning to use PROMs in clinical settings should have a clear strategy on how the data will be collected and how the data would be used for clinical purposes. Other studies suggest that the organisation need to get its staff ready to use PROMs, including persuading clinicians of the value of PROMs and providing them with the adequate training **(27-29)**.

The NIHR programme, considering the configuration and monitoring of vascular services, developed the electronic online vascular PROMs. This instrument followed the successful models in which electronic PROMs were used for patients' diagnosis, assessment, and long term monitoring **(30)**. The aim of this tool was to assess patients' symptoms, disease severity and the impact of the vascular condition/s on quality of life. This questionnaire was incorporated into the electronic patient assessment questionnaire (ePAQ) systems. ePAQ is an electronic web-based system used for patient assessment developed for use in gynaecology clinics in Sheffield, UK. ePAQ instruments have been in regular clinical use in many NHS for over 15 years. The gynaecological dimensions of ePAQ have undergone extensive psychometric testing **(30-33)**. It is being used in an increasing number of NHS

departments, and it has gained recognition for supporting care pathways as well as monitoring outcomes in gynaecology **(34)**.

The peer-reviewed papers included in this PhD present steps taken to develop and validate the electronic patient assessment questionnaire for vascular conditions (ePAQ-VAS). ePAQ-VAS is a single electronic tool with sections to assess the HRQoL of patients with abdominal aortic aneurysm (AAA), peripheral arterial disease (PAD), carotid artery disease (CAD), varicose veins (VVs) and venous leg ulcer (VLU). ePAQ-VAS aims to examine the impact of these conditions on the patients' activities of daily living as well as certain aspects of psychological and social functioning.

The papers of this PhD include two systematic reviews to identify validated, reliable and responsive PROMs for patients with varicose veins (VVs) **(35)** and venous leg ulcers (VLU) **(36)**. Two qualitative evidence synthesis reviews to identify all the themes important to patients with peripheral arterial disease and carotid artery disease **(37-38)**. A fifth paper presents the conceptual framework and the evidence for the content validity of ePAQ-VAS **(39)**. The sixth paper reports the steps taken to develop ePAQ-VAS and the results from psychometric survey analysis, including factor analysis, internal reliability, test-re-test, known group validity and responsiveness **(40)**.

This thesis aims to present an overall summary and critique of the papers included in this PhD and provide details on how the papers presented here are a coherent piece of work that contributed to the development of ePAQ-VAS.

Chapter Two. The role of systematic reviews in the development of ePAQ-VAS

2.1 Context of the ePAQ-VAS

One of the aims of the NIHR Programme grant was to develop a comprehensive patient-reported outcome measure for vascular conditions. The plan was this outcome measure would be used to collect outcomes mainly in clinical settings, including outpatient clinics and wards.

Despite the advantages of PROMs, their use in routine clinical practice remains limited. In the literature, there are many reported patient, health professional and service level barriers, including patient inability to complete PROMs **(41, 42)**, perceived irrelevance of PROMs and their lack of value for the patients' treatment pathway **(43)**. Health professional level barriers include insufficient time to interpret, action and discuss the data collected from PROMs in routine outpatient clinics **(41, 44)**, also perceived uselessness of certain PROMs data as well as the logistical difficulty in integrating PROMs into clinical practice **(45)**. The service level barriers reported in the literature include the inability to integrate routine PROMs use into clinical patient pathways and inadequate information technology infrastructure to enable PROMs collection and interpretation **(418, 45)**.

The proposed outcome measure for vascular conditions was developed in collaboration with ePAQ systems Ltd. ePAQ-VAS was to follow a similar model to the ePAQ-Pelvic floor model, which is used in routine clinical practice in several NHS hospitals **(31-33)**. The ePAQ-Pelvic floor has the necessary information technology infrastructure. The success of ePAQ-Pelvic floor was a result of the items being relevant to clinical assessment and its ability to improve the clinical encounter **(31-33)**. Furthermore, the electronic nature of the tool meant that it was easier to integrate it into the clinical pathway of the patient compared to paper PROMs with real-time feedback.

2.2 Steps in the development of ePAQ-VAS

In the first step of developing ePAQ-VAS, five systematic reviews were completed to identify PROMs the most valid, reliable and responsive PROMs for patients with abdominal aortic aneurysm **(46)**, peripheral arterial disease **(47)**, carotid artery disease (**(48)**, varicose veins **(35)** and venous leg ulcer

(36). I contributed to three of these reviews **(35-36, 48)** two of which are included in this PhD **(35-36)**. The AAA and PAD reviews were completed before I started working on this project. The searches for CAD, VVs and VLU reviews were completed before I joined the group; these searches were updated. The VLU and VVs were not part of the original research plan, and instead, a review to identify validated PROMs for the chronic venous disease was planned. However, the initial searches for this review generated a huge and unmanageable number of titles; following discussion with the chief investigator and other members of the team, two separate reviews for VLU and VVs were completed. My role included sifting of titles, reviewing abstracts and full-length papers to identify the papers relevant to the review question. My main role, however, was to extract the psychometric evidence and assess the methodological quality of each PROM in the papers identified.

2.3 Psychometric criteria

The psychometric criteria used for assessing the included studies in the systematic reviews were adapted by the authors from published recommendations **(14, 49-53)**. The criteria were mainly based on the US Department of Health Food and Drug Administration (FDA) PROMs development guidelines, the COSMIN checklist (Consensus-based Standards for the selection of health status Measurement instruments) and the University of Oxford PROMs development criteria **(14, 49-53)**. The properties that were assessed for each tool can be divided into the following four areas: reliability, validity, responsiveness and acceptability. I reviewed the quality of evidence for internal consistency, test retest reliability, content validity, criterion validity, responsiveness, floor-ceiling effects and acceptability. Previous studies have used similar methods to evaluate the methodological quality of PROMs **(54).**

The group previously used the COSMIN checklist **(47)** to examine the psychometric evidence of each PROMs. The COSMIN checklist used to evaluate the methodological quality of studies on measurement properties of health status measurement instruments, can also be used as guidance for designing or reporting a study on measurement properties **(58)**. However, the authors of COSMIN accept that it was not developed as criteria of adequacy of measurement properties of PROMs **(58)**. Other limitations of the COSMIN checklist are that it is very long, and responsiveness parameters such as effect sizes, standardized response means, or Guyatt's responsiveness ratio, and other well-known parameters in common use are described as "inappropriate" **(59)**. This contradicts the literature on developing PROMs in previous decades **(59)**. It is also worthwhile to note that most PROMs for vascular conditions

were developed using statistical responsiveness methods such as effect size and standardized response means.

The chosen psychometric criteria to measure the validity, reliability and responsiveness were mainly based on classical test theory (CTT) and almost no parameters from the item response theory (IRT). This was in part because it was based on the presumption that most vascular PROMs were developed using CCT and before the advances in IRT and its application to develop modern PROMs. The five systematic reviews later confirmed this assumption.

The first two papers of this PhD presented in chapter 3 and 4 provide an overview of the efforts to identify PROMs for direct inclusion in ePAQ-VAS. These two systematic reviews were based on database searches that identified 3787 papers. The aim was to identify the best PROMs for use for patients with venous insufficiency. However, due to the heterogeneity of PROMs and the volume of the papers found, it was decided that two separate systematic reviews would be used to identify the most appropriate PROMs for patient with VVs and VLU. The latter conditions were chosen because they were the most frequent venous conditions treated in vascular units within the NHS.

2.4 Summary of paper 1

In the next chapter, the systematic review identifies and examines the psychometric evidence for PROMs used in patients with varicose veins. The databases were searched from inception to July 2016 and identified a total of 3787 records; following the review process, only nine studies were identified **(57-65)**. These nine studies reported on four PROMs, one generic and three condition-specific PROMs. The generic instrument was the 36-Item Short-Form Health Survey (SF-36®; Optum, Eden Prairie, Minnesota, USA) **(58-59)**. The condition-specific instruments were the Aberdeen Varicose Vein Questionnaire (AVVQ) **(57-62)**, the Varicose Veins Symptoms Questionnaire (VVSymQ®; BTG International, London, UK) **(63-64)**, and the Specific Quality-of-life and Outcome Response – Venous (SQOR-V) **(65)**.

This study reported that AVVQ was the most rigorously evaluated PROMs in patients with varicose veins, this tool has 13 items including 12 questions and a set of manikin legs; the total score ranges from 0 to 100 **(57-62)**. AVVQ was developed with input from clinicians and then tested for relevance and validity in a survey of patients. The items were not developed based on primary or secondary qualitative data; they were designed by researchers and confirmed by two consultant surgeons. AVVQ

was tested for internal consistency, construct and criterion validity, and acceptability. Internal consistency is a measure of the correlations between different items within a domain or scale of PROMs and whether they measure what they propose to measure. The results of internal consistency analysis for AVVQ was a Cronbach's alpha (α) of 0.72 after removing five items.

The items were removed based on internal consistency calculations only as AVVQ did not undergo any factor analysis during its development. The construct validity was tested using multiple regression and comparison with the Varicose Vein Severity Score. The evidence for acceptability of AVVQ were limited and not much information was given about missing data or the response rate **(57)**. The criterion validity of the AVVQ was assessed by comparing it to SF-36® in patients with varicose veins; it was assumed at the time of the study that the SF-36® was the gold standard. AVVQ had negative correlations with all eight scales of the SF-36® **(60)**. Four of these correlations, including physical functioning, pain, social functioning and role limitations, suggest that AVVQ can assess the adverse effects of varicose veins better than the SF-36® **(60)**. The test–re-test reliability was assessed by asking patients to complete this tool at baseline and at two weeks. The responsiveness of the AVVQ to changes in health over time was assessed by administering the questionnaire to the same respondents at baseline and one year after open surgery. The standardized response means in all items showed improvement after one year **(60)**. For more details about the results of this systematic review please see chapter three of this thesis.

2.5 Critical assessment of the AVVQ

AVVQ was found to be the most validated disease-specific instrument, although there were issues surrounding its content validity and acceptability. The instrument was developed by clinicians and confirmed by two researchers; almost all the international guidelines stress the importance of input from patients when developing the items and the conceptual framework of PROMs **(49-55)**. Furthermore, a common problem with AVVQ is calculating the scores, which is linked to the weighting given to the distribution of varicose vein on the body using a body image on the questionnaire. The clinical relevance of the weighting and score given to each body part is questionable. The AVVQ, therefore, was not chosen for direct inclusion into ePAQ-VAS. The framework and domains in identified

PROMs were used when developing the conceptual framework of ePAQ-VAS and the relevant VVs questions.

2.6 Summary of paper 2

The aim of paper 2 was to recommend the most appropriate disease-specific PROMs for patients with VLU group to be included in ePAQ-VAS directly. If this was not possible, then the aim was to identify the scales/domain of the identified PROMs to be used in the analysis of the qualitative data and for developing disease-specific scales for ePAQ-VAS. Ten studies were identified following sifting of the titles, then the review of full-text articles. These studies reported on the development and validation of ten PROMs including, four generic and six disease-specific conditions **(66-75)**. The generic PROMs were Nottingham Health Profile (NHP), 12-item Short-Form Health Survey (SF-12®), 36-item Short-Form Health Survey (SF-36®), EuroQol Five Dimensions Questionnaire (EQ-5D™). The disease-specific tools were Hyland questionnaire, Venous Leg Ulcer Self-Efficacy Too (VeLUSET), Venous Leg Ulcer Quality of Life questionnaire (VLU-QoL), Sheffield Preference-based Venous Ulcer-5D questionnaire (SPVU-5D), Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms (VEINES-QOL/Sym) and Charing Cross Venous Ulcer Questionnaire (CXVUQ). The most appropriate generic and condition-specific PROMs were the NHP and the VLU-QoL. NHP showed excellent responsiveness, construct validity and acceptability. The evidence for the internal consistency of NHP was mixed with some items not fulfilling the methodological standards as set within the systematic review **(67)**. VLU-QoL was the instrument with the most evidence of validity; the items were developed based on themes generated from focus group and in-depth interviews with patients with VLUs. This instrument had good internal consistency, good criterion and construct validity. VLU-QoL, however, was reported to have poor responsiveness **(69)**. The responsiveness of identified PROMs was examined by assessing whether these studies reported standardized response means, t-test, effect size and Guyatt's responsiveness ratio **(54, 78-80).** The poor responsiveness of VLU-QoL could be because of the short interval between the baseline measurement and post-intervention testing, or it could be due to the small sample size in the study **(69)**. For more details about the results of this systematic review please see chapter four of this thesis.

2.7 Relevance of paper 2 in the development of the ePAQ-VAS

The evidence from this paper was used for the analysis of the qualitative data in the qualitative evidence synthesis review for patients living with VLU. The framework and the items within these tools were used in a triangulation study; the evidence from the triangulation evidence was used to develop the conceptual framework of ePAQ-VAS.

In summary, five systematic reviews were conducted to identify validated PROMs for patients with PAD, AAA, VLU, VV and CAD. A total of 33 PROMs that had undergone some form of validation were identified in 41 studies **(35-36, 46-48)**. In this PhD, two of these five published reviews are included. The evidence from the reviews suggested that none of the PROMs had undergone sufficiently rigorous development and validation. Even when there was some evidence, it fell short of the set criteria **(14, 49-54)**. The evidence from these reviews was used to inform other aspects of developing ePAQ-VAS; for instance, the scales or domains of the identified PROMs were used to help develop the conceptual framework of ePAQ-VAS.

Chapter Three. Paper 1 "Systematic review of patient-reported outcome measures in patients with varicose veins".

Systematic review of patient-reported outcome measuresin patients with varicose veins

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Background: Varicose veins can affect quality of life. Patient-reported outcome measures (PROMs) provide a direct report from the patient about the impact of the disease without interpretation from clinicians or anyone else. The aim of this study was to examine the quality of the psychometric evidence for PROMs used in patients with varicose veins.

Methods: A systematic review was undertaken to identify studies that reported the psychometric properties of generic and disease-specific PROMs in patients with varicose veins. Literature searches were conducted in databases including MEDLINE, up to July 2016. The psychometric criteria used to assess these studies were adapted from published recommendations in accordance with US Food and Drug Administration guidance.

Results: Nine studies were included which reported on aspects of the development and/or validation of one generic (36-Item Short Form Health Survey, SF-36®) and three disease-specific (Aberdeen Varicose Vein Questionnaire, AVVQ; Varicose Veins Symptoms Questionnaire, VVSymQ®; Specific Quality-of-life and Outcome Response – Venous, SQOR-V) PROMs. The evidence from included studies provided data to support the construct validity, test– retest reliability and responsiveness of the AVVQ. However, its content validity, including weighting of the AVVQ questions, was biased and basedon the opinion of clinicians, and the instrument had poor acceptability. VVSymQ® displayed good responsiveness and acceptability rates. SF-36® was considered to have satisfactory responsiveness and internal consistency.

Conclusion: There is a scarcity of psychometric evidence for PROMs used in patients with varicose veins. These data suggest that AVVQ and SF-36® are the most rigorously evaluated PROMs in patients with varicose veins.

Introduction

Varicose veins are enlarged lumpy visible veins caused by reflux of blood in the superficial veins of the leg[1]. They are extremely common, affecting more than half of the population in Western Europe and North America[2–4]. Varicose veins can cause symptoms such as pain, aching, swelling, throbbing, cramping, itching and bleeding[5]. Complications include superficial thrombophlebitis, external bleeding, lipodermatosclerosis, eczema and ulceration[6,7]. Traditionally, treatment comprised surgery with stripping of the great saphenous vein and removal of the varicose

veins through small incisions (avulsions or phlebectomies). However, in the past decade new less invasive treatments have been developed[8]. In 2009– 2010, 35 659 varicose vein procedures were carried out in the National Health Service (NHS)[8].

Patient-reported outcome measures (PROMs) provide a means by which the impact of varicose veins or their treatments on quality of life can be measured. The questionnaires are typically developed from qualitative studies involving patients and clinicians. The items in these questionnaires are then tested for their ability to capture the patient's experience in prospective surveys,

using psychometric analyses to explore the relationship of the items with each other and their overall ability to detect change[9]. The NHS PROMs programme has been collecting PROMs data from patients undergoing varicose vein interventions since April 2009 using generic and disease-specific PROMs[10].

The aim of this study was to identify and examine the quality of the psychometric evidence for PROMs used in patients with varicose veins. This study was divided into two parts; initially a systematic review was undertaken to identify the appropriate papers, and then a psychometric assessment was undertaken to assess the quality of the methods used to validate or design these PROMs.

Methods

A systematic review was undertaken and reported in accordance with the general principles recommended in the PRISMA statement[11]. The protocol for the systematic review was developed and registered in the PROSPERO international prospective register of systematic reviews before the start of the data extraction[12].

Systematic searches were undertaken in MEDLINE and MEDLINE In-Process, Embase, the Cochrane Library, CINAHL, PROQOLID, PsycINFO and Web of Sci- ence. A two-stage search approach was used. The first stage used general terms for PROMs (known generic and condition-specific PROMs) and terms for the condition (varicose veins) to identify studies. These were retrieved, and the title and abstract examined for additional PROM terms used in patients with varicose veins. The second stage incorporated these terms with the preliminary search strategy and a methodological search filter for finding studies on measurement properties. Databases were searched from inception up to July 2016 for search 1 and for search 2. Searches were supplemented by hand-searching reference lists of relevant reviews and included studies, citation search of included studies and contact with experts in the field. Search strategies are shown in *Appendix S1* (supporting information).

Study selection

The titles were reviewed, and the abstracts and full text of the included articles were assessed by at least two reviewers independently. Any disagreements in the selection process were resolved by discussion, with involvement of a third reviewer. Eligible studies included articles published in English of any study design that reported the validation or development of PROMs capturing quality of life, health status or functional limitation in patients with varicose veins in an English-speaking population (*Table 1*).

Data abstraction

Data relating to study design, patient characteristics, type of treatment, PROM used, methods and outcomes were extracted by one reviewer on to a standardized data extraction form, and independently checked for accuracy by a second. Any discrepancies were resolved by discussion, with involvement of a third reviewer. Where necessary, study authors were contacted for missing information or additional data.

Methodological quality assessment (psychometric evaluation)

The methodological quality assessment in developing the PROMs was based on specific psychometric criteria. Owing to lack of consensus on how to appraise PROMs, the study-specific criteria were adapted from published recommendations[13–17] in accordance with US Food and Drug Administration (FDA) guidance 2009[18]. They were mainly based on the Oxford University PROMs Group guidelines and the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN)[19]. These criteria can be divided into four areas: reliability, validity, responsiveness and acceptability (*Table 2*). Two independent researchers appraised these psychometric properties for each PROM independently using the following methods of assessment. A rating scale was designed to allocate a mark for each domain: 0, not reported; –, evidence not in favour; +/–, conflicting evidence; and +, evidence in favour. Any disagreements were resolved through discussion or with involvement of a psychometrics expert.

Assessment of reliability

The reliability of a PROM is its ability to produce the same results when measurements are repeated in populations with similar characteristics[20]. The reliability of each identified PROM was assessed by examining the reported data on reproducibility and internal consistency. The reproducibility of an instrument is commonly examined by performing test– retest at different time points. The degree of correlation is examined between the scores at baseline and those at different time points. PROMs should report test– retest using the intraclass correlation or weighted κ score; this should be at least 0.70 for group comparisons[20].

PROMs commonly use more than one item to measure a single dimension that is important to the patient; this is because several related observations can produce a better estimate than one. These items need to be homogeneous; this means that they all measure aspects of a single attribute rather than different ones and are therefore internally

Table 1 Criteria for considering eligibility of studies

	Inclusion criteria	Exclusion criteria
Population	A defined population of English-speaking participants with a diagnosis of varicose veins	Undefined population of patients with chronic venous disease *or* Non-English-speaking patients with varicose veins
Interventions	No intervention or any intervention indicated for varicose veins	
Outcomes	PROMs covering any of the following: generic or preference-based measures, e.g. EQ-5D™, SF-6D®, SF-36®; directly elicited preference-based measures, e.g. time-trade-off, standard gamble utility values; condition-specific outcome measures; functional outcome measures English version of PROMs	Outcome measures of patient satisfaction or experience, or outcome measures obtained from proxies, carers or health providers Non-English versions of PROMs
Study type	Published validation studies, other than linguistic validation of English versions of relevant PROMs Publication in English	Unpublished studies Studies of linguistic validation of PROMs Review articles, letters, commentaries, abstracts Non-English publications

PROM, patient-reported outcome measure; EQ, EuroQol; SF, Short Form.

Table 2 Psychometric criteria used to assess the quality of the patient-reported outcome measures included in this study

Domain	Criteria
Test–retest reliability	Test–retest: the intraclass correlation/weighted κ score should be ≥0·70 for group comparisons and ≥0·90 if scores are going to be used for decisions about an individual based on their score[19] The mean difference (paired *t* test or Wilcoxon signed-rank test) between time points 1 and 2, and the 95% c.i. should also be reported[12,13]
Internal consistency	A Cronbach's α score of ≥ 0·70 is considered good, and it should not exceed ≥ 0·92 for group comparisons as this is taken to indicate that items in the scale could be redundant. Item total correlations should be ≥0·20[14,20]
Content validity	This is assessed qualitatively during the development of an instrument. To achieve good content validity, there must be evidence that the instrument has been developed by consulting patients and experts as well as undertaking a literature review[20] Patients should be involved in the development stage and item generation. The opinion of patient representatives should be sought on the constructed scale[12–14]
Construct validity	A correlation coefficient of ≥ 0·60 is taken as strong evidence of construct validity. Authors should make specific directional hypotheses and estimate the strength of correlation before testing[12–14]
Criterion validity	A good argument should be made as to why an instrument is standard and correlation with the standard should be ≥0·70[15–17,19]
Responsiveness	There are a number of methods to measure responsiveness, including *t* tests, effect size, standardized response means or Guyatt's responsiveness index. There should be statistically significant changes in score of an expected magnitude[21,22]
Floor and ceiling effects	A floor or ceiling effect is considered if 15% of respondents are achieving the lowest or the highest score on the instrument[12,13]
Acceptability	Acceptability is measured by the completeness of the data supplied; ≥80% of the data should be complete[12]

consistent[13]. Internal consistency is usually measured using Cronbach's α, which should have a value of more than 0·70 and less than 0·90 for the proposed PROM to be psychometrically sound[13,23].

Assessment of validity

Validity is the measure of how well a PROM measures what it is intended to measure. Validity was assessed for each identified PROM by assessing content validity, construct validity and criterion validity. Content validity was measured by examining the relevance of the items in the PROM to their intended use. This was assessed on the basis of whether these items were developed through qualitative studies with patient groups involving clinicians and incorporating published evidence[23]. Criterion validity is concerned with assessing the PROM in question against a standard PROM that provides a benchmark of the true values. The new PROM should demonstrate correlation coefficient scores of more than 0·70. However, in reality this is often very difficult to assess in the absence of such a standard[14,15].

Assessment of responsiveness

This is defined as the ability of a PROM to detect clinically important change over time, if a true change exists. The PROM should be able to distinguish between clinically important changes and measurement error. Responsiveness
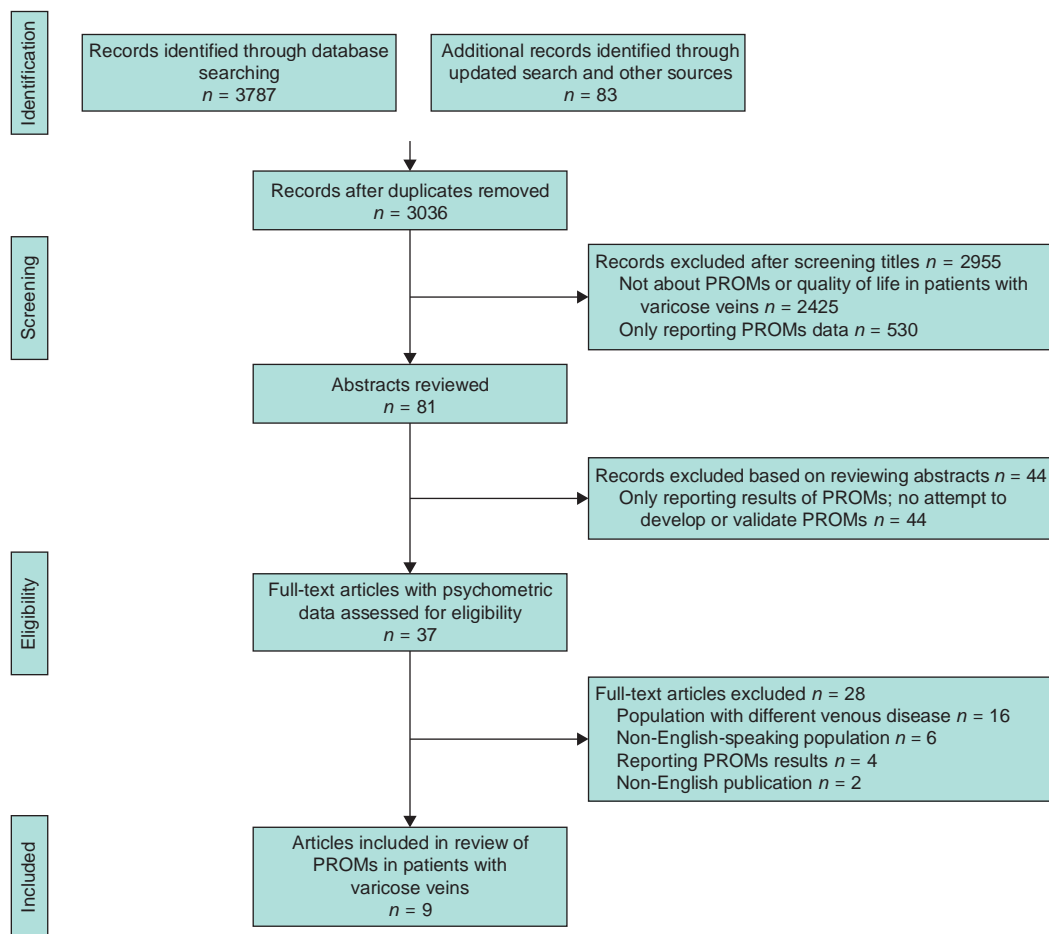
Fig. 1 PRISMA diagram showing selection of studies for review of patient-reported outcome measures (PROMs) in patients with varicose veins.

of a measure can be calculated using methods such as standardized response means, *t* test, effect size and Guyatt's responsiveness ratio[21,22,24].

Assessment of acceptability and floor or ceiling effect
Acceptability is measured by the completeness of the data. For a PROM to show a good level of acceptability, 80 per cent or more of the data should be complete when the PROM is administered to patients[19]. A floor or ceiling effect is considered if 15 per cent of respondents are achieving the lowest or the highest score on the instrument.

Results

A total of 3787 records were identified; following detailed examination, nine studies[25–33] (reporting on 4 PROMs) were included (*Fig. 1*). PROMs that were not specific for varicose veins and examined chronic venous disease in general were excluded; examples of these are the ChronIc Venous Insufficiency quality of life Questionnaire (CIVIQ)-20 and CIVIQ-14, both chronic venous disease PROMs, and the Venous Insufficiency Epidemiologic and Economic Study – Quality of Life/Symptoms (VEINES-QOL/Sym), a PROM validated in patients with deep venous thrombosis and venous leg ulcers.

All the included studies assessed the psychometric properties and suitability of the suggested PROMs in patients with varicose veins (*Table 3*). The studies were prospective in design, and were undertaken in the UK and USA. They were published between 1993 and 2016. The majority of the studies were of a small to moderate size with the number of patients ranging from 40[33] to 1700[26,27]. Patients aged between 16 and 86 years were recruited in the included studies, with the proportion of men ranging from 24 per cent[25] to 48 per cent[29].

Table 3 Studies reporting validation of patient-reported outcome measures in patients with varicose veins

Reference	Country	Treatment	Type of study	Sample size	Age (years)*	Men (%)	Reported PROM(s)	Timing of PROM(s) assessment
Garratt et al.[25]	UK	Usual care	PDVS	373	45·8	24	AVVQ/SF-36®	Administered once
Garratt et al.[26]	UK	Usual care	PDVS	1700	42·7	33·5	SF-36®	2 weeks after baseline
Garratt et al.[27]	UK	Usual care	PDVS	1700	47·9	39·8	SF-36®	Baseline and after 1 year
Garratt et al.[28]	UK	Usual care	PDVS	373	45·8	46·1	AVVQ/SF-36®	2 weeks and 12 months after baseline
Lattimer et al.[30]	UK	EVLA *versus* UGFS	RCT	100	n.r.	42	AVVQ	Baseline, 3 weeks and 3 months
Lattimer et al.[29]	UK	EVLA *versus* UGFS	RCT	84	47·5†	48	AVVQ	Baseline, 3 weeks and 3 months
Paty et al.[31]	USA	EMA and PEM	RCT	395	49·6	26·8	VVSymQ®	Baseline and 8 weeks (daily)
Shepherd et al.[32]	UK	RFA only	PDVS	317	48·9	28·4	AVVQ, SQOR-V	Baseline and 6 weeks
Wright et al.[33]	USA	EMA and PEM	RCT	40	49·7	38	VVSymQ®	Baseline and 8 weeks (daily)

*Mean values except †median. PROM, patient-reported outcome measure; PDVS, PROM development and validation study; AVVQ, Aberdeen Varicose Vein Questionnaire; SF-36®, 36-Item Short Form Health Survey; EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy; n.r., not reported; EMA, endovenous microfoam ablation; PEM, polidocanol endovenous microfoam; VVSymQ®, Varicose Veins Symptoms Questionnaire; RFA, radiofrequency ablation; SQOR-V, Specific Quality-of-life and Outcome Response – Venous.

Patient-reported outcomes measurement data and psychometric evaluation

Overall, data relating to the development and psychometric evaluation of one generic PROM and three condition-specific PROMs for patients with varicose veins were available. The only generic PROM evaluated was the 36-Item Short Form Health Survey (SF-36®; Optum, Eden Prairie, Minnesota, USA)[26,27]. The condition-specific PROMs were the Aberdeen Varicose Vein Questionnaire (AVVQ)[25,28 – 30,32], the Varicose Veins Symptoms Questionnaire (VVSymQ®; BTG International, London, UK)[31,33] and the Specific Quality-of-life and Outcome Response – Venous (SQOR-V)[32].

The protocol regarding timing of PROMs differed between the studies. The shortest follow-up was immediately following the intervention and the longest was 12 months after treatment. The rigour of the psychometric assessment of the PROMs was variable. The AVVQ was the only instrument evaluated in detail, with assessment of all the important psychometric domains (*Table 4*).

Short Form 36-Health Survey

Garratt and colleagues[25 – 28] assessed aspects of the psychometric validity of this generic instrument in patients with varicose veins. In a study of 1700 patients, including 314 with varicose veins, the SF-36® was examined for its suitability as a PROM for patients treated in the NHS. The internal consistency was assessed using two techniques, item scale correlation and Cronbach's α. The first method examined the extent to which an item was related to the rest of the scale, whereas Cronbach's α measured the overall correlation between items in the scale. The correlation for all items was above 0·4, providing evidence of internal

consistency. The Cronbach's α value exceeded 0·8 and satisfied the criteria for internal consistency. The response rate for the SF-36® in this study at baseline was 75·5 per cent, showing some evidence of acceptability for this PROM; however, this dropped to 67·5 per cent after 1 year. The construct validity assessment used ordinary least regression to estimate the effect on each scale in the PROM of varicose veins, age, sex and socioeconomic status of the participants. The impact of varicose veins was significant only on the physical functioning scale. The responsiveness of SF-36® was assessed in the same population after 12 months, with results showing good responsiveness for this PROM. The standardized response mean was used to measure this property, and patients with varicose veins had a significantly higher level of improvement across the SF-36® scales at 1 year than those not referred for treatment.

Aberdeen Varicose Vein Questionnaire

This disease-specific PROM was developed by Garratt *et al.*[25], and the items were generated based on questions commonly used to assess patients with varicose veins. The items generated were confirmed by two clinicians and then pretested in patients for relevance and validity[25]. The AVVQ was tested for internal consistency, construct and criterion validity, and acceptability. The result of internal consistency evaluation after removing five questions that did not fulfil the criteria was a Cronbach's α value of 0·72, satisfying the psychometric criterion for this PROM[34]. The construct validity of the instrument was tested using stepwise multiple regression and comparison with the Varicose Vein Severity Score. The regression model confirmed that AVVQ explains a substantial proportion of the non-random variation in the patients' perceived health. The AVVQ showed high acceptability

Table 4 Summary of the psychometric properties of patient-reported outcome measures in patients with varicose veins

Reference	Internal consistency	Test–retest reliability	Content validity	Criterion validity	Construct validity	Responsiveness	Floor/ceiling effect	Acceptability
Psychometric and operational criteria								
Generic PROMs								
SF-36®								
Garratt *et al.*[26]	+	0	?	0	+/–	+/–	0	+
Garratt *et al.*[27]	0	0	0	0	0	+	0	+/–
Disease-specific PROMs								
AVVQ								
Garratt *et al.*[25]	+	0	+/-	+	+	0	0	+/–
Garratt *et al.*[28]	0	+	0	0	0	+	0	+/–
Shepherd *et al.*[32]	0	–	0	+	–	+/–	0	+/–
Lattimer *et al.*[29]	0	0	0	0	0	+	0	0
Lattimer *et al.*[30]	0	0	0	0	0	?	0	0
VVSymQ®								
Paty *et al.*[31]	+	0	0	+	0	+	+/–	+
Wright *et al.*[33]	+	+	+	+/–	+	+	0	+
SQOR-V								
Shepherd *et al.*[32]	0	–	0	+	–	+/–	0	+/–

0, Not reported (no evaluation completed); –, evidence not in favour; +/–, weak evidence; +, evidence in favour; ?, methodology questionable. PROM, patient-reported outcome measure; SF-36®, 36-Item Short Form Health Survey; AVVQ, Aberdeen Varicose Vein Questionnaire; VVSymQ®, Varicose Veins Symptoms Questionnaire; SQOR-V, Specific Quality-of-life and Outcome Response –Venous.

among patients with 76 per cent complete data when the PROM was administered[25]. The criterion validity of the AVVQ was assessed by comparing it with eight scales of the SF-36® in patients with varicose veins; the AVVQ achieved highly negative correlations with all eight scales of the SF-36®[28]. Four of these correlations exceeded 0·4, including physical functioning, pain, social functioning and role limitations. These correlations suggest that AVVQ can pick up adverse effects of varicose veins better than the generic PROM SF-36®. The test– retest reliability assessment of this PROM showed an intraclass correlation coefficient of above 0·7 in all domains except one, in which patients reported no change in symptoms after 1 year. The responsiveness of the AVVQ to changes in health over time was assessed by administering the questionnaire to the same respondents after 1 year[28]. In an analysis of standardized response means over 1 year, all items showed improvement, especially for patients who received treatment; patients not referred to a specialist had lower perceived health compared with the general population[28].

Lattimer and colleagues[30] attempted to examine the responsiveness of the AVVQ in patients receiving endogenous laser ablation or foam sclerotherapy for varicose veins as part of an RCT. The patients included in the study allhad primary disease with no previous intervention. The Wilcoxon signed-rank test was used to compare differences within the same group before and after intervention. Spearman's ρ was used to assess the correlation between the severity of symptoms and AVVQ outcomes. The study reported improved AVVQ score after 3 weeks and 3 months of follow-up[29,30].

Varicose Veins Symptoms Questionnaire
This electronic PROM was developed in accordance with FDA guidance[18]. This included qualitative studies that involved patients to generate the five items in the PROM, all related to symptoms alone. The psychometric properties were examined as part of two RCTs (VANISH-1 and VANISH-2) evaluating microfoam ablation with varying doses of polidocanol endovenous microfoam in patients with varicose veins[31,33]. Test – retest reliability was examined using intraclass correlation coefficients to assess whether VVSymQ® yielded a reproducible score in patients exhibiting no change in health status. The reported intraclass correlation coefficient was 0·75, demonstrating acceptable test– retest reliability. Cronbach's α value was 0·76 showing good internal consistency of the items included in the PROM. The construct validity was evaluated through Pearson correlation analyses; the score from the PROM showed correlations with reported clinical outcomes[31]. The VVSymQ® score captured meaningful clinical change and treatment impact, with an effect size of 1·6 when the scores were compared between baseline and 6 weeks after intervention. This electronic PROM had between 86·1 and 97 per cent data completion, reflecting good acceptability among the patients[31,33].

Specific Quality-of-life and Outcome Response – Venous
This instrument consists of 46 items divided into five domains: physical discomfort, appearance, restriction in movement, emotional problems and threat to health. All patients in the study[32] underwent radiofrequency ablation. The performance of the PROM was tested against the AVVQ and other clinical outcomes. The scores from the AVVQ and SQOR-V showed strong positive correlation with a Spearman coefficient of $0·702$ ($P < 0·001$). Responsiveness was tested at 6 weeks, with poor results for SQOR-V in some patient groups compared with the AVVQ. The acceptability, as measured by the completeness of the data, was weak (67 per cent complete data)[32].

Discussion

This study identified PROMs that have undergone validation in patients with varicose veins, and assessed the methodology of psychometric validation in accordance with FDA guidance, Oxford University PROMs Group guidelines and COSMIN[13–19]. Patient-reported outcome is an important core outcome recommended to be collected as part of service analysis and clinical studies[35–37]. Clinicians and researchers are faced with a dilemma when deciding on the instrument that measures this outcome. In the UK NHS, the measures used to collect data on PROMs for patients undergoing surgical management for varicose veins are the AVVQ and EuroQoL Five Dimensions (EQ-5D™; EuroQol Group, Rotterdam, The Netherlands[38].

This review identified only one generic measure (SF-36®) and three disease-specific instruments (AVVQ, VVSymQ®, SQOPR-V) that have undergone psychometric assessment in patients with varicose veins. The evidence suggests that the SF-36® exhibits good internal consistency and acceptability among patients with varicose veins, with some evidence of construct validity and responsiveness. The AVVQ had good test–retest reliability, construct and criterion validity, and responsiveness. However, the evidence for the content validity was weak, and clinicians and researchers generated the items with limited input from patients; the weighting of the items was based on the judgement of two clinicians. VVSymQ® had good internal consistency, test–retest reliability, construct, content and criterion validity, and responsiveness. The acceptability of the VVSymQ® was better than that of the AVVQ and SF-36®; this is in part because it is an electronic questionnaire; however, the only domain in this instrument is symptoms.

The main strength of this study was the use of comprehensive search strategies to identify all relevant papers

that reported on psychometric validation of PROMs for patients with varicose veins. The psychometric assessment domains in this study were based on different but overlapping psychometric evaluation criteria[16,18,19,38]. The main limitation of the analysis was the heterogeneity of the patients included in the studies as well as the different protocols for administering the PROMs. Furthermore, the content validity of the disease-specific measures was based on information limited to either that gathered by consulting a small number of patients about items generated by researchers and clinicians, or data from small qualitative research studies, with no systematic review of the qualitative evidence[25,27–31,33]. None of the studies included in the review provided any information on how they dealt with missing data.

The only generic PROM with psychometric evidence to support its use in patients with varicose veins was the SF-36®; no data on the EQ-5D™ were found. The AVVQ was the most evaluated disease-specific PROM, with five studies examining its psychometric validity. Further work is needed to improve the content validity and acceptability of PROMs used in patients with varicose veins. The authors also recommend further research on the use of electronic PROMs based on the acceptability data for the VVSymQ®.

Acknowledgements

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Supporting information

Additional supporting information may be found online in the supporting information tab for this article.

Appendix S1 Search strategy (Word document).

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Chapter Four. Paper 2 "Systematic review assessing the measurement properties of patient-reported outcomes for venous leg ulcers".

Systematic review assessing the measurement propertiesof 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™), Nottingham Health Profile (NHP) and 12-item Short-Form Health Survey (SF-12®) had good acceptability. In general, the EQ-5D™ 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 (VeLUSET).

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.

Introduction

Venous leg ulcers (VLUs) are associated with considerable morbidity and health costs[1,2]. They are the most common kind of chronic leg ulcers; up to 70 per cent of such ulcers are caused solely by venous disease[3,4]. Open unhealed VLUs have estimated point prevalence ranging from 0·1 to 0·3 per cent in the UK[5–7]. They are common in the elderly but relatively rare among patients aged less than 45 years[7,8].

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[8]. 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[9,10]. Even so, there is high risk of recurrence, with some studies reporting a recurrence rate of 45 per cent[11]. Treatment of VLUs is usually associated with high healthcare costs[12]. 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[13].

Healthcare expenditure, patient-reported outcome measures (PROMs) and patient satisfaction are closely related[14]. 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[15,16]. 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) in line with recommendations of the PRISMA statement[17].

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 adaptions and translations of PROMs[18], 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[19,20], University of Oxford PROMs development criteria and other studies[21–28]. 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[29,30]. 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 *t* test or Wilcoxon signed-rank test)[21]
	Internal consistency	Cronbach's α score of ≥ 0.70 indicates good evidence, but the score should not exceed ≥ 0.92 for group comparison
		Item total correlations should be ≥ 0.20[23]
Validity	Content validity	Evidence that the instrument has been developed by undertaking a literature review, consulting patients, clinicians and other experts[19,21,23,26,28]
	Construct validity	Correlation coefficient of ≥ 0.60 indicates strong evidence
		This should be supported by specific directional hypotheses and a previous estimation of strength of correlation[19,21–23,26,28]
	Criterion validity	Justification for selection of standard should be adequate
		Correlation between PROM and standard ≥ 0.70[22]
Responsiveness	Responsiveness	Statistically significant changes in score of an expected magnitude based on methods including *t* tests, effect size, standardized response means, Guyatt's responsiveness index or responsiveness statistics[19,21,26,27]
Acceptability	Floor/ceiling effects	Evidence of floor effect: 15 per cent of respondents are achieving the lowest score on the instrument[19,22]
		Evidence of ceiling effect: 15 per cent of respondents are achieving the highest score on the instrument[19,22]
	Acceptability	Completeness of data supplied ≥ 80 per cent[24,27,28]

PROM, patient-reported outcome measure.

Results

Identified studies

A total of 3870 records were retrieved from searches (*Fig. 1*). Ten studies[31–40] (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[36], 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[33,37,39]. Timing of the PROMs administration also varied across studies. One study[37] reported PROMs data collection at baseline only, whereas the majority reported data collection at baseline and 3 months[33,35,36,39,40]; fewer studies collected PROMs data at 12 months[35,40].

Four studies[32,34,38,39] described the development and validation of the Sheffield Preference-based Venous Ulcer-5D questionnaire (SPVU-5D)[38], CXVUQ[39], Venous Leg Ulcer Self-Efficacy Tool (VeLUSET)[32]

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

A summary of psychometric properties (*Table 3*) revealed that none of the PROMs identified fulfilled all the psycho-metric 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
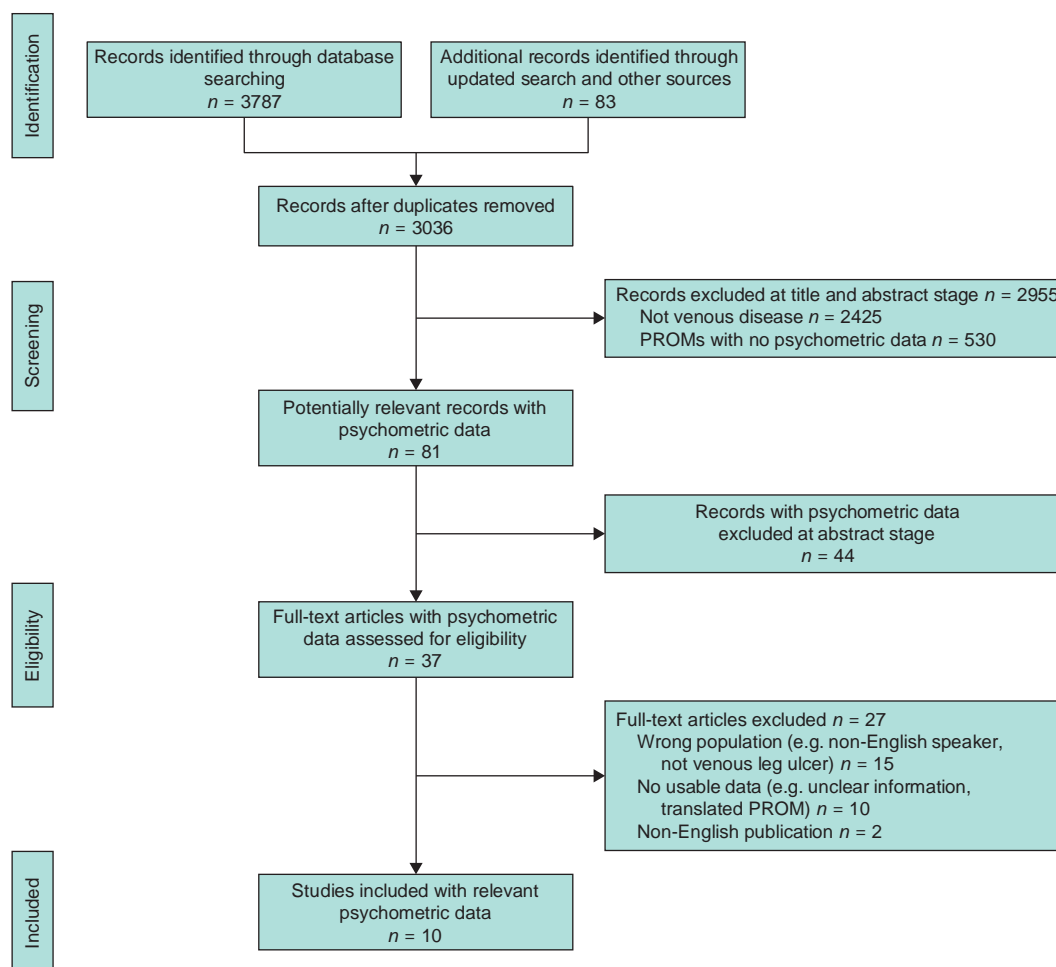
Fig. 1 PRISMA diagram selection of studies for review. PROM, patient-reported outcome measure

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[41]. The responsiveness and acceptability of this instrument were examined as part of the HALT (Honey as Adjuvant Leg Ulcer Therapy) trial[36], VenUS I (Venous Ulcer Study I) study[35] and also by Walters and colleagues[40]. All three studies[35,36,40] 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[40] 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[40] 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 α 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 et al.[31]	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 et al.[32]	PDVS	VeLUSET	Healed or recurrent ulcer of venous or mixed aetiology (205)	74·1	47·8	Usual care	Baseline and 4 weeks
Franks and Moffatt[33]	Non-RCT	NHP SF-36®	Chronic venous leg ulcers (383)	74†	36·6	Compression bandaging	Baseline and 12 weeks
Hareendran et al.[34]	PDVS	VLU-QoL	Active venous leg ulcers (160)	72	31	Compression bandaging	Baseline and 8 weeks
Iglesias et al.[35]	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 et al.[36]‡	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[37]	PDVS	SPVU-5D	Active and chronic venous leg ulcers (152)	66·6	n.r.	Usual care	Baseline
Palfreyman et al.[38]	PDVS	SPVU-5D	Active and chronic venous leg ulcers (19)	n.r.	n.r.	Usual care	n.r.
Smith et al.[39]	PDVS	SF-36® CXVUQ	Active venous leg ulcers (98)	76†	34	Usual care	Baseline, 6 and 12 weeks
Walters et al.[40]	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; VeLUSET, 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[40].

The psychometric properties of this instrument were also examined as part of the HALT trial[36] 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)[35] assess- ing 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 sizewas found to be statistically significant at 6 and 12 monthsfor the MCS only; the change in PCS scores was not significant regardless of whether VLUs healed or not[35].

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[33]. 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[33]	+/−	0	0	0	+	+	−	+
SF-12®								
Iglesias et al.[35]	0	0	0	0	0	+/−	0	+
SF-36®								
Walters et al.[40]	−	0	0	0	−	−		+
Jull et al.[36]	0	0	0	0	0	+/−	0	+
EQ-5D™								
Walters et al. [40]	0	0	0	0	0	−	+	+
Iglesias et al.[35]	0	0	0	0	0	−	0	+
Jull et al.[36]	0	0	0	0	0	−	0	+
Condition-specific PROMS								
VeLUSET								
Brown et al.[32]	+/−	+	+	0	0	0	0	−
VLU-QoL[34]								
Hareendran et al.[34]	+	+	+	+	+	+/−	+	+/−
Hyland questionnaire								
Iglesias et al.[35]	0	0	0	0	+/−	+/−	0	−
SPVU-5D								
Palfreyman et al.[38]	0	0	+	0	0	0	0	0
Palfreyman[37]	+/−	0	+	0	0	0	0	0
VEINES-QOL/Sym								
Bland et al.[31]	+	+/−	0	+/−	+	+	−	+
CXVUQ								
Smith et al.[39]	+/−	+/−	+	+	0	+	−	−
Jull et al.[36]	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®, 12-item Short Form Health Survey; SF-36®, 36-item Short Form Health Survey; EQ-5D™, 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 α value was less than 0·7 when all items were considered. However, most items in individual domains had an α value of more than 0·7, with the exception of energy and social isolation. The study[33] 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[39] 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 α of 0·93, indicating the need for further item reduction. The scores of the eight dimensions of SF-36® were used to examine the criterion validity of this PROM. The reported analysis showed strong correlation between SF-36® scores and those of the CXVUQ ($r^2 > 0·84$, $P < 0·001$), indicating good criterion validity[39]. The instrument's responsiveness was further demonstrated by good correlation between scores and clinical outcomes in two studies[36,39]. Responsiveness of the CXVUQ was

reported to be adequate in patients with healed ulcers at 6 weeks ($P = 0.022$) and 12 weeks ($P = 0.005$)[39].

Hyland questionnaire

The 34-item Hyland leg ulcer questionnaire[35] 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[35]. 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[37,38]. 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™[42] and SF-6D®[43]). 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 $\alpha > 0.93$)[37]. 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)[31]. 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[25]. The VEINES-QOL/Sym was validated as part of the VenUS IV trial[31], which compared two-layer hosiery and a four-layer bandage system[44]. 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 α 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® and clinical measures, were also reported. It also showed moderate responsiveness when outcomes were examined at 4 months in patients with healed ulcers[31]. However, test–retest reliability evidence was weak (κ 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)[34]. 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 $\alpha > 0.8$)[34]. The study also reported strong correlation with the SF-36® 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)[34].

Venous Leg Ulcer Self-Efficacy Tool

The VeLUSET is a self-efficacy questionnaire designed for patients aged 60 years and over[32]. 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[32]. 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[32].

Discussion

With high recurrence rates and complex management pathways[6,45], 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[46–49].

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™ 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[31,35,36,40]. Despite recommending use of the EQ-5D™ for health technology evaluation, the National Institute for Health and Care Excellence (NICE)[50] 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[34].

All studies were conducted in the UK with the exception of one originating from New Zealand[36]. The psychometric criteria applied in the appraisal of PROMs were based on internationally accepted guidelines[20,21,23,24]. 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[51,52].

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[53] and Norwegian version[54] 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[34] needs further evaluation to assess its responsiveness. Further research to validate the SPVU-5D[38], 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.

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Chapter Five. Understanding the experience and impact of living with a vascular condition from the patients' perspective

5.1 Context of the qualitative reviews

The items of ePAQ-VAS, as well as the domains, were developed from multiple qualitative research studies to ensure this tool have the necessary content validity so that it can be used for five vascular conditions, including AAA, PAD, CAD, VVs and VLU.

Prior to joining the group, an initial survey of vascular specialists was completed to identify the main vascular conditions to be covered by the new tool as well as aspects of care that the questions should cover. Furthermore, a qualitative study with patients suffering from AAA, CAD, PAD VVs and VLU was completed to help build the conceptual framework of ePAQ-VAS. The patients were recruited from Sheffield Vascular Institute, and all of them had face to face semi-structured interviews.

The systematic qualitative reviews were not part of the initial research plans. The reviews were conducted to ensure that the qualitative data used to develop ePAQ-VAS considers the views of as many vascular patients as possible. This was done to ensure that qualitative data to develop ePAQ-VAS were not restricted to the opinion of patients who were recruited for the primary qualitative study from Sheffield, UK. In some of the disease categories such as PAD, AAA and CAD not all aspects of the disease spectrum and sates were covered in the qualitative study. There was also difficulty with organising focus groups, therefore, the group decided to conduct these reviews. These were done to ensure that all aspects of the disease that impacts daily living in patients with AAA, CAD, PAD, VLU and VVs are covered. The evidence from these qualitative reviews was important to ensure content validity and overcome limitations of the primary qualitative study that recruited patients from a single vascular surgery institute and did not cover the full spectrum of some of the vascular conditions.

The plan was to complete a single review covering these five conditions; the review protocol was published before I joined the group. However, due to the large volume of titles generated from the searches and difficulty to perform a meaningful analysis due to heterogeneity of the data, the group completed five reviews instead of a single review.

The qualitative evidence synthesis reviews aimed to identify all primary qualitative research studies that investigated the impact of AAA, PAD, CAD, VVs and VLU on quality of life. The identified themes for each condition were mapped against the items and scales of the PROMs that were identified in the previous

reviews discussed in earlier chapters **(35-36, 46-48)**. The mapping was done to find the PROMs that captured the most important issues to patients with the respective conditions.

The data from five qualitative reviews **(37-38, 72, 75-76)** and evidence from the qualitative study at Sheffield **(77)** was used to develop the conceptual framework of ePAQ-VAS, including disease-specific scales and items. The evidence from these qualitative reviews was important to ensure content validity and overcome limitations of the primary qualitative study since it was only conducted in a single centre and it did not cover the full spectrum of some of the vascular conditions.

I contributed to four of these reviews, and two of these are included in this PhD. I led on the review, analysis and the writing of both papers. These two reviews were to identify all primary qualitative data examining the impact of CAD and PAD on the health-related quality of life of patients with these conditions **(37-38)**.

5.2 Methods for the qualitative reviews

The reviews were undertaken and reported in line with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement **(81)**. The searches were conducted in CINAHL via EBSCO, Medline and Medline in Process via Ovid, Embase via Ovid, PsycINFO via Ovid, Social Science Citation Index/ Science Citation Index via Web of Science (Thomson Reuters) and Proquest dissertations and theses. The search strategies were developed to include condition terms, terms for patient-reported outcomes/patient views and terms for qualitative studies to identify all the studies with primary qualitative data for the qualitative literature review.

The searches for these two reviews were performed after I joined the group in April 2017, and I performed the sifting of titles as well as the review of abstracts and full-text papers. I also completed the primary methodological quality check of the included papers and performed the qualitative data analysis. The results of the quality check and data analysis were checked by at least one other author. The Critical Appraisal Skills Programme (CASP) qualitative checklist instrument was used to assess the methodological quality of the included studies; this was selected as it is commonly used in qualitative reviews **(82)**. For more details, please see the next two chapters in this thesis.

Framework analysis was used to analyse the data; the advantage of this form of analysis compared to other thematic analysis is the output, and 'cells' of the summarised data are structured into rows (cases), and columns (codes) to generate themes. The most common disadvantages of framework analysis are that it cannot handle highly conflicting views on the same issues between patients suffering from the same condition **(83)**. Other qualitative approaches based on Grounded Theory, such as interpretative

phenomenological analysis (IPA), use the 'constant comparative method'. This allows the researcher to make comparisons across cases to refine each theme.

The identified papers from the PAD and CAD reviews were uploaded into the data analysis software NVIvo10 (QSR International, Doncaster, Victoria, Australia). The qualitative data generated by patients were analysed using framework analysis. The conceptual scales/domains of the most valid PROMs were used as the basis for the analysis **(47-48)**. The first stage of analysis was to read all the papers identified by the systematic review and identifying themes from within and across the articles. The second stage involved establishing framework by creating a list of themes based on the domains of validated PROMs **(47-48)** and common themes in the identified papers. In the final stages, themes were examined for their similarities and differences. A second author double-checked all the themes that were identified, and differences in conceptualisation were discussed and adjusted involving a third senior author.

In each one of the reviews a triangulation of evidence was performed to assess whether the items within tools identified corresponded to themes from the AAA, CAD, PAD, VVs and VLU qualitative reviews **(47-48 83)**. The aim was to identify PROMs that covered best the themes that are important to patients with vascular disease.

5.3 Results of the qualitative reviews

The five qualitative reviews identified 32 primary qualitative studies investigating the impact of AAA, PAD, CAD, VVs and VLU on the daily living of those patients suffering from the disease **(37-38, 46, 84-85)**. The qualitative evidence from these reviews generated several important themes that affect patients suffering from AAA, PAD, CAD, VVs and VLU. The evidence from these studies that also included a triangulation subsection helped identify where previous disease-specific PROMs fell short in covering issues deemed important to patients.

The themes from these studies were used to develop the conceptual framework ePAQ-VAS and ensure its content validity. These reviews ensured that the opinions of a larger group of patients with the five vascular diseases were used to develop the items and disease-specific scales of ePAQ-VAS. I have included two papers from this work stream in my PhD by publication. These are the PAD and CAD qualitative evidence synthesis reviews **(37,38)**.

5.4 Paper 3 – PAD qualitative review

The searches of the databases for the PAD qualitative evidence synthesis identified 1113 titles and, only eight papers fulfilled the inclusion criteria **(86-94)**. The included papers reported the views of 186

patients with PAD, including patients with intermittent claudication, critical ischaemia and amputation secondary to PAD. The overall quality of the included studies was good per the CASP criteria. Framework analysis identified 35 themes that broadly divided into six main domains: symptoms, impact on physical functioning, impact on social functioning, psychological impact, financial impact and process of care.

Symptoms, as reported by the patients, included pain, altered sensation, cold extremities, weakness, reduced mobility, ulcers, poor sexual functioning and symptom progression. The pain was the most common symptom, and it was mentioned by patients in all the included studies **(86-94).** However, its description differed with patients with new onset of symptoms, only describing only discomfort, ache and cramp. In contrast, patients with severe limb ischaemia described the pain as a burning, sharp pain in their feet and legs. Patients following amputation for PAD reported pain at the site of the amputated leg; however, this phantom pain was tolerable compared to the ischaemic rest pain. This theme is an example of the limitations of framework analysis, and although it is acceptable to group the different pain descriptions themes together; this can easily overlook how pain in PAD is a complex, multidimensional construct that includes several domains, such as pain severity, sensory qualities of pain, pain beliefs, and the functional impact of pain **(95)**.

The altered sensation was another symptom that was reported in five studies **(86-87, 92-93)**. This ranged from a minor tingling sensation in the affected limb to lack of sensation secondary to nerve damage post-intervention. Another symptom described by the patient was "weakness and fatigue"; patients described the loss of power with worsening fatigue as the disease progressed, and many reported that despite

revascularisation, the fatigue symptoms did not resolve **(86, 88).** Both these themes can include symptoms and signs that are not related and conceptually different. The chronically altered sensation caused by nerve damage following intervention is conceptually different to the altered sensation caused by acute or acute on chronic ischaemia. Therefore, although it was practical to follow a framework analysis when developing the conceptual framework of ePAQ-VAS, it was important to consider these differences.

All the included studies reported the varying degree to which PAD impacts patients' mobility. The impact on mobility differed, based on the severity of the disease. It was worse in patients with critical limb ischaemia, with many reporting that their independence was affected and that they lost their ability to walk completely **(87).** The issues with mobility were different from those who had an amputation; the problems included maintaining their balance, moving upstairs or up ramps.

Patients described the impact of PAD on physical functioning in terms of losing their independence **(88)**. Seven studies reported the effect on social functioning and reported a lack of support from their social circle, isolation and the inability to perform their hobbies. This was worse, especially among patients

who had an amputation **(94).** Primary qualitative data reported in this systematic review also showed the psychological impact of PAD, including anxiety caused by fear of loss of independence, fear of amputation or death. Some also reported low mood, low self-esteem, and embarrassment because of PAD symptoms. It is important to note that some primary qualitative studies might have not been included in this systematic review of the qualitative evidence; this is likely due to the search strategy used.

These themes from this qualitative reviews were compared to items from PROMs that were identified previously **(47)**. The PROMs that captured the most important themes was the VascuQoL. However, VascuQoL missed important topics, particularly to patients who had an amputation secondary to PAD.

5.5 Paper 4 – CAD qualitative review

The CAD qualitative evidence synthesis is the second paper from this work stream that is included in this PhD by publication. This review identified four studies and reported on the views of 62 patients **(96-99).** Sixteen themes were generated from the data, and these were divided into five main domains: anxiety, impact on personal roles and activities, effect on independence, psychological impact, and symptoms. The main advantage of this review it included patients awaiting revascularisation post endarterectomy as well as those treated with the best medical therapy as surgery was contraindicated.

The main limitations were the lack of access to the primary data and the lack of data on the clinical condition of the patients. It was not possible to distinguish what was meant by the symptomatic patient and whether this meant that the patient had TIA or stroke prior to their interview. Furthermore, there were conflicting views among those patients about certain aspects of the care, and this meant comparing across the data to ensure that all relevant themes are reported in the review.

The anxiety domain had many themes, including fear of stroke, fear of becoming a burden, uncertainty about the future, and fear of the operation. The impact of anxiety on the daily lives of patients suffering from CAD featured in all the included studies in this review. Participants experiencing symptoms of TIA secondary to CAD felt that their life was put on hold because of fear of disabling stroke that could make them a burden on others **(96).** Fear of sudden stroke affected patients treated with best medical therapy markedly, when compared to patients treated with an operation such as carotid endarterectomy **(95).** However, there were no data on the duration of this anxiety and whether its impact lasted beyond the acute treatment phase. All the included studies reported that patients suffering from symptomatic CAD felt that their independence was compromised because of the disease and its potential consequences **(96, 99).**

The symptom domain from this review was broadly divided into symptoms associated with TIA and post-intervention symptoms. Patients experiencing TIA reported symptoms such as altered sensation, weakness, temporary loss of the ability to speak and loss of vision. Post-intervention, some patients described neck pain and discomfort at the site of the operation. Lastly, some patients described a loss of cognitive function that was more noticeable by their family **(96).** Due to the overlap between the symptoms of stroke and those presenting with symptomatic carotid artery disease, some measure HRQoL in those presenting with CAD with generic or disease-specific PROMs for stroke **(100-101)**.

The identified themes from the qualitative evidence synthesis were compared to items from PROMs that were identified in a systematic review examining the validity of PROMs used in patients with CAD **(48).** The tools that were triangulated against the 18 themes from this qualitative review were the following: carotid artery disease quality of life questionnaire developed by the Carotid Revascularization Endarterectomy versus Stenting Trial [CREST randomised controlled trial (RCT)] group, the Carotid Stenosis Specific Outcome Measure (CSSOM) **(93)**, the Dizziness Handicap Inventory (DHI), the Hospital Anxiety and Depression Scale (HADS), the EuroQoL-5D (EQ-5D™), and the Medical Outcomes Study 36-Item Short Form (SF-36®).

5.6 Conclusion

In summary, none of these PROMs covered all the themes important to patients with CAD, including the fear of stroke and uncertainty about the future caused by CAD. Many of the symptoms described in the qualitative evidence synthesis of this study were not included in the PROMs. The qualitative evidence from these reviews generated several important themes that affect the daily living of those suffering from the following vascular conditions: AAA, PAD, CAD, VVs and VLU. The evidence from these studies identified issues deemed important to patients with vascular disease, and the evidence from the triangulation studies helped develop the conceptual framework ePAQ-VAS. The qualitative data from these reviews ensured that the opinion of many vascular patients was included to cover the breadth of the conditions and that ePAQ-VAS items would have content validity. In chapters six and seven, the qualitative evidence synthesis review for PAD and CAD are presented. These two peer-reviewed papers present some of my contribution to the qualitative work stream towards the development of ePAQ-VAS.

Chapter Six. Paper 3 "Themes that Determine Quality of Life in Patients with Peripheral Arterial Disease: A Systematic Review."

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Themes that Determine Quality of Life in Patients with PeripheralArterial Disease: A Systematic Review

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Abstract

Objectives The aim of this study was to identify domains that determine quality of life in patients with peripheral arterial disease and find the patient-reported outcome measures that can examine the identified themes.

Methods A systematic review of all the main six databases was undertaken to identify primary qualitative studies reporting on the health and/or quality of life of patients with peripheral arterial disease. The quality of studies was assessed using the Critical Appraisal Skills Program criteria. Findings from the included studies were analysed using framework analysis methodology. The identified themes were mapped against the items/domains of validated patient-reported outcome measures used in patients with peripheral arterial disease.

Results The systematic review identified eight papers that fulfilled the inclusion criteria. The included papers reported the views of 186 patients with peripheral arterial disease including patients with intermittent claudication, critical ischaemia and amputation secondary to peripheral arterial disease. The overall quality of the included studies was good based on Critical Appraisal Skills Program criteria. Framework analysis identified 35 themes that were divided into six main groups: symptoms, impact on physical functioning, impact on social functioning, psychological impact, financial impact and process of care. The best-fit generic and disease-specific patient-reported outcome measures were the Nottingham Health Profile and the Vascular Quality of Life Questionnaire, respectively. None of the patient-reported outcome measures covered all the themes important to patients with peripheral arterial disease.

Discussion The findings from the review identified the important domains that affect patients living with peripheral arterial disease. None of the current generic and disease-specific patient-reported outcome measures provide a comprehensive measure for all themes that impact the daily living of patients with peripheral arterial disease.

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Key Points

Peripheral arterial disease is a spectrum of conditionsranging from asymptomatic disease and minor claudication to limb loss

Understanding and measuring quality of life in thesepatients is of paramount importance to guide intervention

This systematic review is the most comprehensive attempt to measure the impact of this disease in itsdifferent manifestations and can help improve current measures used

1 Introduction

Population studies suggest that one in five people above the age of 60 years have some degree of peripheral arterial disease (PAD) in the lower limbs. The incidence of this disease increases with age [1]. Most patients with PAD are asymptomatic; however, patients can present with a spectrum of symptoms, reflecting different stages of the disease. The most common clinical presentation is intermittent claudication (IC), which is pain in the leg on walking; only 20% of these patients develop severe symptoms of critical limb ischaemia (CLI) [2]. Patients with CLI can present with rest pain, non-healing leg ulcers or gangrene; if they do not receive treatment they may losepart of their lower limbs [3, 4]. Patients with CLI have a high risk of mortality with nearly 25% dying and 30% requiring major lower limb amputation within 1 year [5, 6].Symptomatic PAD results in significant functional limita- tions and reduced health-related quality of life in affected patients [5].

Peripheral arterial disease is a chronic disease and patients with this condition need support to choose the best treatment strategy to reduce the impact on their quality of life. Health-related quality of life can be measured using either generic or disease-specific patient-reported outcome measures (PROMs). Patient choice over treatment and care is a central feature of most advanced healthcare systems, it is proposed that information gathered by PROMs from patients directly can help inform the choice of treatments and promote equity as well as excellence [7].

Patients' experience of treatment and care is a major indicator of quality and there has been a huge expansion in the development and application of PROMs. These instruments examine the most important issues to the patients by asking them directly about any changes. Patient-reported outcome measures provide an insight into the manner in which patients perceive their health and the impact that treatments have on their quality of life.

The aim of this study was to systematically review the qualitative evidence of people's experiences of living with PAD. The identified domains were then mapped against the items/domains of identified validated generic and disease-specific PROMs [8]. The intention was to find the PROMs that captured the most important issues to patients with PAD.

2 Methods

The review aimed to find all the primary qualitative research studies (interview and/or focus groups) that explicitly investigated the impact of PAD on daily living, health and quality of life. The inclusion criteria included any patients with PAD (IC, CLI, ischaemic ulceration, necrosis, gangrene and amputation as a result of PAD). Any studies with undefined populations or mixed popula- tions that included the views from patients not experienc- ing PAD were excluded.

For further information regarding the inclusion and exclusion criteria, refer to Table 1. This systematic review was undertaken and reported in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. In accordance with the study protocol [9], searches were conducted from inception up to April 2017 in bibliographic databases including CINAHL via EBSCO, MEDLINE and MEDLINE in Process via Ovid, EMBASE via Ovid, PsycINFO via Ovid, Social Science Citation Index/Science Citation Index via Web of Science (Thomson Reuters), and Proquest dissertations and theses. No language or date constraints were applied.

The search strategy combined condition terms, terms for patient views and terms for qualitative studies (which augmented a qualitative study filter) [9]. Further details of the search strategy are provided in Appendix 1 (supporting information).

2.1 Study Selection

The search results were entered into Endnote X8™ (Thomson Reuters, Philadelphia, PA, USA) and two reviewers (AA, PP) independently screened the titles for inclusion and exclusion in accordance with the set criteria in the protocol. All titles were examined, and any citations that clearly did not meet the inclusion criteria (for example, mixed-population quantitative PROM data, unrelated to PAD) were excluded. For included titles, abstracts were

Table 1 Summary of the inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patient's health, health-related quality of life or experience of one of the 5 vascular conditions listed below	Studies not in English
	Clinicians views
	Studies with participants under 16 years of age
PAD: a defined population of participants with a diagnosis of PAD, also described as: peripheral vascular disease, peripheral obliterate arteriopathy and peripheral arterial occlusive disease OR patients with clinical evidence of any or a combination of the following, where PAD is the confirmed or stated underlying cause: rest pain, claudication, vascular spasms, ischaemic ulceration, necrosis or gangrene of the limb amputation	Undefined population of patients with PAD and patients with claudication, lower limb ulcers or amputations as a result of any cause other than PAD
Studies that include semi-structured interviews, descriptions and focus groups either as stand-alone studies or embedded in a quantitative study. Must include both data collection and data analysis	Quantitative studies with no primary qualitative data reported
Published or unpublished; full text or structured abstract will all relevant information	Published or unpublished; full text or structured abstract with incomplete or unclear evidence

PAD peripheral arterial disease

read and for the included abstracts, full-text articles were obtained.

2.2 Quality Assessment

The Critical Appraisal Skills Program qualitative checklist instrument was used to assess the methodological quality of the included studies in the review [10]. This was selected as it assesses both the appropriateness and the quality of reporting of the studies included and is com- monly used in qualitative reviews of evidence [11]. The Critical Appraisal Skills Program consists of ten questions about the qualitative methodology that are answered either as yes, no or unclear. Two of the authors (A.A. E.L.)independently examined the quality of each study and any inconsistencies were resolved by discussion or involving a third author (G.J.).

2.3 Data Extraction and Analysis

The data on authors, year of publication, country of study, number of participants, research aims, methods of recruit- ment, method of data collection, key results and analysis were extracted and tabulated for all the included studies. The first author (A.A.) uploaded all the papers into the qualitative data analysis software NVIvo10 (QSR Interna- tional, Doncaster, VIC, Australia) and the primary and secondary texts (patient quotes reported in the articles and themes) were analysed. Framework analysis was used to identify common and variable themes within the text of each article [12]. The first stage of the analysis was undertaken by reading all the included papers to identify common terms and themes from within and across the

articles. The second stage involved identifying a thematic framework by creating an initial coding scheme for the main themes; and eventually creating an index of themes. In the third stage, the thematic framework was applied toall the primary and secondary data in the included papers. A framework matrix was created to arrange the data per the thematic references in the fourth stage. In the fifth and final stage, themes were examined for their conceptual similar- ities and differences (mapping and interpretation stage). A second reviewer (E.L.) checked all the themes that were identified and differences in conceptualisation were dis- cussed and adjusted.

2.4 Triangulation of Patient-Reported Outcome Measure Items with Qualitative Themes

To examine the extent to which the items within generic and PAD disease-specific PROMs corresponded to themes from the qualitative review, a triangulation approach was followed [13, 14]. The items from generic and disease- specific PROMs validated in patients with PAD [8] were examined in detail. The items from these instruments were mapped against the themes identified, and two researchers (A.A., E.L.) reviewed both the themes from the qualitative review and the PROM items/domains to evaluate whether the concepts were the same (agreement), offered similar concepts (partial agreement) or were not present (silence). The aim was to identify whether any of the instruments covered all the important issues from the PAD patients' perspective.
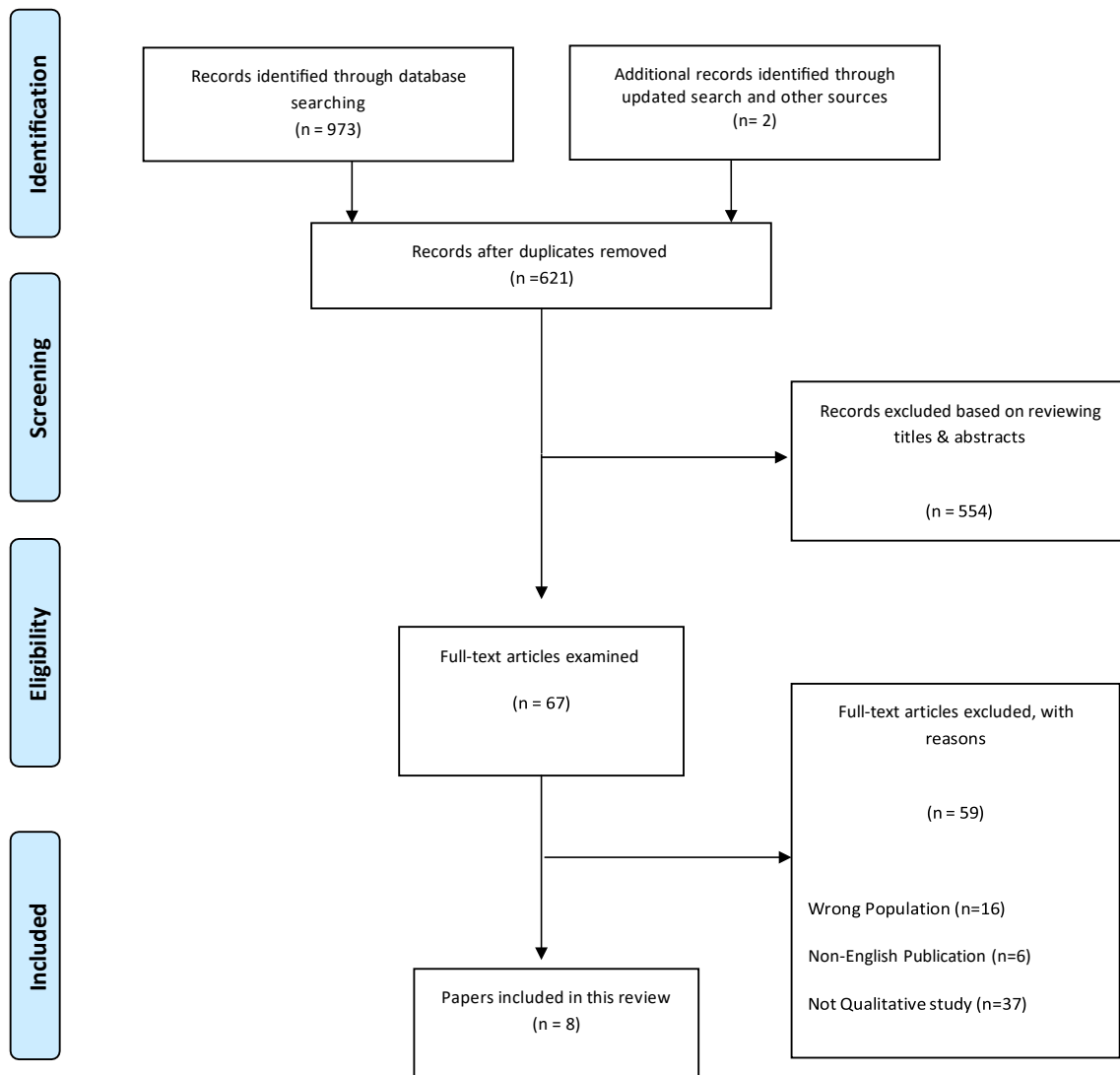
Fig. 1 Preferred reporting items for systematic reviews and meta-analyses diagram: peripheral arterial disease qualitative systematic review

3 Results

The database searches identified 1113 citations; after removing duplicates, 779 titles were assessed and subsequently 65 full-text papers were reviewed in detail. Finally, only eight papers fulfilled the inclusion criteria and were included in the qualitative evidence synthesis (see Fig. 1). The characteristics and main findings of the studies included in the qualitative synthesis are summarised in Table 2.

Two of the studies were conducted in the UK [15, 16], three in Sweden [17–19] and three in USA [20–22]. The studies were published between 1998 and 2015; the mean age of the participants in the included studies ranged from 64 to 77 years, and the percentage of male participants was 50–79%. The included studies reported the views of 186 patients with PAD including patients with IC, CLI and amputation of lower limbs as a result of PAD.

3.1 Quality Assessment

The overall quality of the included studies was good and all the studies scored ''yes'' for almost all the criteria set in the Critical Appraisal Skills Program checklist [10]; however, four studies scored ''can't tell'' regarding consideration of the relationship between participants and the researcher[16, 19–21]. Only one study scored ''can't tell'' whenassessing if the recruitment strategy was appropriate to the aims of the research [20]. For further detail on the quality of the included studies, see Appendix 2 (supporting information).

3.2 Analysis

The framework analysis of the primary and secondary data in the included papers identified six main issues including symptoms, physical functioning, impact on social

Table 2 Qualitative studies exploring individuals living with peripheral arterial disease (PAD)

Author, year	Country	Research design	Method of analysis	Study aims and objectives	Sample	Diagnosis/treatment	Eligibility criteria	Main findings
Cunningham et al. 2014 [16]	Scotland	Qualitative semi-structured interviews	Thematic analysis	Explore illness and treatment belief and walking behaviour	20 Participants Age, y: mean 70.9, range (64–77) Male (%): 55	IC Bypass graft %: 60 Angioplasty %: 40	Diagnosis of IC and revascularisation surgery or angioplasty between 6 and 24 mo	Ongoing symptoms, avoiding walking, patients unaware of the cause of the disease, unaware of increased risk of future cardiovascular risk
Eberg et al. 2012 [19]	Sweden	Qualitative semi-structured interviews	Thematic analysis	Describe individuals' experiences of living with IC from an insider's perspective	17 Participants Age, y: mean 73, range (64–81) Male (%): 53	IC No intervention	Diagnosis of IC and were able to read and speak the Swedish language	The main theme was ''Adjusting to a restricted life.'' Six themes were identified: ''Experiencing discomfort in the legs'', ''Moving around in a new way'', ''Feeling inconvenient when forced to stop'', ''Missing previous life'', a strenuous life''
Gibson and Kenrick 1998 [15]	England	Face-to-face, descriptive interviews	Open and axial coding techniques	Explore the lived experience of peripheral vascular disease	9 Participants Age, y: Mean 65, range (62–75) Male (%): 67	Post-bypass surgery for severe ischaemia	Post-bypass surgery for severe ischaemia	Patients experienced powerlessness in relation to the direct effects of their condition and in relation to its treatment modalities
Schorr et al. 2015 [21]	USA	Qualitative semi-structured interviews Face-to-face, descriptive interviews PAD symptom questionnaire	Qualitative content analysis	Describe the symptom experience of individuals diagnosed with PAD	38 Participants Age, y: mean 67.6, range (49–83) Male (%): 79	PAD	21 y of age and older, diagnosed with PAD, reporting exercise-limiting symptoms, cleared for exercise, able to read, write and speak English	Six themes emerged: symptom descriptors (claudication and atypical), maintaining equilibrium, temporal fluctuations, the role of exercise, perceived impact on quality of life, and disease presence and treatment
Suckow et al. 2015 [22]	USA	Focus groups	Thematic analysis	Describe which domains vascular amputees consider	26 Participants	Major amputation	Patients had to have undergone at least one major lower extremity	Patients stated that their current QOL was determined by

important in determining their health-related QOL	Age, y: mean 64, range (39–87) Male (%): 73	as a result of PAD	amputation (above or below knee), able to read, write and speak English	impaired mobility, pain, progression of disease in the remaining limb and depression/frustration

Table 2 continued

Author, year	Country	Research design	Method of analysis	Study aims and objectives	Sample	Diagnosis/ treatment	Eligibility criteria	Main findings
Treat-Jacobson et al. 2002 [20]	USA	Open-ended interviews	Grounded theory analysis	To evaluate the effects of PAD on health-related quality of life from the patient's perspective	38 Participants Age, y: mean 65, range (44–83) Male (%): 63	PAD	Range of PAD severity	Seven major themes were identified: (a) delay in diagnosis and frustration with management of disease; (b) pain; (c) limitation in physical functioning; (d) limitation in social and role functioning; (e) compromise of self; (f) uncertainty and fear; and (g) adaptation to the effects of the disease and demonstration of resiliency
Wann-Hansson et al. 2005 [17]	Sweden	Qualitative semi-structured interviews	Manifest and latent content analysis	To investigate patients' experiences of living with PAD and the influence on activities of daily living	24 Participants Age, y: mean 77, range (62–92) Male (%): 50	PAD before intervention	A purposive sampling technique was used to recruit 4 patients with severe claudication intermittence and 20 patients with critical ischaemia who offered different perspectives on the experience of living with PAD	Living with PAD meant carrying a hard-to-bear physical, social and emotional burden, and struggling for relief. The experience of burden was interpreted in the following themes representing consequences and strategies for gaining control in daily life: [1] ''being limited by the burden'', [2] ''striving to relieve the burden''
Wann-Hansson et al. 2008 [18]	Sweden	Qualitative semi-structured interviews	Manifest and latent content analysis	To illuminate the long-term experience of living with PAD and the recovery following revascularisation	14 Participants Age, y: mean 75, range (61–85) Male (%): 64 Endovascular: 8 patients Surgery: 3 patients Endovascular and bypass: 3 patients	Patients with PAD following intervention	Patients who: [1] had undergone vascular intervention; [2] were able to participate in interviews; [3] had not undergone a major lower limb amputation	Transition from being in an acute phase of PAD to the recovery after revascularisation and entering a chronic phase of PAD: [1] 'becoming better but not cured'; [2] 'recapturing control over life'; [3] 'reappraising meaning in life'

IC intermittent claudication, *QOL* quality of life

Table 3 Themes identified from qualitative research studies

Themes	Cunningham et al. [16]	Eberg et al. [19]	Gibson and Kendrick [15]	Schorr et al. [21]	Suckow et al. [22]	Treat-Jacobson et al. [20]	Wann-Hansson et al. [17]	Wann-Hansson et al. [18]
Symptoms								
Pain	H	H	H	H	H	H	H	H
Pain on walking	H	H	H	H	H	H	H	H
Rest pain	H		H	H	H			H
Night pain	H		H	H	H		H	H
Phantom pain					H			
Altered sensation	H		H	H		H	H	
Cold extremities	H		H				H	H
Weakness/fatigue	H	H				H	H	
Mobility	H	H	H	H	H	H	H	H
Ability to walk	H	H	H	H	H	H		H
Walking distance	H	H		H		H	H	
Stair climbing, walking uphill		H			H			
Balance		H			H			
Ulcers					H		H	H
Sexual functioning					H			
Symptoms progression			H	H		H	H	H
Impact on physical functioning								
Personal care	H	H		H	H	H	H	H
Daily activities	H	H	H	H	H	H	H	H
Exercise	H	H		H	H		H	H
Impact on social functioning								
Personal role	H	H	H	H	H	H	H	H
Social support		H	H	H	H	H	H	H
Hobbies	H	H	H	H	H	H	H	H
Isolation	H	H	H	H	H		H	
Psychological impact								
Lack of control	H	H	H	H	H	H	H	H
Self esteem	H	H		H		H		
Self-perceptions	H	H		H		H	H	H
Impact on mood	H	H		H		H	H	H
Fear of amputation	H				H	H	H	
Fear of loss of independence					H	H	H	H
Fear of death						H		
Financial impact								
Employment						H		
Process of care								
Diagnosis	H	H			H	H	H	H
Adaptation		H	H	H	H	H	H	H
Treatment	H	H	H	H	H	H	H	H
Smoking	H		H			H		
Lack of information	H		H		H	H		

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Table 3 continued

Themes	Cunningham et al. [16]	Eberg et al. [19]	Gibson and Kendrick [15]	Schorr et al. [21]	Suckow et al. [22]	Treat-Jacobson et al. [20]	Wann-Hansson et al. [17]	Wann-Hansson et al. [18]
Expectations	H		H		H			H
Communication barriers	H		H		H			

functioning, psychological impact, financial impact and process of care. In total, 35 themes were identified. Table 3 shows the themes and subthemes and the sources from the included papers in this review.

3.2.1 Symptoms

This theme included several subthemes such as pain, altered sensation, cold extremities, weakness, mobility, ulcers, sexual functioning and symptom progression.

Pain This was identified in all the included papers, severity of the disease resulted in different experiences of pain and this was reflected in the pain subthemes. Patients described different experiences with the initial appearance of the symptoms. Pain was most commonly described as discomfort, ache, cramp and creeping feelings of fatigue that got worse the farther they walked.

> ''I get a cramping in the left calf.'' ''My legs get tired. I can feel it in my thighs.'' [21]

> ''I get this terrible cramp in my legs and then I don't know where to go.'' [17]

The description of pain in the legs and feet was different for patients with CLI. Some of these patients described rest pain and burning sharp pain in their feet and legs. Patients with vascular-related amputation described the same type of continuous rest pain prior to their amputation.

> ''If I could, I would have taken an axe and chopped off my leg sooner just to get rid of the pain.''

> ''When asked, 85% of patients felt that intolerable ischemic rest pain is the most appropriate threshold for having their limb amputated, as opposed to ulceration, gangrene, or when their physician stated that limb salvage was no longer possible.''

> ''I definitely would have had the amputation at the same time point. My pain got so bad, I could not walk.'' [25]

Rest pain was also reported to be particularly troublesome during the night causing sleep disturbances. Patients had to adapt their position to deal with this pain. Some reported sleeping in a chair to overcome the severity of this pain.

> ''Experiences such as being forced to sit in a chair during the nights to stand the pain contributed to tiredness and feelings of exhaustion.'' [17]

> ''The greatest benefits of revascularisations were the relief from pain, the ability to sleep again.'' [18]

Patients with failed revascularisation and subsequent amputation reported pain at the site of the amputated limb; however, the phantom pain experienced was tolerable compared to the ischaemic rest pain [22]. Furthermore, patients who underwent revascularisation complained of some residual pain following the procedure. Participants in one study reported that they avoided exercise following their intervention and some believed that the pain on walking was an indication that activity causes damage to their muscles and legs [16].

Altered Sensation Participants in five studies [15–17, 20, 21] reported altered sensation in the affected limb; these symptoms were experienced by patients prior to and following the procedures. The description of this altered sensation ranged from feeling ''a dead weight'', especially in patients with CLI [15], to a minor intermittent tingling feeling in patients with IC [21]. Altered sensation secondary to revascularisation was caused by either nerve damage or swelling post-interventions [16].

Cold Extremities Patients with chronic severe lower limb ischaemia complained of cold feet and legs; some of these patients reported that despite revascularisation the symptom persisted [18]. One participant described this symptom in the following terms:

> ''I can get up and walk a little and so on. Yes, I have to live with it. It's sleeping now here and it gets cold, like, but when I'm moving the circulation is better. So I see that I'm never going to get rid of it but I can live with it because it doesn't hurt in that way that it did before the operation.'' [18]

In one study, some participants experienced coldness in the affected limb pre-operatively, postoperatively and after

discharge; however, it was worse before revascularisation [15].

Weakness and Fatigue Weakness and fatigue was reported by participants in four studies [16, 17, 19, 20]. Some reported this symptom to be the first they experienced; describing fatigue on walking followed by pain and cramps the more they continued to walk [16, 19]. Some experienced loss of power with worsening fatigue as the disease progressed and many complained that despite intervention, the fatigue symptoms did not completely resolve. One patient described this symptom in the following terms:

''Yes, it's just like it has taken the strength and power from me.'' [17]

Many patients described that PAD meant living with long-term fatigue and powerlessness [17, 20].

Mobility All the included studies in this review highlighted problems with mobility to be the most important issue experienced by patients with PAD. The impact on mobility differed per the type of symptoms experienced, and the severity of the disease. The impact was worse in patients with CLI and amputees. Patients with IC reported reducing their walking to avoid the symptoms of pain.Patients with IC also reported employing specific strategiesto avoid pain and discomfort on walking by stopping reg- ularly, or avoiding walking uphill or upstairs [19–21].

''It depends completely on how hard I walk. If I walk very slowly, I can go many, many blocks, more than a dozen, or so. If I walk aggressively, I can start to feel something in maybe two blocks.'' [21]

''I usually shy away from places where I won't be able to sit down and rest.'' [21]

Another patient reported:

''You know hills and stairs; they're the worst. And carrying things up the stairs is even worse.'' [19]

Patients with CLI felt that their personal independence was compromised because of their problems with mobility. They felt the disease took away their ability to walk completely or reduced their walking ability. This meant for many of them limited daily activities such as housework, shopping and cleaning [17]. Many patients used aids such as walking sticks, walking frames and sometimes wheelchairs to overcome issues with mobility; these changes occurred over a long time to adjust to the symptoms [18]. Many patients with amputation secondary to PAD reported that problems with mobility had the biggest impact on their quality of life. The major issues with mobility included maintaining their balance, walking upstairs or up ramps. Most patients with amputations relied on using wheelchairs, even if they had prosthesis. Many also reported that they wished that they had met the pros- thesis specialists prior to amputation, to prepare them for life after amputation [22].

Non-Healing Ulcers One of the most distressing symptoms experienced by patients with CLI was non-healing ulcers or wounds. Patients used terms like 'painful' and 'disgusting' to describe their ulcers. Many were concerned about the shape and colour of their leg; the shape of the ulcer had an impact on the type of clothes and shoes they could wear. Several patients also complained of recurrent leg ulcers as a result of PAD.

''It's troublesome because it runs. That's the hard thing and sometimes it hurts. It's hard to wear shoes.'' [17]

''Well, the district nurse came and looked at it and bandaged it. Then it was all right and then it came back, and then it was all right and then it came back again, so it is there now.'' [17]

3.2.2 Sexual Functioning

Some patients described a decline in their sexual functioning as a result of PAD. Although only a minority of patients reported that this was important to their overall quality of life. The decline in sexual function was associated with progression of symptoms of the disease [22].

3.2.3 Symptom Progression

Participants in four studies understood that PAD is a chronic condition and that it can get worse [17, 18 20, 21] some reported that they are focusing on avoiding the pro- gression of symptoms and worsening of PAD. Many patients' post-intervention adopted new strategies to avoid further intervention by modifying their lifestyle and giving up causative agents such as smoking [18]. The perception of the amount of control participants had over their disease progression varied considerably across the studies. These perceptions ranged from having little or none, to having a great deal of control [20].

3.2.4 Impact on Physical Functioning

Participants in all the included studies described varying impacts on their ability to care for themselves independently [15–22], participate in exercise or perform their daily activities. The symptoms of pain and reduced mobility had the main impact on physical functioning. [22]Patients with severe lower limb ischaemia also suggested that their physical function was affected by a lack of sleep

owing to their PAD symptoms, in addition to pain at rest or walking. [20].

3.2.5 Impact of Peripheral Arterial Disease on Social Functioning

Seven studies described the impact of PAD on social life. Many patients reported that their social life was compromised including not being able to maintain their personal role, lack of support from their social circle, isolation and the inability to perform their hobbies. Problems with isolation and lack of social support were worse among patients with amputations secondary to PAD; many of these patients felt that a social support group may improve their quality of life [22]. Patients with IC and CLI felt that their symptoms prevented them from keeping their hob- bies, visiting family and friends, and taking part in many activities that they enjoyed [15–21].

3.2.6 Psychological Impact of Peripheral Arterial Disease

The papers reported that patients felt they had no control over their disease. This feeling was more common amongst patients who had undergone revascularisation but still had some residual symptoms, or those that developed complications [16]. Many patients had low self-esteem, and felt embarrassed because of their symptoms; for example, some participants described feeling embarrassed because they stopped frequently to ease the pain. Some reported making up excuses to stop, for example, pretending to be waiting for someone [19]. Patients also experienced issues of per- sonal image and self-perception, with some patients feeling ''old before their time'' [19]. Patients also reported the emotional burden of PAD with many experiencing low mood and a sense of loss as a result of the disease or its complications [16–21]. Patients also reported symptoms of anxiety caused by fear of loss of independence, of ampu- tation or of death [15–18, 20–22].

3.2.7 Financial Impact of Peripheral Arterial Disease

One study described the impact of the disease on partici- pants' employment, and their ability to carry out their tasks at work. Many participants in that study thought that these limitations may lead to job loss or the loss of an opportu- nity to be promoted. Some patients planned to change jobs because of their new symptoms [20].

3.2.8 Process of Care

All the studies reported that patients had limited under- standing about the consequences of surgery. Patients with a diagnosis of IC and no intervention were not clear about their management, and did not understand why they were not offered interventions [15, 16]. Many patients did not view walking as therapy for their disease, and therefore avoided walking as they believed the claudication pain was a sign of damage caused to the leg by walking [16].

Many patients attempted to change their habits and devised strategies to manage their symptoms; this included alterations in walking by controlling pace, as well as planning stops for longer walks and taking pain relief [15, 16, 19]. However, side effects of pain relief medica- tions were a cause for restricted use [17]. Some participants wished that their risk factors were modified earlier in the community including assistance to give up smoking [20].

Post-amputation, many participants felt that intolerable severe continuous ischaemic rest pain was the most appropriate threshold for amputation and saw no point in the revascularisation attempts at that stage. On patient said:

''Most people would try anything to save the leg.'' [22]

''I definitely would have had the amputation at the same time point. My pain got so bad, I could not walk.'' [22]

Patients with amputations also reported that meeting with the prosthetics specialists, and spending some time familiarising themselves with the rehabilitation services available, prior to the amputation would have helped their recovery [22].

Three main subthemes emerged in relation to shared decision making in this review; these were lack of knowledge, expectations and communication barriers. Several patients reported a lack of information about the disease and its progress [16]. Exercise therapy was rec- ommended for some patients with claudication or post- operatively; however, patients did not understand the importance and relevance of this therapy, and some deci- ded to do the opposite and avoid walking [15–17]. This was mainly because of communication barriers between clini- cians and patients.

''When I was in the last time he (surgeon) was talking to a lady doctor and he said I was needing more but he started talking funny words that I did not under- stand.'' [16]

''While I was told I had artery disease, I wasn't told that I could lose my leg. I would have taken better care of myself.'' [22]

However, sometimes this was because of a lack of engagement by the patients and handing control of the decision making to the clinicians.

''The likes of [surgeons], they know what they are talking about, they don't say things unless they are sure so I accept what they want to do.'' [15]

Patient expectation was also a significant issue. Some had no knowledge of the overall impact of the atherosclerosis on their health generally, and othersexpected the intervention to fully cure the disease.Although most patients reported satisfaction with their intervention, some were disappointed with the results post-operatively as they expected to return to their pre-disease state with no symptoms or disability [15, 16, 18, 22].

3.2.9 Triangulation

The identified themes were compared to items from validated PROMs that were identified in a recent study [8]. These PROMs include the Peripheral Artery Disease Quality of Life Questionnaire, Vascular Quality of Life Questionnaire (VascuQoL), Australian Vascular Quality of Life Index, Peripheral Artery Questionnaire, Intermittent Claudication Questionnaire, Walking Impairment Questionnaire, EuroQoL-5D-3L (EQ-5D-3L), Nottingham Health Profile and the Medical Outcomes Study 36-Item Short Form. Two reviewers examined the overlap between the themes in the qualitative review and items in the validated PROMs; when there was a complete overlap between the theme and an item in a PROM, an agreement score (?) was awarded; however, when the theme was covered in a general question, a partial agreement score was awarded (±). For instance, EQ-5D has a domain about pain, this domain overlaps completely [is in agreement(?)] with the pain theme; the same domain overlaps with themes such as pain on walking, rest pain, night pain and phantom pain; although this domain in EQ-5D-3L does notask about them specifically. When the theme is not coveredat all, a silence score (−) was awarded; for example, in EQ-5D-3L, there are no questions about sexual functioning or altered sensation.

The best generic PROMs that captured all the important issues for patients with PAD was the Nottingham Health Profile and the disease-specific PROMs and the best fit with the themes from the qualitative review was the VascuQoL. However, VascuQoL did not cover issues important to patients who had an amputation secondary to PAD. The Walking Impairment Questionnaire only covered important symptoms, whereas the Intermittent Claudication Questionnaire only covered some of the themes important to patients with IC. For further details on the results of triangulation, see Table 4.

4 Discussion

We identified 35 themes associated with quality of life for those with different forms of PAD. These themes were divided into six groups: symptoms, physical functioning, impact on social functioning, psychological impact, financial impact and process of care

Measuring quality of life for people with PAD including patients with IC, CLI and amputation is of interest currently because of the introduction of new treatment modalities such as drug-eluting stents and drug-coated balloon angioplasty, as well as emerging evidence from trials comparing bypass operation to endovascular therapies. Outcome measures, such as limb salvage, patient survival, patency of bypass or vascularised artery, and re-intervention rates, have been used to compare outcomes between therapies for patients with PAD, and to inform decision making for patients with PAD. However, quality of life and functional status are what matters the most to patients [23, 24].

One of the strengths of this study is that the qualitative review included studies of patients with different manifestations of PAD, as PAD can present with a spectrum of symptoms, and with varying severity. The inclusion in the review of patients with IC, CLI and amputation ensured the variation of impacts on quality of life was captured. This is important owing to the complexity of PAD presentation because patients could have IC or CLI or had an amputation in one leg and experience a different stage of thedisease in the other leg. Validated PROMs in this field cover only a stage of the disease. A comprehensive mea-sure can be used to examine the outcomes of patients at different stages of the disease.

This review incorporated evidence from a previous systematic review [8] also conducted by the same research team, which identified PROMs validated for use with patients with PAD. In the triangulation section of this study, the themes from this qualitative review were mappedagainst the domains from the validated generic and disease-specific PAD PROMs that were identified in the separate review.

The main limitations of this study are that some of the included papers in the qualitative review did not specify the severity of PAD in the patients included. In other studies, the investigators reported the severity but did not distinguish between the themes based on the type of PAD. Furthermore, there was only one study that reported on the quality of life of patients with PAD-related amputation.

The review identified the important symptoms from the patients' perspective, these included pain, altered sensation, cold extremities, fatigue/weakness, issues of mobility, ulcers, sexual functioning and symptom progression. This

Table 4 Themes identified from the qualitative review mapped against items of validated patient-reported outcome measures

Themes	WIQ	ICQ	PADQOL	VascuQol	AUSVIQUOL	PAQ	EQ-5D-3L	SF-36	NHP
Symptoms									
Pain	±	±	?	±	±	?	?	?	?
Pain on walking	?	?	?	?	?	?	±	±	?
Rest pain	–	±	–	?	–	?	±	±	–
Night pain	–	±	–	?	–	?	±	±	?
Phantom pain	–	–	–	–	–	–	–	–	–
Altered sensation	–	–	–	?	–	–	–	–	–
Cold extremities	–	–	–	?	–	–	–	–	–
Weakness	–	–	±	?	–	–	–	–	–
Mobility	?	?	?	?	?	±	?	–	–
Ability to walk	?	?	?	?	?	±	–	–	?
Walking distance	?	?	±	?	–	?	–	–	?
Climbing stairs/walking uphill	?	?	–	?	–	–	–	–	–
Balance	–	–	–	–	–	–	–	–	–
Ulcers	–	–	–	?	–	–	–	–	–
Sexual functioning	–	–	?	±	–	–	–	–	?
Symptom progression	±	–	±	±	–	±	–	±	–
Impact on physical functioning									
Personal care	–	?	±	±	?	?	?	±	–
Daily activities	–	–	?	±	–	?	?	–	?
Exercise	–	–	?	?	?	?	–	–	?
Impact on social functioning									
Personal role	–	?	±	?	–	–	±	?	?
Social support	–	–	?	–	–	?	–	–	?
Hobbies	–	?	?	?	?	?	–	–	?
Isolation	–	–	?	?	–	±	–	±	–
Psychological impact									
Lack of control	–	–	?	?	±	?	–	–	–
Self-esteem	–	–	±	–	±	?	–	–	–
Self-perceptions	–	–	?	?	±	?	–	?	?
Impact on mood	–	–	?	?	?	?	?	?	?
Fear of amputation	–	–	?	?	–	–	–	–	–
Fear of loss of independence	–	–	±	±	–	±	–	–	–
Fear of death	–	–	–	–	–	–	–	–	–
Financial impact									
Employment	–	–	–	–	–	–	–	–	–
Process of care									
Diagnosis	–	–	–	–	–	?	–	–	–
Adaptation	–	–	±	±	±	±	–	–	–
Treatment	–	–	–	±	–	?	–	–	–
Smoking	–	–	–	–	–	–	–	–	–
Lack of information	–	–	–	–	–	±	–	–	–
Expectations	–	–	?	–	–	?	–	–	–
Communication barriers	–	–	–	–	–	?	–	–	–

AUSVIQUOL Australian Vascular Quality of Life Index, *EQ-5D* EuroQoL-5D, *ICQ* Intermittent Claudication Questionnaire, *NHP* Nottingham Health Profile, *PADQOL* Peripheral Artery Disease Quality of Life Questionnaire, *PAQ* Peripheral Artery Questionnaire, *VascuQoL* Vascular Quality of Life Questionnaire, *SF-36* Medical Outcomes Study 36-Item Short Form, *WIQ* Walking Impairment Questionnaire, - indicates silence, ± indicates partial agreement, ? indicates agreement

study also revealed that patients with critical ischaemia and IC post-intervention complained of some of these symptoms in varying degree. Furthermore, many patients with critical ischaemia expressed their views that quality of life and severity of symptoms should be considered when deciding the timing and type of intervention, whether that is revascularisation or amputation.

Amongst some academic and clinical circles, quality of life has confusingly come to be known as anything that is not clinical [25]. However, this review indicates that, when patients with PAD are asked, the distress related to symptoms is integral to their quality of life, and in some instances seeing beyond the distress of pain and lack of mobility is difficult. The type of pain, its onset, as well as the location, was different depending on the severity of disease; the same applied to fatigue, weakness, altered sensation and mobility. Mobility issues were different between a patient post-amputation, and someone with claudication; however, the issue remained relevant to both groups.

Issues relating to the impact on psychological well-being included the following subthemes: lack of control over life, negative impact on self-esteem, self-perception, impact on mood, fear of amputation, loss of independence and death. The impact of these problems differed between patients depending on whether they experienced claudication symptoms only, if they had severe ischaemia or if they had undergone an amputation.

One of the strongest findings of this study is that when the themes generated from the review were mapped against the generic and disease-specific PROMs validated in patients with PAD, none of them covered all of the important issues revealed by the review. This is likely because the review included studies that interviewed patients with IC-, CLI- and PAD-related amputations; therefore, including all the themes important to patients with symptomatic PAD. This provides important evidence for critically examining the content of PROMs currently being used in patients with PAD and particularly the generic measures such as the EQ-5D-3L and the Medical Outcomes Study 36-Item Short Form.

Both PROMs are used commonly to inform resource allocation decisions as well as to monitor quality of life. There are several concerns with generic PROMS, for instance, the EQ-5D-3L and Medical Outcomes Study 36-Item Short Form were designed by experts with no input from patients with PAD and their coverage does not include all the important issues to patients with IC, CLI and amputation secondary to PAD. The EQ-5D-3L has five dimensions of health: mobility, self-care, usual activities, pain and discomfort, and depression and anxiety. Respondents are asked to report their level of problems (no problems, slight/moderate problems or severe/extreme problems) on each dimension to provide an overall score for the health state. A key concern raised about this measure is the focus on physical health with little focus on psychological well-being.

5 Conclusions

The findings of this study can help to provide useful evidence for examining the content validity of different measures. This evidence can be used alongside quantitative psychometric evidence to design a new disease-specific measure. Our group designed this instrument and aims to perform a factor analysis and well as a further psychometric analysis in a large survey of patients with PAD.

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Chapter Seven. Paper 4 "Impact of Carotid Artery Stenosis on Quality of Life: A Systematic Review."

SYSTEMATIC REVIEW

Impact of Carotid Artery Stenosis on Quality of Life: A Systematic Review

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Abstract

Objectives The aim of this study was to identify themes that determine health-related quality of life (HRQoL) in patients with carotid artery stenosis and identify the patient-reported outcome measures (PROMs) that best cover the identified themes.

Methods A systematic review of the main six databases from inception to September 2018 was undertaken to identify primary qualitative studies reporting on the HRQoL of patients with carotid artery stenosis. The quality of studies was assessed using the Critical Appraisal Skills Programme (CASP) criteria. Findings from the included studies were analysed using framework analysis methodology. The identified themes were mapped against the items/domains from the PROMs used previously in patients with carotid artery stenosis.

Results The systematic review identified four papers that fulfilled the inclusion criteria. The included papers reported the views of 62 patients with symptomatic carotid artery stenosis; 24 of the patients were awaiting assessment for intervention, 26 had carotid endarterectomy, and 12 were turned down for intervention and received best medical therapy. The overall quality of the included studies was good based on CASP criteria. Framework analysis identified 16 themes that were divided into five main domains: anxiety, impact on personal roles and activities, effect on independence, psychological impact, and symptoms. The best-fit generic and disease-specific PROMs were the Medical Outcomes Study 36-Item Short Form (SF-36®) and the Carotid Stenosis Specific Outcome Measure (CSSOM), respectively. None of the PROMs covered all the themes identified in the qualitative systematic review.

Conclusion The findings from the review identified the important themes that affect patients with carotid stenosis disease. The current generic and disease-specific PROMs do not cover all themes that impact the HRQoL of patients suffering with this disease. The proposed themes can be used to develop a new disease-specific PROM to measure HRQoL.

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Key Points

Carotid artery disease is the main cause of stroke; some patients with this disease can benefit from surgical intervention to reduce the risk of future stroke.

Understanding and measuring quality of life in these patients can guide intervention decisions.

This systematic review provides a detailed overview of the impact of this disease on quality of life.

1 Introduction

Carotid artery stenosis (CAS) is a major cause of stroke, accounting for about 20% of all cases [1, 2]. It is caused by either carotid artery lesion thrombosis or embolism of this lesion.

△ Adis

Patients with CAS can be asymptomatic or present with transient ischaemic attack (TIA) or stroke. Evidence shows that patients who present with disabling stroke with previous evidence of CAS can benefit from preven- tive procedures including carotid endarterectomy (CEA) and stenting [3–10]; however, these procedures are notrisk free and can be complicated with perioperative stroke. The symptoms and the uncertainty of outcome can impact the daily lives of patients with CAS. Therefore, several clinical studies that investigated the efficacy and safety of different preventative interventions used patient-reported outcome measures (PROMs) to investigate the impact of the disease and treatment on health-related quality of life (HRQoL). However, due to a lack of validated PROMs, they either used generic PROMs [11–14] or developed and used questionnaires without validation [14].

Patients presenting with symptomatic and asymp- tomatic CAS need support to choose the best treatment strategy to help reduce their risk of stroke and improve their HRQoL. Patients' experience of disease and impact of treatment is a major indicator of quality, and it is only through better understanding of the impact of the disease on HRQoL that PROMs can be developed. It is argued that PROMs, when designed carefully (e.g. based on input from patients' experiences), can measure the issues of greatest importance to patients and any changes to their HRQoL due to the disease or as a consequence of the treat- ment they may receive [15].

The aim of this study was to systematically review the qualitative evidence to identify the impact of CAS and treatment pathway on patients' HRQoL. The identified themes were then mapped against the items and domains from the generic and disease-specific PROMs we had previously identified [16, 17]. The mapping was done to find the PROMs that captured the most important issuesto patients with CAS.

2 Method

The systematic review aimed to identify all primary quali- tative research studies that investigated the impact of CAS on HRQoL. The inclusion criteria included any patients with CAS, and any studies with undefined population were excluded. For further information regarding the inclusion and exclusion criteria, refer to Table 1.

This systematic review was undertaken and reported in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement. In accordance with the study protocol [18], searches were conducted from inception up to April 2017 and further updated to September 2018, in the following bibliographic databases: CINAHL via EBSCO, Medline and Medline in Process via Ovid, Embase via Ovid, PsycINFO via Ovid, Social Science Citation Index/Science Citation Index via Web of Science (Thomson Reuters) and Proquest dissertations and theses. No language or date con- straints were applied.

The search strategy combined condition terms, termsfor patient views and terms for qualitative studies (which augmented a qualitative study filter) [19]. Further details of the search strategy are provided in Appendix 1 (see the electronic supplementary material).

2.1 Study Selection

The search results were uploaded into Endnote X8™ (Thom- son Reuters, Philadelphia, USA). Two reviewers (AA, AH) independently screened the titles for inclusion and exclu- sion in accordance with the set criteria in the protocol. All titles were examined, and any citations that clearly did not meet the inclusion criteria (for example, mixed population, quantitative PROMs data) were excluded. For included titles, abstracts were read, and for the included abstracts, full-text articles were obtained

Table 1 Summary of the inclusion and exclusion criteria

Inclusion	Exclusion
Patients' experience of living with CAS and its impact on their health-related quality of life	Studies not in English
	Studies with participants under 16 years of age
A defined population of participants with a diagnosis of CAS who need, have had or are undergoing surgical treatment. Participants undergoing treatment for stroke or TIA secondary to a diagnosis of CAS	Patients with stroke or TIA not related to CAS
Studies that include semi-structured interviews, descriptions, focus groups either as stand-alone studies or embedded in a quantitative study. Must include both data collection and data analysis	Quantitative studies with no primary qualitative data reported
Published or unpublished; full-text or structured abstract with all relevant information	Full-text or structured abstract with incomplete or unclear evidence

CAS carotid artery stenosis, *TIA* transient ischaemic attack

2.2 Quality Assessment

The Critical Appraisal Skills Programme (CASP) qualitative checklist instrument was used to examine the methodological quality of the included studies [20]. This was selected for its appropriateness as it is commonly used in qualita- tive reviews of evidence [21]. Two of the authors (AA, AH) independently examined the quality of each study, and any inconsistencies were resolved by discussion or involving a third author (GJ).

2.3 Data Extraction and Analysis

The data on authors, year of publication, country of study, number of participants, research aims, methods of recruitment, method of data collection, key results and analysis were extracted and tabulated for all the included studies by the first author. The included papers were uploaded into the qualitative data analysis software NVIvo10 (QSR International, Doncaster, Victoria, Australia) and the primary and secondary text (patient quotes reported in the articles and themes) were analysed. The inductive process of framework analysis was used for the qualitative evidence synthesis. In another systematic review [17], the PROMs used for this condition were examined for their validity; their conceptual domains were used to give a basis for the qualitative data synthesis [22]. The first stage of the framework analysis was reading all the included papers and identifying com- mon themes from within and across the articles. The second stage involved establishing a thematic framework by creating a list of the main themes based on the domains of validated PROMs and common themes in the identified papers. In the third stage, the thematic framework was applied to all the primary and secondary data. In the final stage, themes were examined for their conceptual similarities and differences. The second author (AH) checked all the themes that were identified, and differences in conceptualisation were discussed and adjusted involving a third senior author (GJ).

2.4 Triangulation of PROMs Items with Qualitative Themes

A triangulation of evidence was performed to examine how the items within generic and disease-specific PROMs corresponded to themes from the qualitative review [23, 24]. The items from generic and disease-specific PROMs used in patients with CAS [17] were examined in detail. The items from these instruments were mapped against the themes identified, and two researchers (AA, AH) reviewed both the themes from the qualitative review and the items from each PROM to evaluate whether the concepts were the same (agreement), offered similar concepts (partial agreement) or were not present (silence). The aim was to identify whether

any of the instruments covered the issues that are important to patients with carotid artery disease.

3 Results

The database searches identified 1095 citations; after removing duplicates, 874 titles were assessed, and subsequently, 15 full-text papers were reviewed in detail. Finally, only four papers fulfilled the inclusion criteria and were included in the qualitative evidence synthesis (see the PRISMA chart in Fig. 1). The studies included in the qualitative synthesis are summarised in Table 2.

Three of the included studies were from the UK [25, 27, 28] and one from Sweden [26]. The studies were published between 2002 and 2013; the age of patients with carotid artery disease in the included studies ranged from 50 to 80 years, and the percentage of male participants was 50– 65%. The included studies reported the views of 62 patients with symptomatic carotid artery stenosis; 24 of the patients were awaiting assessment for surgery, 26 had under- gone surgery, and 12 were turned down for intervention and received best medical therapy.

2.5 Quality Assessment

The quality of the included studies was assessed independently by two authors (AA, AH) using the CASP checklist [10] for qualitative studies; any disagreement on the final score was resolved through discussion and/or involving a third senior author (GJ). The overall quality of the included studies was good, and all the studies scored "yes" for almost all the criteria set in the CASP checklist; only one study scored "can't tell" on the rigour of the data analysis [25]. For detail on the quality of the included studies see Table 3.

2.6 Analysis

The framework analysis of the primary and secondary data of the included papers identified 18 themes. These were divided into five main domains comprising anxiety, impact on personal roles and activities, effect on independence, psychological impact, and symptoms. Please see Table 4 for further details.

2.6.1 Anxiety

The anxiety domain had several themes, including fear of stroke, fear of becoming a burden, worry and uncertainty about the future, and fear regarding the consequences of the operation. These four themes were grouped together

Fig. 1 PRISMA diagram for the carotid stenosis qualitative systematic review. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses
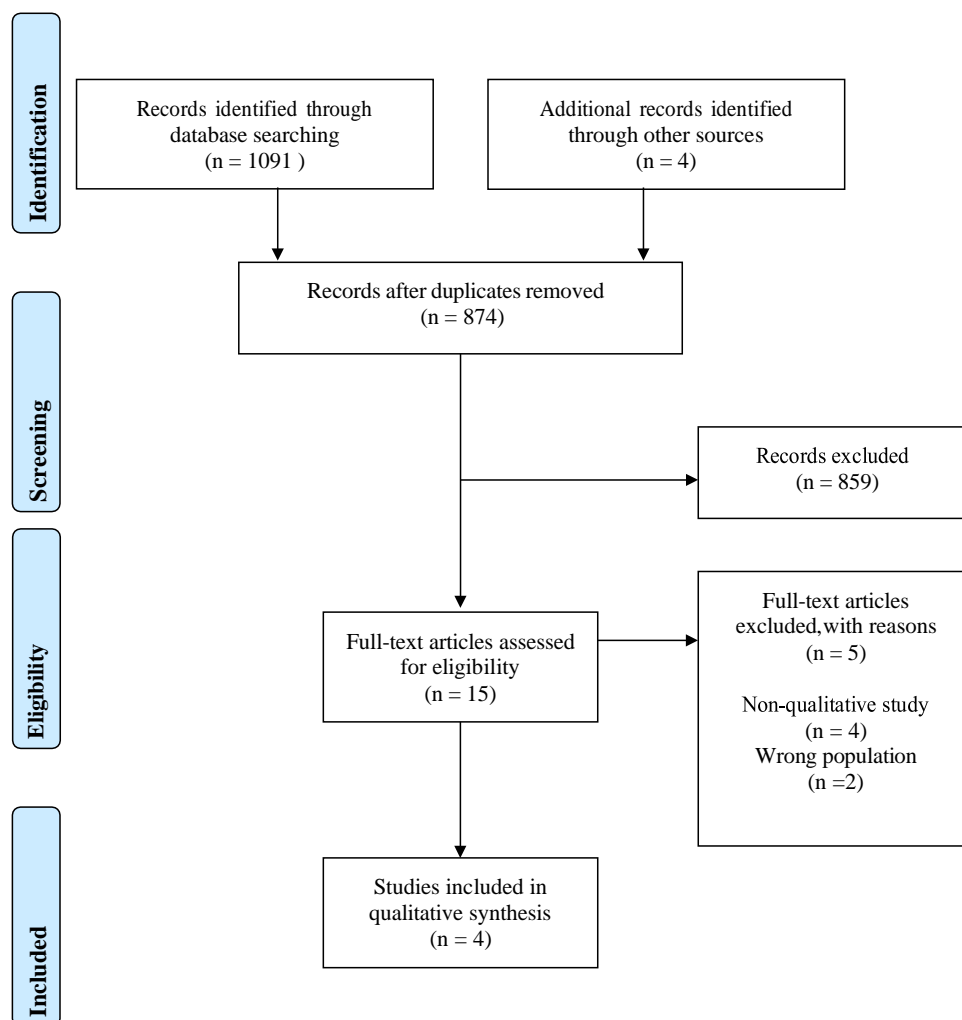
because of overlapping. The impact of anxiety on the daily lives of patients suffering with CAS featured in all four studies. Patients experiencing symptoms of TIA secondary to CAS expressed concern about fear of stroke. Patients said:

"I'm afraid of having a stroke and then becoming paralysed." (Pre-operative patient, age not reported) [26]

"I'd be worrying a lot, yes, wondering when or where or how it (stroke) was going to happen…it would be in the back of my mind…which takes some of the pleasure out of life." (Patient experienced TIA—before CEA) [27]

"Well, I wouldn't like to be here and have one (stroke) on my own." (Patient experienced TIA—before CEA) [25]

Two of the major causes for worry from having symptomatic CAS that can cause stroke were uncertainty and fear

of becoming a burden. Participants in the included studies reported feeling that their life was put on hold, and many were worried that a disabling stroke may make them a burden on others, including their family members.

"It's the unknown isn't it, that's what makes you fearful, you don't know what's going to happen." (Patient after the CEA reflecting on experiences prior to the surgery) [25]

"I'm afraid of becoming dependent on care." (Pre-operative patient) [26]

Uncertainty about the future and fear of sudden stroke affected patients treated with best medical therapy when compared to patients treated with preventive procedures such as CEA or stenting [27]. Another source of anxiety was the worry about complications of surgery, including death or stroke. Many patients' perceptions about the risk of stroke from the preventive procedures were disproportionate [25]; some patients thought that their risk of stroke

Table 2 Qualitative studies exploring living with carotid artery stenosis

Author (year)	Country	Research design	Method of analysis	Age: mean (range), years	Sample	Diagnosis/treatment	Study aims and objectives
Gibson (2002) [25]	UK	Qualitative semi-structured interviews	Grounded theory	70.9 (50–79)	6 participants; male (%): 50	Symptomatic carotid stenosis. Medical management: 1. Post-CEA: 5	Explore ways in which patients comprehend and live with risk of CEA or medical management only for carotid stenosis
Hallin et al. (2002) [26]	Sweden	Mixed methods including a qualitative component using semi-structured interviews	Thematic analysis	71 (56–80)	20 participants; male (%): 60	Symptomatic carotid stenosis. Medical management, no intervention: 1. Post-CEA: 11. Pre-CEA or stent: 8	Assess quality of life of patients with carotid artery stenosis
Gibson and Watkins (2012) [27]	UK	In-depth interviews	Grounded theory	71.6 (50–80)	16 participants; male (%): 65	Symptomatic carotid stenosis	Explore the lived experience of patients with TIA secondary to carotid stenosis
Gibson and Watkins (2013) [28]	UK	In-depth semi-structured interviews	Thematic analysis	70.2 (50–80)	20 participants; male (%): 65	TIA/recovered stroke. Post-CEA: 10. Medical management: 10	To examine the use of formal and informal knowledge by patients in making decisions about CEA and medical treatment after TIA/recovered stroke caused by carotid stenosis

CEA carotid endarterectomy, *TIA* transient ischaemic attack

Table 3 CASP checklist final score for included

CASP quality appraisal

Study	1. Was there a clear statement of the aims?	2. Is a qualitative methodology appropriate?	3. Was the research design appropriate to address the aims of the project?	4. Was the recruitment strategy appropriate to the aims of the research?	5. Was the data collected in a way that addresses the research issue?	6. Has the relationship between researcher and participants been adequately considered?	7. Have ethical issues been taken into consideration?	8. Was the data analysis sufficiently rigorous?	9. Is there a clear statement of findings?	10. How valuable is the research?
Gibson (2002) [25]	✓	✓	✓	✓	✓	✓	✓	?	✓	✓
Hallin et al. (2002) [26]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gibson and Watkins (2012) [26]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gibson and Watkins (2013) [28]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

CASP Critical Appraisal Skills Programme

from the surgery was 50%, and this is higher than the 2% reported by clinical studies [3, 4]. Furthermore, many patients had an inaccurate recall of the risks of treatment options offered to them [25].

> "[I]f somebody tells you there's a 50% chance of having a stroke (without surgery) that's in your mind all the time." (Patient after the CEA reflecting on experiences prior to the surgery) [25]

> "You're damned if you do and damned if you don't, I mean I'd have a stroke if I didn't have it, and I might have the stroke under the operation." (Patient experienced TIA—before CEA) [25]

Patients with successful revascularisation reported improved psychological wellbeing and felt that they could move on with their lives compared to the time prior to their procedure when they felt that their daily lives were overshadowed by the worry associated with the CAS diagnosis and possible stroke [25].

> "I'm a happier person, physically and emotionally." (Patient after the CEA reflecting on experiences prior to the surgery) [25]

2.6.2 Impact on Personal Roles and Activities

Some participants in the included studies described the onset of symptomatic CAS to have put a hold on their life, and without the preventative surgery, they would have not been able to carry on with their personal roles and daily activities [25]. Some patients took many measures in their daily lives to avoid activities that they perceived might increase their risk of further TIA or major stroke. For instance, some patients made changes to their diet [26].One patient said:

> "I'd have been worried about having a stroke, it curtailed my activities." (Post-operative patient) [26]

The anxiety associated with further TIA or strokes as well as residual symptoms of strokes had an impact on the physical functioning of the patients [25]. Patients also suggested that the symptomatic CAS causing TIA dramatically changed their perception about their physical health. Furthermore, the attitudes of family and friends reinforced this view of diminished physical function [27].

> "I've always kept my health…this has absolutely shattered me." (Patient experienced TIA) [27]

> "[Y]ou're not as fit as you thought you were, everybody's always telling me to be careful, and have a rest…people around me have sort of convinced me that I'm a bit fragile…" (Patient experienced TIA) [27]

Table 4 Themes identified from qualitative research studies of patients with carotid artery stenosis

Themes (domains in **bold**)	Gibson (2002)	Hallin et al. (2002)	Gibson and Watkins (2012	Gibson and Watkins (2013)
Anxiety				
Fear of stroke	√	√	√	√
Fear of becoming a burden	√	√	√	√
Fear of operation	√	√		√
Uncertainty about future	√	√	√	√
Impact on personal roles and activities	√	√	√	√
Effect on independence	√	√	√	√
Psychological impact				
Happiness	√		√	√
Health perception	√			
Symptoms				
Weakness			√	
Numbness or loss of sensation			√	
Loss of ability to speak			√	
Loss of vision			√	
Cognitive function			√	
Duration of symptoms			√	
Neck stiffness	√		√	

3.2.3 Effect on Independence

All the included studies reported that patients sufferingwith CAS felt that their social life and independence were compromised because of the disease and its potential consequences. Patients expressed concerns about the impact of the disease and its possible consequences on their independence.

> "I'm afraid of becoming paralysed and dependent on care." (Patient reporting after surgery) [25]

> "I'm enjoying life and I want it to go on, without having a stroke." (Patient reporting after surgery) [28]

3.2.4 Psychological Impact

Patients suffered issues related to their health perception; the diagnosis had adverse consequences for many patients, with some reporting that they felt their daily life was being shattered with the new diagnosis [27].

Some patients developed low mood when they understood the risks associated with their disease; however, on the other hand, patients who had the operation and did not experience any complications reported that they felt happier emotionally having dealt with a potentially significant disease that made them feel unhappy [25, 27, 28]. One patient reported:

> "I'm a happier person, physically and emotionally." (Patient reporting after surgery) [25]

3.2.5 Symptoms

The symptomatic outcomes that were reported by the patients could be divided broadly into two main groups: symptoms associated with TIA and post-intervention symptoms. Patients experiencing TIA reported classical symptoms including loss of sensation, weakness, temporary loss of the ability to speak and loss of vision [27].

> "I couldn't pick anything up at all, I had great difficulty in using the knife and fork…and then suddenly it came back." (Patient reporting TIA symptoms) [27]

> "I just thought a film had come over my eye." (Patient reporting TIA symptoms) [27]

Patients described symptoms of neck pain and discomfort at the site of the operation to treat CAS following CEA [25]

> "[D]id feel better, apart from residual minor discomfort from surgical incision pain and neck stiffness." (Patient reporting after surgery) [25]

Lastly, some patients described loss of cognitive function that was noticeable by their family and caused con- cern for the patient [25].

"I have difficulties taking part in advanced discussions." (Patient with CAS) [25]

2.7 Triangulation

The identified themes were compared to items from PROMs that were identified in a recent study [17]. These PROMs include the carotid artery disease quality of life questionnaire developed by the Carotid Revascularization Endarterectomy versus Stenting Trial [CREST randomised controlled trial (RCT)] group, the Carotid Stenosis Specific Outcome Measure (CSSOM) developed by Ivanova et al. [29], the Dizziness Handicap Inventory (DHI), the Hospital Anxi- ety and Depression Scale (HADS), the EuroQoL-5D (EQ- 5D), and the Medical Outcomes Study 36-Item Short Form(SF-36®). Two reviewers (AA, AH) examined the overlap between the themes in the qualitative review and the items in the PROMs. When there was complete overlap between the theme and an item in an instrument, an agreement score (+) was awarded; however, when the theme was covered in a general question, a partial agreement score was awarded (+/−).

None of the identified PROMs covered important HRQoL themes such as fear of stroke or fear about the operation as well as uncertainty about the future caused by the diagnosis of the disease. Many of the symptoms described in the qualitative evidence synthesis of this study were not included in the PROMs used previously. The generic PROM that captured most of the important issues for patients with CAS was the SF-36®, and the disease-specific PROM was the PROM for carotid artery disease developed by Ivanova et al.[29]. However, both PROMs did not cover all the themes identified in this review. For further details on the results of triangulation, see Table 5.

4 Discussion

We identified five domains that impacted upon the HRQoL of patients with CAS throughout their care pathway. These included anxiety, impact on personal roles and activi- ties, effect on independence, psychological impact, and symptoms.

The HRQoL of patients with CAS undergoing either revascularisation or best medical therapy has only been measured using generic PROMs, anxiety-specific PROMs and questionnaires developed by clinicians with no validation (RCT) [5–11]. A single RCT attempted to develop a disease-specific PROM for patients with CAS [11]; however, the instrument was made of the six items suggested by clinicians and, more importantly, patients were not consulted. Furthermore, there was no further validation for this PROM.

Clinical outcomes such as 30-day mortality, stroke-free survival, and re-stenosis have been used to compare the efficacy of surgical, radiological and medical therapies for patients with CAS. These are important outcomes; however, HRQoL, when measured using a validated PROM, can provide comprehensive data about the impact of differ-ent therapies. The themes from this review can be used to develop a more tailored PROM that can be used in routine clinical practice both to inform discussion between patients and clinicians and as a quality measure of the carotid revascularisation service.

One of the strengths of this study is that the qualitative review included patients at different stages of their care pathway, including 62 patients with symptomatic CAS; 24 of the patients were waiting to meet a clinician to decide whether they were suitable for surgery or stenting, 26 patients had CEA with no complications, and 12 patients had been turned down for surgical or interventional radiology procedures. This review used the evidence from an earlier systematic review [11] by the same group to evaluate the validity of PROMs used in patients with CAS. This earlier systematic review was performed to examine the psychometric validation evidence for PROMs used in patients with CAS. In the triangulation section of this study, the themes from the qualitative review were mapped against the items from the generic and disease-specific CAS PROMs that were identified.

The main limitation of this study is that it relied on the primary and secondary data of existing studies. The patients sampled in one of the studies only included those with CAS waiting for an operation [27], whereas, the other three studies included patients on best medical therapy for CAS as well as patients waiting for preventive surgery and patients following their operation. Furthermore, the included studies, beside investigating aspects of HRQoL, also examined issues such as decision making about management thatwere not related to HRQoL. Additionally, few patients whowere treated with best medical therapy or turned down for revascularisation were included in any of the studies. The included papers did not distinguish clearly between patients with resolved stroke symptoms and TIA. Some papers mentioned important themes such as denial of diagnosis and depression, but failed to report any primary evidence to support these themes [27, 28].

Amongst some clinical academic circles HRQoL has confusingly come to be known as anything which is not clinical [30]. However, this study demonstrates that patients with CAS experience distress related to diagno-sis and the risks associated with the intervention. These have an adverse impact on their wellbeing and should be taken into consideration by the clinician. The review iden- tified anxiety to be an important domain that impacts the

Table 5 Themes identified from the qualitative review mapped against items of validated PROMs

Themes (domains in **bold**)	CREST PROMs	CSSOM	DHI	HADS	EQ-5D	SF-36®
Anxiety	−	+	+/−	+	+	+
Fear of stroke	−	−	−	−	−	−
Fear of becoming a burden	−	+	−	−	−	−
Fear of operation	−	−	−	−	−	−
Uncertainty about future	−	−	−	−	−	−
Impact on personal roles and activities	−	+	+	+/−	−	−
Effect on independence	−	−	+/−	−	−	−
Psychological impact	−	+	+	+	+/−	+
Happiness	−	+	+	+	−	+
Health perception	−	−	−	−	−	−
Symptoms	+/−	+	+	−	−	−
Weakness	−	+	+/−	−	−	−
Numbness or loss of sensation	−	+	−	−	−	−
Loss of ability to speak	−	−	−	−	−	−
Loss of vision	−	+	−	−	−	−
Cognitive function	−	+	−	−	−	−
Duration of symptoms	−	−	−	−	−	−
Neck stiffness	+	+	−	−	−	−

Scores: − silence; +/− partial agreement; + agreement

CREST Carotid Revascularization Endarterectomy versus Stenting Trial, *CSSOM* Carotid Stenosis Specific Outcome Measure, *DHI* Dizziness Handicap Inventory, *EQ-5D* EuroQoL-5D, *HADS* Hospital Anxiety and Depression Scale, *PROMs* patient-reported outcome measures, *SF-36®* Medical Outcomes Study 36-Item Short Form

HRQoL of patients with CAS, and this is related to fear of stroke, uncertainty about the future, fear of becoming a burden on others, and fear of the operation. Carotid artery disease also had an impact on patients' independence and personal functioning, and beyond anxiety, had a further psychological effect on patients.

This systematic review of the qualitative evidence combined all the relevant data concerning the impact of CAS and its treatments on the patients. One of the strongest findings of this study is that none of the generic and disease-specific PROMs covered all the important issues for CAS patients revealed by this qualitative systematic review.

5 Conclusions

The identified themes that impact the HRQoL of patients with CAS can be used to develop a disease-specific PROM. Our group has designed such an instrument and is currently validating this PROM in an extensive survey of patients with CAS. The aim is to perform a factor analysis as well as further psychometric studies to ensure the PROM's validity, reliability, and responsiveness.

Data Availability Statement The analysis data cannot be shared since some of the papers included in the systematic review have copyright agreements that prohibit their publication in other journals but allow researchers to use them for secondary analysis. These papers were uploaded into the software in which we performed the analysis. Supplementary materials are included regarding the search strategy and analysis.

Author Contributions Ahmed Aber contributed to the analysis and interpretation of data, drafting of the manuscript, and critical revision. Aoife Howard contributed to the analysis and interpretation of data and drafting of the manuscript. Helen Buckley Woods performed the searches for the systematic review and helped in drafting of the manuscript. Georgina Jones contributed to the study conception and design, analysis and interpretation of data, and drafting of the manuscript. Jonathan Michaels contributed to the study conception and critical revision.

Compliance with Ethical Standards

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Chapter Eight. The conceptual framework of ePAQ-VAS.

In this chapter, I will present an overview of my contribution to the development of the conceptual framework of ePAQ-VAS. This includes the design of the sections and questions of this new instrument. The chapter will provide further insights into the methods used in the fifth paper of this PhD by publication "Mixed methods study to develop the content validity and the conceptual framework of the electronic patient-reported outcome measure for vascular conditions" and provide a critique **(39).** Ethical approval for this study was approved by National research ethics service (NRES) committee in Yorkshire & Humber – Bradford Leeds (REC Number: 14/YH/1117) on 25th of September 2014.

The next stage in developing ePAQ-VAS following the qualitative study and the reviews was the development of the hypothesised framework based on the input from the patients and clinicians. This was completed in accordance with international guidelines such as the FDA PROMs development guidance **(53)**. FDA guidance emphasises that PROMs should have strong evidence of 'content validity' supported by a process involving the development of a hypothesised conceptual framework based on literature review and expert opinion and qualitative interviews with patients, with subsequent adjustment of the conceptual framework as needed.

The development process of PROMs, in general, is an iterative rather than linear process, often requiring PROMs developers to re-examine previous steps to ensure adequate and accurate information related to PROMs structure and to fully document the content validity of the tool. Therefore, necessary changes to the structure and content of the PROMs can be applied.

The first step in developing a hypothesised framework for ePAQ-VAS is to identify the conditions it would cover and the target populations of this instrument. Twenty-three clinicians involved in the care and management of patients with vascular conditions were invited to a survey to list the most common vascular conditions seen by them in their clinical practice. They were also asked to list the key themes to be included in PROMs that could be used in routine clinical practice. The information obtained was the first building blocks for the new instrument. Twelve clinicians including 10 surgeons and two general practitioners responded to this survey (10 males). The main vascular conditions to be included were AAA, PAD, CAD, VVs and VLU.

The second step in developing a conceptual framework was to identify the context in which the new tool will be used and how it will be used by the service users. For ePAQ-VAS, the aim was for this tool to be completed online by patients before their outpatient clinic appointment. This was to follow the existing models of other ePAQ instruments in clinical use in National Health Service (NHS) hospitals in the United Kingdom, such as

ePAQ-Pelvic floor and ePAQ-Pre-assessment **(30-33)** The third step was to use the findings from the triangulation studies that were published along with the qualitative reviews of AAA, PAD, CAD, VVs and VLU to develop an item from each theme identified. I was responsible for developing items for the AAA, CAD and PAD sections. The process involved reviewing the original qualitative data and extracting the terms expressed by patients when referring to their conditions to design the questions. The number of scales (also called domains) within each questionnaire were decided by the ePAQ- development group following the review of identified PROMs and discussion with four members of the clinical advisory group at Sheffield. This ensured that the content of items as well as the structure of ePAQ-VAS were based on the primary qualitative interviews with vascular patients, input from clinicians, systematic reviews examining the validity of existing PROMs and qualitative reviews of the impact of vascular diseases on the quality of life. However, this led to the creation of many items and the repetition of similar questions in different sections. The limitations of such an inclusive process were that the data, especially from the qualitative studies, were large and difficult to integrate fully into the ePAQ-VAS without increasing the burden of the questionnaire or repeating the same questions for different conditions. The primary qualitative study alone reported 45 themes, and the five qualitative reviews identified 31 papers. Furthermore, although some common themes were identified for different conditions, the concepts of the themes were broad and perceived differently by people with different conditions. For instance, the pain was identified as a theme in PAD, VVs and VLUs; clinically PAD rest pain is very different in quality to the ache caused by VVs or burning pain of a chronic venous leg ulcer. Therefore, designing a questionnaire to differentiate between the severity of pain in these groups was more complex than previously anticipated. It was decided to create disease-specific symptom scales for PAD, VVs and VLU conditions in consultation with the clinical advisory group in Sheffield. I organised these meetings with the clinicians and integrated the changes agreed to the conceptual framework of ePAQ-VAS.

The lower limb section was designed to include the following scales: PAD symptoms, VVs symptoms, VLU symptoms and a scale about the impact of the lower limb vascular disease on activities of daily living. There were also standalone items about lower limb amputations. The organisation of this section was because these three conditions predominately affect the lower limbs, and by organising the items into this dedicated lower limb disease section, the burden of the questionnaire was reduced. The electronic platform of ePAQ-VAS with well-designed skipping rules also helped by only presenting relevant sections of the questionnaire. Some questions were designed to help this skipping process, and the respondents are presented with sections only if they have responded positively to one of these questions.

A consensus exercise with 30 clinicians and two rounds was carried out to confirm the conceptual framework of ePAQ-VAS. A multidisciplinary panel of clinicians with expertise in care for patients with vascular were

invited by the author of this thesis to participate in this study. Potential participants were identified from members of the Vascular Society of Great Britain and Ireland) and further recommendation by the participants. An invitation letter was sent via e-mail providing a brief outline of the project, its objectives, the expected number of rounds and anticipated time commitment. As the study was conducted in English, the ability to communicate in English was a prerequisite for participation. A positive response to the invitation letter served as informed consent. The study was conducted in two rounds. In the first round, the expert panel was presented with a list of all the questions in ePAQ-VAS. They were asked, based on their clinical experience and knowledge, to rate the appropriateness and relevance of each question on a 5-point Likert scale of 'strongly disagree' (=0) to 'strongly agree' (=4). Space was also provided for experts to present new questions that they felt were appropriate, and they could provide comments about the structure of ePAQ-VAS.

The summary of responses obtained in round 1, new questions and comments were incorporated into the second survey. During this round, experts were given the opportunity to view the group results and provide their own ratings considering their colleagues' responses. The results of this survey were not used to drop items from ePAQ-VAS at this stage. Involving more clinicians was important at this stage to ensure the tool is useful for clinicians and it captures important aspects of care from their perspective. ePAQ-VAS was designed to be relevant to a vascular specialist so that it can be adopted into routine clinical use. This was to avoid the common problem of the existing PROMs that are rarely used for clinical assessment or outcome measurement. Following two rounds, five further items were added to ePAQ-VAS, including questions about associated symptoms with AAA, family history of AAA, questions about severity, recurrence and duration of TIA and stroke symptoms. 13 clinicians participated in both rounds of the consensus study; this included 9 males and 4 females (Seven vascular and endovascular surgeons, three specialist vascular nurses, two professors of vascular surgery and one vascular surgery associate specialist). The initial plan in the grant application was to perform a Delphi study, and the option was there to make items redundant based on the Delphi study. However, the decision was made by the ePAQ development group to keep all items based on the qualitative data at this stage regardless of the consensus relevance score from the clinicians. This decision was made to make sure no item suggested by patients is deleted without input from patients.

The final stage in refining the items and the conceptual framework of ePAQ-VAS was a face validity study. Both the electronic and paper format of ePAQ-VAS were presented to vascular patients treated at Sheffield Vascular Institute. The format of this study was a semi-structured interview asking the patients about the clarity of the instrument and individual items within it. The study also aimed to examine the relevance of the items (both the questions and the responses) to the service user and ways to improve the wording of questions. The face validity study also examined the impression of the patients about the usefulness of

adopting this tool and whether they felt this would be a useful adjunct to help them along their treatment pathways. In the face validity study, there were plans for a focus group but organising this was restricted by the time limitations and the need to move to the survey stage in which ePAQ-VAS was to be presented to vascular patients for use so that the instrument's psychometric properties can be examined. The focus group could have provided further valuable information about the tool as participants could have compared their experiences with others, and it could have been a rich source of data about the relevance of this PROMs. This is a major limitation of the face validity study.

Four patients with AAA, three patients with CAD, four with PAD, four with VLU and four with VVs were recruited from the Sheffield Vascular Institute for the face validity study. The transcript of the audiotaped interviews was analysed using a pragmatic approach in which the comments from the study participants were presented back to members of the ePAQ-VAS development group who made consensus decisions on changes to the wording of items in ePAQ-VAS.

Comments from the participants in the face validity study helped rephrase twelve questions in ePAQ-VAS. The comments from the participants were about the use of abbreviations, response options and scales, the use of free-text boxes and the language and wording used, when and how to use the skip button, and the possibility of emotional distress associated with questions about the possibility of health deterioration and death.

In summary, the development of the ePAQ-VAS conceptual framework was based on the findings of a qualitative study with vascular patients treated at Sheffield Vascular Institute, five systematic reviews to identify existing PROMs for the five vascular conditions, five systematic qualitative reviews, a consensus study with clinicians and a face validity study with patients. I contributed to seven systematic reviews supporting this work and conducted the clinician consensus study.

The ePAQ-VAS development group identified 168 items; five of these items were suggested by the clinicians; in an iterative process, 59 items were eliminated to avoid unnecessary overlap between questions and repeating the same questions in different sections. The overlap was identified by comparing the proposed questions and returning to the qualitative evidence. The tool was divided into a generic, AAA, CAD, lower limbs and a final generic section with EQ-5D. These sections were divided into eight scales, including CAD-related anxiety, the impact of CAD on activities of daily living (ADLs), AAA-related anxiety, the impact of AAA on ADL, PAD symptoms, VLU symptoms, VV symptoms and impact of LL vascular disease on ADL. The generic section included questions about pain, altered sensation, weakness, weight/height, smoking habit, previous medical history and regular medication. The data from this section were important for the assessment of vascular conditions, and the items did not contribute to a domain or scale structure or score. The use of this mixed methods approached enabled us to use qualitative reviews, direct qualitative evidence from patients

and clinicians. The iterative approach ensured that the proposed structure was revised and refined based on the evidence from the different studies. This PROMs was supported by ten reviews, a large qualitative review, clinicians' consensus study and a face validity study. This comprehensive approach is one of the strengths of ePAQ-VAS and no other vascular PROMs used this approach in the past.

Chapter Nine. Paper 5 "Mixed methods study to develop the content validity and the conceptual framework of the electronic patient-reported outcome measure for vascular conditions".

BMJ Open

Mixed methods study to develop the content validity and the conceptual framework of the electronic patient-reported outcome measure for vascular conditions

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ABSTRACT

Objective The aim of this paper is to describe the stages undertaken to generate the items and conceptual framework of a new electronic personal assessment questionnaire for vascular conditions.

Design A mixed methods study: First a survey of vascular clinicians was completed to identify the most common conditions treated in vascular clinics and wards. Quantitative systematic reviews were done to identify validated patient-reported outcome measures (PROMs) for direct inclsuion in the new instrument. However, due to scarcity of validated PROMs, the items of the new instrument were mainly based on a large qualitative study of patients and systematic reviews of the qualitative evidence . This was followed by a quantitative clinicians' consensus study and, finally, a qualitative face validity study with patients.

Participants Vascular patients participated in the primary qualitative study and the face validity study. In the qualitative study, 55 patients were interviewed, and for the face validity, 19 patients gave feedback. Twelve clinicians completed the survey and 13 completed two cycles of the clinicians' consensus study.

Results The items and scales in the electronic personal assessment questionnaire for vascular conditions (ePAQ-VAS) were generated based on the results of five systematic reviews evaluating existing PROMs for possible inclusion in ePAQ-VAS, five systematic reviews of qualitative evidence, a primary qualitative study involving 55 patients and clinicians' input. One hundred and sixty-eight items were initially generated, of which 59 were eliminated by the expert panel due to repetition. The instrument was divided into one generic and three disease-specific sections (abdominal aortic aneurysm, carotid artery disease and lower limb vascular conditions). In each section, items were grouped together into putative scales. Fifty-five items were grouped across eight scales; the remaining items were kept as individual items, because of relevance to service users.

Conclusions This multidimensional electronic questionnaire covers the most common vascular conditions. This is particularly important for patients

Strengths and limitations of this study

- ► This electronic patient assessment questionnaire for vascular conditions was developed with input from patients and clinicians.
- ► The themes generated from previously published five comprehensive qualitative reviews and a qualitative study of vascular patients were used to develop the items.
- ► Vascular clinicians were surveyed to ensure clinical-ly relevant conditions and questions were included.
- ► The burden of questionnaire is its main limitation; however, providing strict skipping rules, the patient were only be presented with the relevant sections and questions of the instrument.
- ► The face validity study examined the clarity and relevance of the items; however, the comprehensiveness of these PROMs was not assessed.

presenting with mixed symptoms or multiple conditions. This tool captures symptomatology, health related quality of life (HRQoL) and other clinically relevant data, such as experience with services and comorbidities.

INTRODUCTION

Vascular conditions can cause problems throughout the body; epidemiological studies suggest that both venous and arterial diseases are very common.[1 2] It therefore makes sense to assess individuals with vascular disease holistically, investigating existing or potential manifestations of vascular disease and the impact of conditions on health-related quality of life. Patient-reported outcome measures (PROMs) are questionnaires or instruments, designed to elicit information directly from the patient and can be used as part of such an assessment.
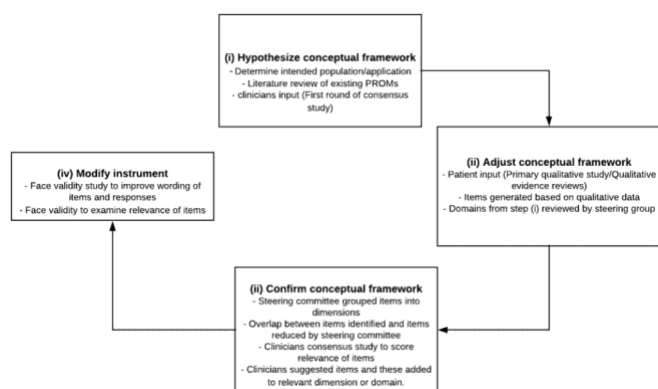
Figure 1 Development of ePAQ-VAS conceptual framework. PROMs, patient-reported outcome measures; ePAQ-VAS, electronic personal assessment questionnaire for vascular patients.

Validity and reliability are integral to developing or selecting a PROMs. A key aspect of validity is *content validity*, and international guidelines including the US Food and Drug Administration (FDA) guidance stress the importance of this psychometric property.[3]

Many generic and condition specific PROMs have been adopted to examine impact of vascular conditions on patients and measure outcomes. This is despite a lack of evidence that they have been developed and evaluated inline with accepted guidelines; in addition, these instruments are rarely used or formally evaluated in routine patient assessment in day-to-day clinical practice. We conducted scoping searches and informal discussions with vascular clinicians to identify any existing PROMs; however, these preliminary stages in the research process suggested an absence of valid and reliable PROMs for use in vascular populations.

In this paper, we report the stages in developing an electronic personal assessment questionnaire for vascular patients (ePAQ-VAS). This includes:

1. Identifying the main vascular conditions to be included in this electronic measure based on a survey of clinicians treating vascular disease.
2. Developing a hypothesised framework for the sections for different disease categories based on the previous systematic reviews that identified PROMs used in patients with abdominal aortic aneurysm (AAA), carotid artery disease (CAD), peripheral arterial disease (PAD), venous leg ulcers (VLU) and varicose veins (VV).[4–8]
3. Developing the items within each section of ePAQ-VAS based on qualitative systematic reviews[9–12] and a primary qualitative study.[13]
4. A consensus study with clinicians to rate the relevance of included items and to add items to ePAQ-VAS basedon the opinion of vascular surgeons, radiologists and nurses.
5. A face validity study with vascular patients to examine the clarity and relevance of the items within ePAQ-VAS.

The aim of these steps was to develop a single electronic instrument covering most vascular conditions in line with international guidance.[3] The conceptual framework and items were developed in a way to ensure this assessment tool can be used in patients with mixed symptoms and multiple vascular conditions. Every patient to receive a unique voucher code along with their clinic letters. The code can be used to access and complete ePAQ-VAS at home or in the outpatient clinic using computers or other electronic devices.

The server of ePAQ is hosted and integrated with National Health Service (NHS) N3-based informatics systems. Other ePAQ questionnaires such as ePAQ-Pelvic floor and ePAQ-preassessment are in clinical use in different NHS hospitals. ePAQ Ltd is an NHS spin-out technology company, and the patient data collected by the company can be linked to the unique NHS number of each patient, and although there is a lack of integrated

Table 1 Results from the systematic reviews of psychometric evaluation of vascular PROMs

Condition	Number of citations	Number of included papers	Results	Conclusions
AAA	1232	3	4 validated PROMs identified: 1 generic, 1 vascular generic and 2condition specific	This review has highlighted a gap in the evidence for validated PROMs in AAA. Due toa lack of rigorous psychometric testing.
CAD	1670	5	6 validated PROMs identified: 4 generic and 2 condition specific	There was a lack of validated PROMs tomeasure outcomes for CAD patients.
PAD	6981	14	13 validated PROMs identified: 6 generic and 7 condition specific	VascQol was the most psychometrically robustinstrument.
VV	3879	7	3 validated PROMs identified: 1 generic and 2 condition specific	Aberdeen Varicose Vein Questionnaire is the most psychometrically robust disease-specific PROMs for use with VV patients.
VLU	3879		7 validated PROMs identified: 3 generic and 4 condition specific	The most valid and reliable condition specific PROMs was VLU-QOL.

AAA, abdominal aortic aneurysm; CAD, carotid artery disease; PAD, peripheral arterial disease; VLU, venous leg ulcer; VLU-QOL, venous leg ulcer quality of life; VV, varicose veins.

Table 2 Participant characteristics of the primary qualitative study

	AAA	CAD	PAD	VV	VLU	Total
Gender, n (%)						
Male	10 (77)	5 (56)	11 (79)	5 (50)	8 (80)	39 (70)
Female	3	4	3	5	2	17
Age range (mean)	53–87 (72)	52–86 missing	47–82 (69)	35–77 (50)	47–84 (59)	35–87 missing

AAA, abdominal aortic aneurysm; CAD, carotid artery disease; PAD, peripheral arterial disease; VLU, venous leg ulcers; VV, varicose veins.

digital infrastructure in the NHS, the technology is available for future use to link records collected by different NHS providers.

METHODS

Clinicians involved in the care of vascular patients were invited to identify the common vascular conditions treated by vascular surgeons and vascular specialists. They were asked to list the key issues, symptoms and the impact of these conditions on patients suffering with these diseases. Data from this round were used to inform qualitative evidence synthesis.

The conceptual framework of ePAQ-VAS was based on primary qualitative interviews with vascular patients, input from clinicians, systematic reviews examining the validity of existing PROMs and qualitative reviews of the impact of vascular diseases on quality of life. Figure 1 illustrates the process used to develop ePAQ-VAS in accordance to s guidelines.[3]

Systematic reviews to identify and appraise existing PROMs

Systematic searches were conducted of bibliographic databases including CINAHL via EBSCO, MEDLINE and MEDLINE in Process via Ovid, Embase via Ovid, PsycINFO via Ovid, Social Science Citation Index/Science Citation Index via Web of Science (Thomson Reuters) and Proquest dissertations and theses. PROMs were included where there was evidence that they had undergone some form of psychometric evaluation that would allow the validity, reliability and responsiveness of the PROMs to be assessed. Included PROMs were categorised per type (generic or condition specific) and the vascular population(s) in which they had been validated. Quality assessment[3 14] was conducted to identify high-quality existing PROMs for possible direct inclusion in ePAQ-VAS or to be used as a basis to inform the qualitative evidence synthesis. For further information about the appraisal criteria to examine the robustness of the psychometric analysis and samples of search strategies, please see the online supplementary materials.

Table 3 Findings from the primary qualitative study with vascular patients

Condition	Sample size	Key findings
AAA	13	No physical symptoms, a small number of participants reported abdominal pain and pain in their legs. Uncertainty, anxiety and fear of rupture and death appeared to impact most greatly on people's QoL.
CAD	9	This condition seemed to have had the least impact on physical and social function, although psychologically it created a sense of worry and anxiety for some participants. The main reported outcome was fear of having a major stroke.
PAD	14	Pain and mobility were the most commonly reported themes. The extent to which they impacted on QoL was associated with the severity, age expectations and social support. Fear of the symptoms worsening and amputation was evident.
VV	10	VV do not appear to have had a major impact on overall QoL for most the participants. Pain was the most common issue. The perceived unpleasant appearance of the VV seemed to have the greatest psychological impact. Many of the participants had had their VV for very long periods of time, often just 'putting up with it' for numerous years before seeking help.
VLU	10	The impact of VLU on QoL differed within the group. For some, there were no major issues, and having a VLU was accepted as part of their current life, with the hope that it would heal eventually. For others, there was a far more significant effect. Pain was quite severe for some participants leading to a significantly reduced QoL. VLU appeared to have a significant psychological impact causing a high degree of distress for some.

AAA, abdominal aortic aneurysm; CAD, carotid artery disease; PAD, peripheral arterial disease; QoL, quality of life; VLU, venous leg ulcer; VV, varicose veins.

Table 4 Map of symptoms and quality of life concepts across five conditions

	PAD	AAA	CAD	VV	VLU
Symptoms					
No symptoms		×	×		
Pain	×	×	×	×	×
Neck pain			×		
Leg pain	×	×	×	×	×
Abdominal pain	×	×			
Arm pain	×				
Cramp/aching	×	×		×	×
Burning sensation					×
Pain severity	×	×	×	×	×
Pain on walking	×	×		×	×
Pain at rest	×			×	
Pain when standing				×	×
Mobility	x	x	x	x	x
Distance	x	x		x	x
Speed	x	x			
Stairs/slopes	x	x			
Non-healing wounds	x				x
Comorbidities	x	x	x		x
Progression of symptoms	x	x		x	x
Sleep	x		x	x	x
Swelling			x	x	
Loss of balance			x		
Confusion			x		
Impact on physical functioning					
Hobbies	x			x	x
Exercise	x	x		x	x
Daily activities	x				x
Social impact					
Travel	x	x	x		
Social activities	x	x		x	x
Social support	x	x	x		
Psychological impact					
Anxiety	x	x	x	x	x
Depression	x	x			x
Feelings of loss	x			x	x
Health expectations	x	x	x	x	x
Unsightly appearance				x	

Continued

Table 4 Continued

	PAD	AAA	CAD	VV	VLU
Feeling self-conscious	x			x	x
Fear of worsening symptoms	x	x	x	x	x
Fear of rupture death		x			
Fear of amputation				x	x
Fear of stroke			x		
Financial impact					
Income	×	×			×
Time off work				×	×
Lifestyle					
Smoking	×	×	×	×	×
Exercise	×	×	×	×	
Diet	×	×	×		×
Weight				×	×

AAA, abdominal aortic aneurysm; CAD, carotid artery disease; PAD, peripheral arterial disease; VLU, venous leg ulcer; VV, varicose veins.

Primary qualitative study

Semistructured interviews were conducted with 55 vascular patients from Sheffield Teaching Hospitals NHS Foundation Trust following purposeful sampling to ensure a range of participants of different age and gender, at different stages of treatment and covering the main five vascular conditions (AAA, PAD, CAD, VLU and VV). A consultant vascular surgeon or specialist nurse approached each patient either in clinic or over the telephone to explain about the project and ask if the patient would be interested in participating in the study. If the initial approach was by the clinician in clinic, the researcher would then speak to the patient and give further information about the project including a participant information sheet (PIS) before taking contact details. For those patients who were first contacted over the phone, the clinician would then gain verbal consent to pass on their contact details to a researcher. Copies of the PIS were sent out through the mail to those who had not been initially approached in clinic. The researcher gave at least 24 hours for the patient to read throughthe PIS and consider the information before contacting each person by telephone to ask if they would be inter- ested in participating in an interview. If they were inter-ested in taking part, a date and time was agreed for a researcher to visit the participant at home to carry out an interview. Questions were asked about the signs, symptoms and impact of the condition on function and lifestyle. On the day of the interview, the trained qualitative researcher checked if the participant understood the PIS and took informed written consent. Field notes

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Table 5 Results from qualitative reviews examining the impact of the major vascular conditions on quality of life

Condition	Numbers of citations	Number of included studies	Key themes
AAA	315	3	Anxiety and *lack* of physical symptoms.
CAD	964	3	Symptoms, psychological and social impact, risk and service experience.
PAD	973	9	Pain, compromised physical function and impact on social life.
VV	1804	3	Adaptation – coping strategies employed to limit various impacts, appearance of VV.
VLU	1804	13	Pain, odour and exudate – impact on sleep, mobility and mood.

AAA, abdominal aortic aneurysm; CAD, carotid artery disease; PAD, peripheral arterial disease; VLU, venous leg ulcer; VV, varicose veins.

were taken to aid interpretation of the interview data. Each interview was recorded and transcribed verbatim. Personal details were removed from the transcript to enhance participant anonymity. The interview transcripts were typed and uploaded into NVIVO V.11 (QSR International, Warrington, UK) for management and analysis.

Systematic reviews of the qualitative evidence

Systematic searches of the following databases; CINAHL via EBSCO, MEDLINE and MEDLINE in Process via Ovid, Embase via Ovid, PsycINFO via Ovid, Social Science Citation Index/Science Citation Index via Web of Science (Thomson Reuters) and Proquest dissertations were conducted to identify existing qualitative research detailing vascular patients' experience of living with AAA, PAD, CAD, VLU and VV. For further samples of search strategies, please see the online supplementary materials.

Analysis of the qualitative evidence

Qualitative data from the primary study and each of the systematic qualitative reviews were analysed separately. Framework analysis was used to analyse the interviews.[15] This analysis includes five stages:

► The first stage involved familiarisation by reading of the transcripts and reading the primary data.
► The second stage involved identification of a thematic framework; the thematic framework was based either on clinical opinion for areas with no valid PROMs, such as AAA and CAD, or a combination of clinical opinion and, when available, the scales of PROMs with good content validity.
► In the third stage, the data were coded and indexed by applying the thematic framework to the whole data set until saturation was achieved. An second researcher checked all the themes that were identified, and differences in were discussed and adjusted involving a third senior author (GJ).
► At the fourth stage, a framework matrix was created by arranging the data per the thematic references.
► Finally, mapping and interpretation, including examining patterns within the data and associations with it.

Clinicians' input and consensus exercise

Twenty-three clinicians involved in the care and management of patients with vascular conditions were invited to a survey to list the most common vascular conditions managed by them and to list the key issues, symptoms and the impact of these diseases on patients. Data from this round were used to inform qualitative evidence synthesis.

Different group of clinicians involved in the care of vascular patients were invited to a consensus study to score the relevance of items (questions) in the provisional version of ePAQ-VAS. In total, 30 clinicians including vascular surgeons, interventional radiologists, vascular nurses, physiotherapists and occupational therapists were invited. Participants were asked to rate the appropriateness of each question on a 5-point Likert scale of 'strongly disagree' (=0) to 'strongly agree' (=4). This process was repeated, and members of the clinicians' panel were presented with the aggregate findings of the previous round and again asked to score each question. This process aimed to examine the relevance of each item from the clinicians' perspective and to identify any new items suggested by the clinicians.[16]

Developing scales and items

The ePAQ development team (AA, EL, PP, GJ and SR) employed an iterative process, incorporating evidence from the systematic reviews, qualitative study and the clinicians' consensus study. In line with the FDA guidance,[3] items (questions) were developed from the qualitative data using the following three steps: interpretation, translation and triangulation of themes.

Interpretation involved familiarisation with the language used in the primary data included in the synthesis. This enabled translation of descriptions of apparently diverse issues affecting vascular patients into a single set of harmonised themes. The resulting themes were used to develop the items for ePAQ-VAS. The items were grouped into sections, and each section further divided into scales consisting of a connected group of items. Triangulation was performed across evidence sources to ensure the items comprehensively covered all issues of importance to patients with AAA, PAD, CAD, VLU and VV.

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Table 6 Structure of the main ePAQ-VAS with evidence base for inclusion of individual items, scales and sections

Section	Scale	Clinicians' consensus study	Most valid condition specific PROMs			Qualitative study					Qualitative reviews					Question text
			VLU-QOL	PADQOL	AVVQ	AAA	CAD	VV	VLU	PAD	AAA	CAD	VV	VLU	PAD	
Generic	Pain	4	×	×	×	×	×	×	×	×	×	×	×	×	×	Do you suffer with any pain?
Generic	Pain	4	×	–	–	×	×	×	×	×	×	×	×	×	×	Use the image below and click on body parts where you experience pain or discomfort.
Generic	Pain	–	×	–	–	×	×	×	×	×	×	×	×	×	×	Please use your own words to describe this problem.
Generic	Pain	4	×	×	×	×	×	×	×	×	×	×	×	×	×	How often do you experience a significant amount of pain?
Generic	Pain	4	–	–	–	×	×	×	×	×	×	×	×	×	×	How much do problems caused by pain affect your overall enjoyment of life?
Generic	Sensation	4	–	–	–		×	×		×	×	×	×		×	Do you experience any numbness or pins and needles in any part of your body?
Generic	Sensation	4	–	–	–		×	×		×	×	×	×		×	Please use the image below to select where you experience sensation change in your body.
Generic	Sensation	–	–	–	–		×	×		×	×	×	×		×	Please use your own words to describe this problem.
Generic	Sensation	4	–	–	–		×	×		×	×	×	×		×	How often do you experience numbness or pins and needles?
Generic	Sensation	4	–	–	–		×	×		×	×	×	×		×	How much do problems caused by numbness or pins and needles affect your overall enjoyment of life?
Generic	Weakness	4	–	–	–						×	×			×	Do you have any loss of strength or weakness in any part of your body?
Generic	Weakness	3	–	–	–						×	×			×	Please use the image below to indicate the areas where you experience any physical weakness.
Generic	Weakness	–	–	–	–						×	×			×	Please use your own words to describe this problem.
Generic	Weakness	4	–	–	–						×	×			×	How often do you experience loss of strength or weakness?
Generic	Weakness	3	–	–	–						×	×			×	How much do problems caused by weakness affect your overall enjoyment of life?

Continued

Table 6 Continued

Section	Scale	Clinicians' consensus study	Most valid condition specific PROMs VLU-QOL	PADQOL	AVVQ	Qualitative study AAA	CAD	VV	VLU	PAD	Qualitative reviews AAA	CAD	VV	VLU	PAD	Question text
Carotid	Anxiety	4					×					×				Do you worry about having a stroke?
Carotid	Anxiety	3					×					×				Does carotid artery disease make you feel anxious?
Carotid	Anxiety	New item														Are you worried about your health getting worse because of carotid artery disease?
Carotid	Anxiety	New item														Are you worried about losing your independence because of carotid artery disease?
Carotid	Symptoms	2					×									Do you have any problems with maintaining your balance?
Carotid	Symptoms	2					×									Do you suffer with any problems with your memory? (eg, forgetting or losing things)
Carotid	Symptoms	4					×					×				Have you had any problems with your speech? (eg, slurring your words or not being able to speak or say things properly)
Carotid	Symptoms	New item														Do you have any problems with swallowing food?
Carotid	Symptoms	4					×					×				Have you had any problems with partial or complete loss of vision in either of your eyes?
Carotid	Symptoms	4					×					×				How would you describe any loss of vision in your right eye?
Carotid	Symptoms	4					×					×				How would you describe any loss of vision in your left eye?
Carotid	ADL	3					×					×				How much do problems caused by carotid artery disease (anxiety associated with diagnosis or physical symptoms) affect your overall enjoyment of life?

Continued

Table 6 Continued

Section	Scale	Clinicians' consensus study	Most valid condition specific PROMs			Qualitative study					Qualitative reviews					Question text
			VLU-QOL	PADQOL	AVVQ	AAA	CAD	VV	VLU	PAD	AAA	CAD	VV	VLU	PAD	
Carotid	ADL	4					×					×				How much do problems caused by carotid artery disease (eg, mini-stroke or stroke memory balance speech visual or other related issues) affect your physical activities such as exercise walking or running?
Carotid	ADL	3					×					×				How much do problems caused by carotid artery disease (eg, mini-stroke or stroke memory balance speech visual or other related issues) affect your ability to undertake personal roles and responsibilities such as caring for others study or work?
Carotid	ADL	4					×					×				How much do problems caused by carotid artery disease (eg, mini-stroke or stroke memory balance speech visual or other related issues) affect your ability to look after yourself?
Carotid	ADL	3					×					×				How much do problems caused by carotid artery disease (eg, mini-stroke or stroke memory balance speech visual or other related issues) affect your social activities such as visiting friends and family?
Carotid	ADL	2					×					×				How much do problems caused by carotid artery disease visual or other related issues) affect your mood?
AAA	Symptoms	4				×					×					Do you have any abdominal (tummy) pain?
AAA	Symptoms	New item (3)														Do you experience a throbbing feeling in your abdomen (tummy)?
AAA	Anxiety	4				×					×					Do you worry about aortic aneurysm?
AAA	Anxiety	4				×					×					Do you worry about any symptoms you experience that may be caused by aortic aneurysm?

Table 6 Continued

Section	Scale	Clinicians' consensus study	VLU-QOL	PADQOL	AVVQ	AAA	CAD	VV	VLU	PAD	AAA	CAD	VV	VLU	PAD	Question text
			Most valid condition specific PROMs			**Qualitative study**					**Qualitative reviews**					
AAA	Anxiety	4				×					×					Do you worry about possible increase in the size of your aneurysm?
AAA	Anxiety	4				×					×					Do you fear sudden death or rupture of your aortic aneurysm?
AAA	Anxiety	4				×					×					Do you avoid physical exertion because of having an aortic aneurysm?
AAA	Anxiety	3				×					×					Do you avoid travelling independently because of aortic aneurysm?
AAA	ADL	3									×					How much do problems caused by aortic aneurysm affect your overall enjoyment of life?
AAA	ADL	4				×					×					How much does aortic aneurysm affect your physical activities? (eg, exercise walking or going out)
AAA	ADL	3				×					×					How much does aortic aneurysm affect your ability to undertake personal roles and responsibilities? (eg, caring for others study or work?
AAA	ADL	3									×					How much do you feel aortic aneurysm affects your ability to look after yourself? (eg, rest wash toilet or feed yourself)
AAA	ADL	4									×					How much does aortic aneurysm affect your social activities? (eg, visiting friends or family)
AAA	ADL	4				×					×					Do you suffer from low mood because of having an aortic aneurysm?
LL	Ischaemic Pain	4	±	±				×	×	×			×		×	Do you experience any cramping pain in your legs or feet?
LL	Ischaemic Pain	4		±				×		×					×	Do you experience cramping pain in your legs or feet when walking?
LL	Ischaemic Pain	4		±						×					×	How far can you walk before you experience any cramping pain in your legs or feet?

Continued

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Table 6 Continued

| Section	Scale	Clinicians' consensus study	Most valid condition specific PROMs			Qualitative study					Qualitative reviews					Question text
			VLU-QOL	PADQOL	AVVQ	AAA	CAD	VV	VLU	PAD	AAA	CAD	VV	VLU	PAD	
LL	Ischaemic Pain	4		±						×					×	Do you walk more slowly than you would choose to in order to avoid cramping pain in your legs and feet?
LL	Ischaemic Pain	4		−						×					×	Do you experience cramping pain in your legs or feet when walking uphill?
LL	Ischaemic Pain	4		−						×					×	Do you experience pain in your legs or feet when you climb stairs?
LL	Ischaemic Pain	4		−				×	×	×			×	×	×	Do you experience pain in your feet at night?
LL	Ischaemic Pain	4		−												Do you dangle one or both of your legs over the side of the bed to help reduce foot pain?
LL	Ischaemic Pain	4		−				×	×	×			×	×	×	Do you experience severe pain in your legs or feet when you are resting or sitting?
LL	Ischaemic Pain	2		−											×	Are you troubled by cold feet?
LL	Ulcer	4	X	−					×	×			×	×	×	Have you ever had any ulcers on your legs or feet now or at any time in the past?
LL	Ulcer	4		−					×	×			×	×	×	Please use the image below to show where you currently have any leg or foot ulcers.
LL	Ulcer	4	−	−					×					×	×	Are you concerned about the smell of your leg ulcers?
LL	Ulcer	4	×	−										×	×	Are you concerned about the appearance of your leg ulcers?
LL	Ulcer	4	−	−										×	×	Do you have leg ulcers that leak fluid (watery liquid)?
LL	Ulcer	4	−	−										×	×	Do you experience infections in your leg ulcers? (eg, foul smell or pus)
LL	Ulcer	4	−	−				×						×	×	Do you experience repeated leg ulcers?

Continued

Table 6 Continued

Section	Scale	Clinicians' consensus study	Most valid condition specific PROMs			Qualitative study					Qualitative reviews					Question text
			VLU-QOL	PADQOL	AVVQ	AAA	CAD	VV	VLU	PAD	AAA	CAD	VV	VLU	PAD	
LL	Ulcer	4	×	−					×				×	×		Do you worry about your leg ulcers? (eg, not healing becoming infected losing part of your leg or foot).
LL	VV	4		−	−								×			Do you experience any bleeding from veins in your legs or feet?
LL	VV	4		−	×			×					×			Do you have any problems with the skin over your varicose veins?
LL	VV	4		−	×			×					×			Do varicose veins make you feel self-conscious or embarrassed?
LL	VV	4	×	−	×			×					×	×	×	Do leg or foot problems affect what clothing or shoes you can wear?
LL	VV	4		−	×			×					×	×		Do you experience any swelling in your legs or feet?
LL	VV	4		−	×			×					×	×	×	Do you experience itching in your legs or feet?
LL	VV	4		−	×			×					×	×		Do you wear compression stockings or tights for your legs?
LL	Tissue loss	4		−	−				×	×					×	Have you lost any part of your legs or feet through amputation or gangrene?
LL	Tissue loss	4			−				×	×					×	Please click on the appropriate part or parts of your legs feet or toes that you have had amputated or have been lost.
LL	Anxiety	3	×	×	×			×	×	×			×	×	×	Do you worry about your leg problems getting worse in the future?
LL	ADL	3	±	×	±			×	×	×			×	×	×	How much do leg or foot problems affect your overall enjoyment of life?
LL	ADL	3	±	×	−			×	×	×			×	×	×	How much do leg or foot problems affect your ability to carry out physical activities? (eg, walking housework or exercise)
LL	ADL	3	±	×	±			×	×	×			×	×	×	How much do leg or foot problems affect your personal responsibilities? For example, caring for others study or work.

Continued

Table 6 Continued

Section	Scale	Clinicians' consensus study	Most valid condition specific PROMs			Qualitative study					Qualitative reviews					Question text
			VLU-QOL	PADQOL	AVVQ	AAA	CAD	VV	VLU	PAD	AAA	CAD	VV	VLU	PAD	
LL	ADL	3	−	×	±			×	×	×			×	×	×	How much do leg or foot problems affect your ability to look after yourself? (eg, rest wash toilet or feed yourself)
LL	ADL	3	±	×	±			×	×	×			×	×	×	How much do leg or foot problems affect your social activities? (eg, going out visiting friends or family)
LL	ADL	4	Xx	×	−			×	×	×			×	×	×	Do you suffer from low mood because of leg or foot problems?
Generic	Personal data		−	×	−	×	×		×	×	×	×		×	×	Do you rely on any people to help you with your everyday activities?
Generic	Personal data		−			×		×	×	×	×			×	×	Do you experience financial problems because of your vascular condition?

The items of the eight scales are coloured in this table.
AAA, abdominal aortic aneurysm; ADL, activity of daily living; AVVQ, Aberdeen Varicose Veins Questionnaire; CAD, carotid artery disease; LL, lower limb; PAD, peripheral arterial disease; PADQOL, peripheral arterial disease quality of life; VLU, venous leg ulcer; VLU-QOL, venous leg ulcer quality of life; VV, varicose veins.
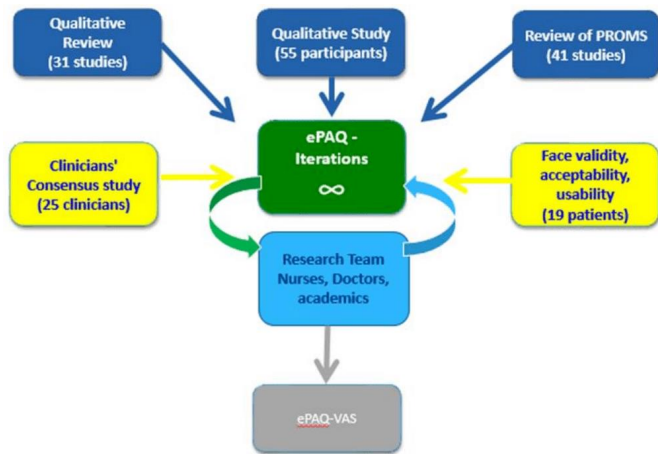
Figure 2 Evidence synthesis to develop of ePAQ-VAS. ePAQ-VAS, electronic personal assessment questionnaire for vascular patients; PROMs, patient-reported outcome measures.

Face validity of ePAQ-VAS

A second phase of semistructured patient interviews was conducted by (EL and PP) with 19 participants, purposefully sampled from the vascular populations previously described. This sample included patients with AAA, CAD, PAD, VLU and VVs. ePAQ-VAS (version 1) was presented to these patients, and a focused interview was conducted to investigate vascular patients' perceptions of the questionnaire in its entirety as well as the relevant items to the individual being interviewed. Questions were asked under the following headings of:

► Overall impressions.
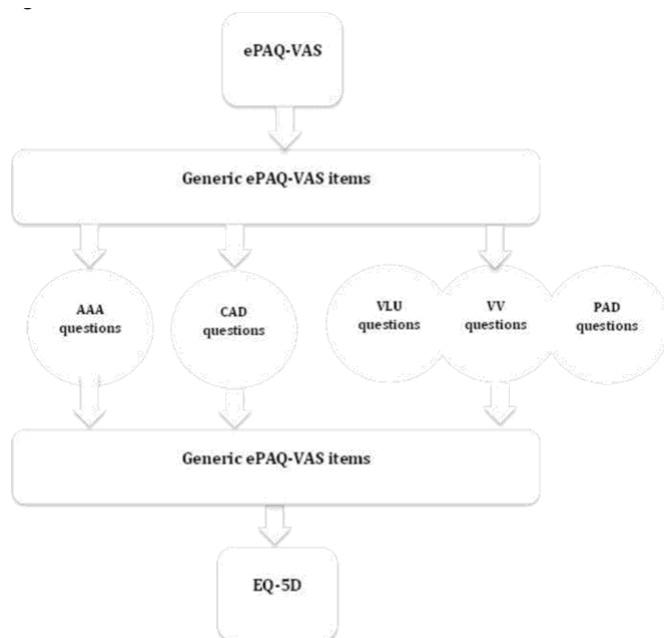
Figure 3 Overview of ePAQ-VAS structure. AAA, abdominal aortic aneurysm; CAD, carotid artery disease; ePAQ-VAS, electronic personal assessment questionnaire for vascular patients; PAD, peripheral arterial disease; VLU, venous leg ulcers; VV, varicose veins.

► Clarity.
► Relevance and emotional response.

Interviews were audio taped, transcribed and analysed. A pragmatic approach was used for the analysis, with comments collated and presented back to the working group who made consensus decisions on revisions to ePAQ-VAS. Written consent was obtained from the participants.

Patient and public involvement

The research question and output were developed in consultation with patients and public. The authors would like to thank the Cardiovascular Research Patient Panel at Sheffield Teaching Hospitals NHS Foundation Trust. The aim of the research was to develop a patient focused outcome measure. In this process, patients were recruited for two qualitative studies to ensure content validity and face validity of this tool. Patients were involved in every stage of the development of the study. The developed ePAQ-VAS has been used by patients in a clinical study, and there are plans for regular clinical use. The results will also be disseminated in relevant meetings and among patient groups.

RESULTS

In total, 12 clinicians completed the first survey and identified PAD, AAA, VLU, VV and CAD as the most common vascular conditions treated by them. They listed common issues such as pain on walking, rest pain, reduced mobility or lack of mobility for patients with PAD and no physical symptoms for those with AAA but need for multidisciplinary approach to manage these patients. For patients with VLU, the main issues included burning pain, recurrence and healing; for patients suffering with VV, skin changes, appearance of leg and ulcer as well as ache were the main issues raised. The clinicians felt the key issue for patients with CAD was identifying patients benefiting from intervention and reducing the risk of stroke. The result from this survey was used to inform the analysis of qualitative data used to develop ePAQ-VAS.

Systematic reviews and assessment of psychometric evaluation were conducted for PROMs validated for use in PAD, AAA, VLU, VV and CAD. A total of 33 PROMs that had undergone some form of validation were identified in 41 studies (table 1).

No PROMs were identified that had undergone sufficiently rigorous development and validation to suggest that they were suitable for direct use in ePAQ-VAS, the details of these reviews have been reported previously[4–8]. Where evidence existed, this fell short of required standards.[3 14] For instance, the review investigating VV PROMs[4] found some evidence for, and discussion of, content validity in relation to the Aberdeen Varicose Vein Questionnaire (AVVQ) and suggest that it is the most appropriate existing condition-specific measure for use in a VV population. However, item generation for these PROMs involved a literature review and assessment

by clinicians of relevance of included items with no direct involvement of patients, therefore suggesting a deficiency in terms of content validity.[17] The scales from these reviews were used to provide a framework for the systematic qualitative reviews and the primary qualitative study.[5 9–13]

In total, 111 patients were approached, but only 55 patients (69.1% male) were interviewed about their experience of living with vascular disease, ages ranged from 35 to 77 years. For further information about the study participants, please see table 2.

Six overarching themes relating to the impact of the five vascular conditions were identified. These were symptoms (including pain), impact on physical function, social impact, psychological impact, financial impact and lifestyle. Pain and mobility were the most commonly reported themes by participants with PAD. The extent to which they impacted daily living was dependent on the severity of the disease, age expectations and social support. Fear of symptoms worsening and future amputation had a significant impact on daily living.

Most participants with AAA reported having no physical symptoms; a small number of participants reported abdominal pain and pain in their legs. Uncertainty, anxiety and fear of sudden death had the most impact on their quality of life. This was similar for patients with CAD who reported few lasting symptoms since the majority had what they described as a 'mini-stroke'. However, CAD patients reported the widest range of signs and symptoms, with nine different symptoms. This condition had the least impact on physical and social function, although psychologically it caused a sense of worry and anxiety. This was mainly caused by fear of having a major stroke.

Pain was the most common issue reported by patients with VVs; other issues included swelling of the legs and the impact of this on mobility. The perceived unpleasant appearance of the VV seemed to have had the greatest psychological impact and was described by many of the participants. The impact of VLU on daily living and quality of life differed within the group that was interviewed. For some, there were no major issues, and having a VLU was accepted as part of their life, with the hope that it would heal eventually. For others, there was a far more significant effect with reports of severe sharp pain that significantly reduced their quality of life. This had a bearing on people's mobility and their ability, or desire, to go out and socialise. Sleep was also disturbed due to pain. The progression of VLU had resulted in participants suffering for long periods of time. In addition, the non-healing or reoccurring nature of the condition had a significant impact for many. VLU appeared to have a significant psychological impact causing a high degree of distress for some patients. Summary results are shown in table 3.

Identified signs, symptoms and impact of the conditions were then mapped and tabulated to see which themes were relevant to which condition and where the similarities and differences lay (table 4).

A total of 31 studies were included across the five reviews of existing qualitative research.[6 10–13] A short summary of the main themes to emerge for each condition is shown in table 5.

The themes from the first round of the clinicians' consensus study, as well as scales of identified PROMs, were used to inform the framework analysis of the qualitative data. Items from existing PROMs were then mapped against emerging themes from the qualitative study, and the qualitative review synthesis for each condition, to explore which PROMs items or scales captured themes deemed to be the most pertinent to patients. A triangulation approach was followed, whereby researchers evaluated whether the concepts were the same (agreement), offered similar concepts (partial agreement), were in contradiction (dissonance) or were not present (silence). An example of this triangulation approach is provided in the online supplementary material. The results of the triangulation study were only used to group symptoms together and avoid repetition. No items were deleted based on the triangulation.

The ePAQ-VAS development team used the findings from the triangulation for AAA, PAD, VV, VLU and CAD to develop themes for distinct sections relevant for each of these vascular conditions. The primary qualitative data were used to create each item. Items were then grouped into sections, and within each section, there were scales consisting of items that measured the same latent variable such as anxiety related to the diagnosis of AAA. The results of the clinicians' consensus study were considered to add further items to the relevant sections (table 6).

The items of ePAQ-VAS were arranged into four sections: generic, AAA, CAD and lower limb (LL) vascular conditions. A single LL section was developed as common themes were identified for conditions affecting the legs, regardless of whether the underlying pathology was venous or arterial. An inclusive approach to development was used and a comprehensive questionnaire was produced with 168 questions (see figure 2 for an overview of the process to develop ePAQ-VAS).

ePAQ-VAS was presented to 19 vascular patients. Overall, the response was positive; the participants felt the generic, and the relevant disease specific were comprehensive, fit for purpose and potentially useful. There was little consistency in items that participants found difficult and no individual item was identified with which most participants had difficulty.

Discussion included the use of abbreviations, font size and contrast between text and background, response options and scales, electronic format versus paper format, relevance to patients and clinicians, the use of free-text boxes and the language and wording used, when and how to use the skip button, repetition of items and subject matter and the possibility of emotional distress associated with questions about the possibility of deterioration or death.

Based on the findings from the face validity exercise, and input from the vascular PROMs group, further

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revisions were made in an iterative process, culminating in the development of ePAQ-VAS. The structure of the questionnaire is illustrated in figure 3. Fifty-nine items were eliminated for overlap; these include questions asking about common symptoms experienced across most vascular conditions. Five items were added based on suggestion from clinicians. Generic items for all respondents were presented in the first section and include questions about pain, altered sensation, weakness, weight/height, smoking habit, previous medical history and regular medication. This information was deemed important for assessment of vascular conditions both by patients and clinicians.

The next three sections are condition specific relating to CAD, AAA and LL vascular disease sections. These sections are further divided into scales. There are 55 items within eight scales and the remainder of questions do not contribute to scales but are kept due to their clinical relevance. The eight scales are part of the condition-specific sections and include CAD-related anxiety, impact of CAD on activities of daily living (ADLs), AAA-related anxiety, impact of AAA on activities of ADL, PAD symptoms, VLU symptoms, VV symptoms and impact of LL vascular disease on ADL. Individual items, scales and sections of ePAQ-VAS in its initial version can be viewed on https://demo-questionnaire.epaq.co.uk/home/project?id=VASC_1.6&page=1.

The evidence used to develop each item in ePAQ-VAS is made explicit in table 5; this table show whether the source for the item is the qualitative study, reviews or consensus study.

DISCUSSION

This study documents stages undertaken to develop ePAQ-VAS and the conceptual framework underpinning this new tool for use in undifferentiated vascular populations. The main strength of this new instrument is that it can be used as a holistic clinical assessment tool that can be completed by patients before meeting the vascular surgeon in the clinic. The information generated can be used to help shared decision making by focusing on patient priorities. This tool has the further advantage of being an electronic online PROM since it can be used to monitor impact of the disease and/or interventions overtime. Furthermore, this instrument is preference based, unlike the identified vascular PROMs[4–8]; once further validated, the disease-specific scales can be used to generate utility values either by mapping to the values of a generic utility measure or by further utility studies.[18]

This instrument has been developed in line with FDA guidelines for developing PROMs.[3] Items were developed based on themes extracted from primary qualitative data, systematic qualitative evidence synthesis and clinicians' consensus exercise.[9–13] We have made efforts through purposive sampling to ensure that we have included diverse demographic groupings in the primary research, and this is augmented by the inclusion of systematic reviews that include evidence gathered in national and international studies. Another strength of this study is that the qualitative evidence in the review and the primary study included patients at different stages of their disease. The data collected included the impact of disease, including symptoms, on daily living and the impact of diagnosis and treatment on the daily living. The vascular clinicians' input into developing and rating the items was sought, and new items were incorporated based on recommendation from 25 vascular clinicians.

The work of developing individual items and their assignment to putative scales and sections was based both on the framework of existing PROMs[4–8] and on input from vascular clinicians. In this stage of the ePAQ-VAS development, an inclusive approach was chosen, and all relevant items were incorporated except for those with clear repetition. The main limitation of this draft version of ePAQ-VAS is that it is long and potentially repetitive; it is expected that factor analysis and psychometric testing will lead to a reduction in the number of individual items and will confirm (or refute) the putative scales identified in the current version. Furthermore, skipping rules embedded within the questionnaire will only present the items relevant to the patient completing the online instrument.

Another limitation is that ePAQ-VAS only cover the five main vascular conditions, and it might not be relevant to patients with other vascular disease. However, including all vascular conditions in one instrument is not possible, and the evidence to include only these conditions was based on input from clinicians treating vascular disease. As stated by the FDA,[3] a fundamental consideration in the development of PROMs is the adequacy of item generation. Due to the heterogeneous nature of vascular disease, it was not straightforward to identify what exactly should be measured when developing and defining the initial conceptual framework for the ePAQ-VAS. To this end, as recommended by the FDA, the initial conceptual framework was based on information gathered from reviews of the literature, patients and expert opinion.

The findings of the qualitative study indicated an overlap in patient experiences of the various conditions. However, there was also a clear difference in how each condition impacted on different aspects of quality of life. There were conditions with many physical symptoms and others with none. This demonstrated that while it may be possible to develop a PROM for use across a variety of vascular conditions, it would also need to include condition-specific items to fully capture the impact and clinically relevant information for each disease or condition. A further limitation is that the face validity study was not able to examine the comprehensiveness of ePAQ-VAS since it covered multiple conditions, and it was difficult to expect from any of the patient groups interviewed to comment on diseases they have not experienced. Therefore, they only commented on the generic questions and the disease-specific items relating to their condition.

In conclusion, ePAQ-VAS is a multidimensional measure developed for use in a range of vascular conditions. It isa single electronic tool, covering most vascular condi- tions. This is important for those patients presenting with mixed symptoms or multiple conditions. The items inePAQ-VAS can capture information about disease symp-toms, HRQoL, comorbidities, medical history and other relevant healthcare issues. This type of information can aid communication between healthcare professionals and patients and support shared decision making. The electronic format may make it easier to monitor patientsover time, especially those with chronic conditions and those treated with lifestyle modification or conservatively. Based on methods used in its construction, this tool has a strong degree of content validity; however, further psycho- metric testing for reliability, responsiveness and validity is needed. Once this electronic PROMs is validated, it can be used as an outcome measure in clinical practice and research.

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Chapter Ten. ePAQ-VAS validation.

10.1 Introduction

In this chapter, further details are provided about the validation ePAQ-VAS following the development of the conceptual framework of this new instrument. The methods are discussed followed by the results from the factor analysis to assess the construct validity of the ePAQ-VAS. The additional psychometric properties of reliability, responsiveness and acceptability are also reported.

10.2 Psychometric survey data collection

To examine the psychometric properties of ePAQ-VAS, all patients attending the outpatient clinics of Sheffield Vascular Institute between June 2018 to January 2019 were invited to complete the questionnaire online, using the established encrypted voucher system. The patients received vouchers along with a unique personalised code to access the tool. If unable to complete the questionnaire online, the option to complete it in the clinic using electronic tablets or laptops computers was available to the patients. The participants in the survey were invited to complete the questionnaire before their outpatient consultation. New and follow up patients alike were invited to the study. A participant information leaflet about the study was provided to the patient before taking part. The participants were aware that the completion of the ePAQ-VAS, in this phase, was for research purposes only. Once completed, the data was stored on the N3 secure NHS server. The ethical approval for this study was granted by the National research ethics service (NRES) committee in Yorkshire & Humber – Bradford Leeds (REC Number: 14/YH/1117).

I was the local study coordinator at Sheffield Teaching Hospitals following the departure of the primary investigator for this study. I worked alongside clerical staff to ensure the ePAQ vouchers were included with the appointment letters. I was also responsible for recruiting patients in the outpatient clinics and on the wards.

The results of the survey were used to perform factor analysis and assess the reliability, validity as well as responsiveness of ePAQ-VAS. The research plan was to use methods from classical test

theory **(102)** and item response theory **(103)** to identify the scale structure and reduce the number of items on the questionnaire.

10.3 Factor analysis and item reduction

The plan was to first perform a factor analysis on the results of the survey. The aim of this statistical method is to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. The most common types of factor analysis are exploratory factor analysis and confirmatory factor analysis. Exploratory factor analysis has been used to explore the possible underlying factor structure of a set of observed variables without imposing a preconceived structure. In theory, by performing exploratory factor analysis, the underlying factor structure can be identified. On the other hand, confirmatory factor analysis was designed as a hypothesis *testing* analytic approach. Confirmatory factor analysis allows testing the hypothesis that a relationship between observed variables and their underlying latent constructs exists **(104, 105)**. The NIHR grant plan for the factor analysis for ePAQ-VAS was to perform exploratory factor analysis, but because of the strong theoretical underpinning of ePAQ-VAS with *a priori* themes, and the extensive qualitative evidence from clinicians and patients in designing ePAQ-VAS, confirmatory factor analysis was justified. This decision was also approved by the ePAQ-VAS development group.

There are various recommendations regarding the appropriate sample size when conducting factor analysis. The recommendations in the literature for a minimum sample size vary; with some researchers recommending that the sample size should be a ratio of the number of respondents to the number of items involved in the factor analysis, whereas other researchers suggesting absolute ranges from 100 to over 1,000 **(106)**. The suggested sample calculations to perform factor analysis on ePAQ-VAS in the research plan were based on a ratio of 3 or 4 respondents per item **(107)**. However, this plan was revised while recruitment for the survey was ongoing; this happened after discussion with the psychometric experts and the chief investigator. The revised plan was to recruit enough patients, so we have at least ten respondents per item **(108)**. The sample size calculations in the research protocol estimated that ePAQ-VAS would have at least 150 items and the calculations suggested recruiting 600 patients. However, ePAQ-VAS before psychometric analysis had 114 items, and these were divided into sections, including a generic section asking about common vascular symptoms,

relevant medical conditions, medications, clinically relevant questions (e.g. smoking, weight, diabetes) and screening questions to ensure only relevant questions are presented to the patients based on their specific vascular complaint. There were threedisease-specific sections - AAA, CAD and lower limbs sections. In these disease-specific sections, there were eight scales with 55 items. The eight scales were CAD-related anxiety, the impact of CAD on activities of daily living (ADL), AAA related anxiety, the impact of AAA on ADL, PAD symptoms, VLU symptoms, VV symptoms and impact of lower limb vascular disease on ADL. Based on 55 items within ePAQ-VAS contributing to eight scales, up to 550 patient completions were considered necessary.

In total, 721 patients completed ePAQ-VAS, and the results were used to perform confirmatory factor analysis. I performed this analysis using MPlus version 8.2 (Muthen & Muthen, Los Angeles, California, USA) **(109).** A one-factor confirmatory factor analysis model was fitted to each of the eight scales to test whether the results from the survey supported the eight scales identified in the conceptual framework of ePAQ-VAS **(110)**. The confirmatory factor analysis model for each scale was assessed by examining the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). CFI is equal to the discrepancy function adjusted for sample size. CFI ranges from 0 to 1, with a larger value indicating better model fit. Acceptable model fit is indicated by a CFI value >0.95. RMSEA is related to residual in the model. RMSEA values range from 0 to 1, with a smaller RMSEA value indicating better model fit. Acceptable model fit is indicated by an RMSEA value of < 0.08 **(111)**. Item factor loadings (>0.4), model residual correlations, and modification indices (MI) were examined to assess local dependence within domains **(112)**. The magnitude of these three indices was evaluated in comparison to other items in the scale; when the MI were>100 and residual correlations (RC) >|.10| this was taken as the indicator of lack of fit, and items were removed from the scale **(109)**.

The CFA was to examine which items within the scale contribute to the latent construct (e.g. what specific questions explore the impact of AAA on ADL). The model goodness of fit was acceptable; this was done after dropping six items. This was done after consulting the ePAQ-VAS development group, the clinicians and revising the qualitative evidence.

Two items from the "Impact of CAD on ADL" domain were dropped. The first item was a generic item asking about the impact of CAD diagnosis on the enjoyment of life. This item had high MI & RC with two other items; the other deleted item was about the impact of CAD diagnosis on mood, it was removed as it had low factor loading, this was done after checking the wording and the local

dependence. In the AAA section, only one item was deleted from the "Impact of AAA on ADL"; this was due to high MI & RC with two items within the same scale. In the lower limb section, an item asking about the impact of lower limb symptoms on the enjoyment of life was removed. A question asking about "cold feet", was removed from the PAD ischaemic symptoms scale. This item had low factor loading, and when deleted, the model output improved. A single item was deleted from the VLU symptoms domain due to low factor loading. For further information about the model fit data, please review the paper in the next chapter.

The main limitation of this method was that patients were not directly consulted about the changes including the items that were dropped. However, local clinicians working with the ePAQ-VAS development group were consulted. Future research can explore the opinion of patients about the items dropped.

10.4 Internal and test re-test reliability

Following the confirmatory factor analysis, the internal consistency of the items within each of the eight scales was investigated. Internal consistency/reliability assesses the degree to which items in scale/domain or test are interrelated. Good internal consistency is desirable as it indicates that the individual items relate to the same construct and so together will produce a more reliable estimate of that dimension than any individual item alone. The best method to measure internal consistency is Cronbach's alpha coefficient. Cronbach's alpha varies from 0 to 1; values between 0.70–0.95 are considered good. However, it is important to note that the coefficient is influenced by the number of items in scale/ domain or test; the more items, the higher the value of Cronbach's alpha and caution should be taken when values are greater than 0.92 because this may indicate that there are redundant items **(113)**.

Following factor analysis and item reduction, I performed the internal consistency analysis for the eight scales within ePAQ-VAS; all scales had a Cronbach's alpha coefficient ≥ 0·70, and none exceeded 0·92. For further details please table 1.

Table.1 Internal consistency of the ePAQ-Vascular Scales

Scale	Cronbach's alpha coefficient
CAD related Anxiety	0.90
Impact of CAD on ADL	0.91
AAA related Anxiety	0.89
Impact of AAA on ADL	0.83
PAD symptoms	0.91
VLU symptoms	0.80
VVs symptoms	0.80
Lower limb related ADL	0.79

The main limitation of this method was that only the internal consistency of the scale was examined and not the entire section, such as CAD or AAA. It was not possible to perform an internal consistency examination of ePAQ-VAS in its entirety as patients completed disease-relevant sections only.

We also assessed re-test reliability for the eight scales. Test-retest reliability measures the stability of the scores of a construct obtained from the same person on two or more separate occasions. Intra-class correlation is then calculated between these two scores to assess the stability or consistency of the score across time. I identified the patients for test re-test reliability while recruiting them from the outpatient clinics, and I agreed to contact them to complete ePAQ-VAS for the second occasion, if there has been no change to their overall health. The patients in the test re-test survey completed the questionnaire again between 3-7 days following the first time they completed it. The patients were contacted on the phone and helped, if needed, to complete the questionnaire. The only patient groups that could have been recruited for this test were patients with PAD, VVs and VLU.

Patients with AAA and CAD were excluded from this type of reliability analysis as their condition was not expected to have remained stable for the following two reasons. First, patients included in our survey with AAA, usually were informed of their diagnosis or the need for intervention in the clinic. In

either case, patients may develop anxiety. Second, patients with CAD usually presented as an emergency requiring urgent revascularisation leaving no time gap to administer the re-test survey after the baseline survey. Therefore, and based on these reasons, these two patient groups were excluded from this type of reliability analysis. I cleaned the data and performed the calculation for this test as well as the other psychometric tests. The methods and results of these analyses were reviewed by senior researchers in the team.

Test re-test reliability is assessed by calculating the intra-class correlation; I performed this analysis using SPSS (IBM, New York, USA). There is no universal consensus for how the magnitude of the correlation should be interpreted **(114)**. Some have proposed a classification for the strength of test-retest reliability based on the intra-class correlation as follows: < 0.40 poor, 0.40–0.75 fair to good and > 0.75 excellent **(115)**. Other researchers suggested that intra-class correlation exceeding 0.7 are generally regarded as reliable for population-based research **(116)**.

In total, 150 patients including 60 with PAD, 39 with VLU and 51 with VVs were recruited for the test re-test survey. All the patients completed the relevant sections twice, and the time between the two episodes was 3-7 days. Test-retest results were calculated for the symptom scale and impact of the lower limb vascular disease on ADL for patients with PAD, VLU and VVs separately. The results test re-test reliability analysis are shown in table 2.

Table.2 Test- retest Intra- class correlation (ICC) of the ePAQ-VAS Scales

Scale	Intra- class correlation (ICC)
PAD symptoms	0.98
VLU symptoms	0.99
VVs symptoms	0.65
Lower limb related ADL	0.98

The results of internal reliability and test re-test reliability were not presented in the main body of the sixth paper of this PhD and therefore are presented here. Future examination of test re-test can also include other analysis methods, including the Wilcoxon's Rank Sum test. The research protocol suggested performing both intra-class correlation and Wilcoxon's Rank sum test; however, after consulting the senior statistician, it was decided to perform the latter test only.

10.5 Known group validity

One way to test the construct validity of a questionnaire is known-group validity. Known group validity is confirmed when a questionnaire can discriminate between two groups that are known to differ on the variable, such as the severity of a clinical condition. The questionnaire is completed by two groups that are known to have different levels of the same condition **(117)**. To examine this aspect of the construct validity of ePAQ-VAS, I helped organised a meeting with vascular specialists to define these hypotheses for the different conditions covered by ePAQ-VAS. For details of these hypotheses and their postulated directions, please see table 3.

Table 3 Proposed hypotheses with postulated direction of correlation to examine ePAQ-VAS known group validity

Section	Topic	Direction of scale score
CAD	Patient presented with stroke compared with patients with no stroke	Scale scores will be higher in patients with stroke
CAD	Patient presented with multiple TIAs compared to those with single TIA	Scale scores will be higher in patients with multiple TIAs
AAA	Size of the Aneurysm	Scale scores will be higher for patients with larger AAA
AAA	Surveillance versus pre-operative patient	Scale scores will be higher for pre-operative patients

PAD	Patients with rest pain compared to those without rest pain	Scale scores will be higher in patients with rest pain
PAD	Patients with ulcer with compared to those without ulcer	Scale scores will be higher in patients with PAD and ulcer
VLU	Ulcer recurrence	Scale scores will be higher in patients with ulcer recurrence
VV	Varicose vein in both legs versus in one leg	Scale scores will be higher in patients with VV in both legs
VV	VLU presence versus no VLU	Scale scores will be higher in patients with VLU

Known group validity was examined using the Pearson correlation coefficient index.

Correlations were considered low if r < 0.3, moderate if r lies between 0.30 and 0.49 and high if r < 0.5 **(117)**. I performed this analysis using the data from ePAQ-VAS and identified the different clinical groups.

The results of the analysis were examined by other researchers and presented to the group.

The results of this analysis are presented in the final paper of this PhD, and in summary, the results of known group validity were mixed, with some being in line with proposed clinical hypotheses. However, some clinical hypotheses, particularly in CAD scale scores, were not in line with what was proposed by the clinical group. This could be because, from 721 patients completing ePAQ-VAS, only 50 patients had CAD. The small sample size for this clinical group could be the cause of the results low correlation coefficient index. Furthermore, the small number of patients with stroke or multiple TIAs meant that the results of correlation studies were not powered.

When ePAQ-VAS is adopted for routine clinical use, the data could be used to re-examine this aspect of analysis for CAD within ePAQ-VAS.

10.6 Responsiveness

Responsiveness is the ability of PROMs to measure changes that are clinically important, where participants or patients respond to therapeutic interventions. PROMs are considered sensitive to change if they can accurately measure increases and decreases in the construct measured. ePAQ-VAS responsiveness was analysed among patients undergoing interventions for VVs and PAD. I recruited the patients before their procedures, and they were invited at least six weeks following their procedure to complete ePAQ-VAS again. This subset of patients was selected from two groups who have undergone a treatment of known efficacy such as endovenous laser treatment/surgical stripping for varicose veins or angioplasty for intermittent claudication. The records of the patients were checked to ensure they had a successful intervention and had no immediate post-operative complication; this was further confirmed when inviting the patients to complete the questionnaire for the second time. The research protocol was changed after consulting the senior researchers and the clinicians. The interval between the intervention and administration of ePAQ-VAS to the patients for the second time was agreed with the input of vascular specialists; this was changed from 12 weeks to 8 weeks. The statistical methods to measure responsiveness described in the research protocol were standard response means, effect sizes, the index of responsiveness and the minimally important differences. There is no clear consensus as to how to measure responsiveness. I consulted the group and the senior statistician about the most appropriate tests, and the plan was slightly altered to measure responsiveness using standardised effect size and Standardised response means. The Standardised response mean is calculated by dividing the mean score change by the standard deviation of the change. The standardised effect size score is calculated between post-operative patient score and pre-operative score divided by standard deviation at baseline. The responsiveness is regarded as small if the score from these two tests is 0.3-0.5, moderate for a score of 0.5-0.8 and large for scores above 0.8 **(118).** We recruited 92 patients for the responsiveness survey, 55 patients who had VVs surgery (Endovenous ablation of varicose veins) and 37 patients who had an intervention for PAD (Angioplasty and bypass surgery). The likely lower response rate at this stage of the survey could have been because the participants knew that the completion of ePAQ-VAS was purely for research purposes and it will not directly affect their care. All the patients had to be reminded to complete ePAQ-VAS. The aim of the protocol was to recruit 100 patients equally divided between those undergoing PAD revascularisation procedures and VVs surgery. Only patients with a clinically successful outcome and

no complications were recruited for this survey. The scales that were examined for responsiveness reported moderate to large effect size, indicating that they are responsive to a clinically detectable change in the health status of the patients. For more information about the results, please refer to the next chapter and the final paper in this PhD.

Although these specific methods used for examining ePAQ-VAS responsiveness are accepted worldwide, there is no clear consensus on the gold standard methods to examine responsiveness **(119)**. For instance, there are three main approaches to assess responsiveness in PROMs. The first is conceptual, and it related to whether the content of PROMs can identify meaningful change between health conditions. The second approach is by completing the PROMs before and after a therapeutic intervention and examining the responsiveness as explained earlier. This is described as internal responsiveness, and the effect size statistics are used to measure it. The third approach, which is also described as external responsiveness, involves comparing the change using a separate measurement tool and comparing the scores between this tool and the score from the PROMs. It is important in this method to define the minimal clinically important difference that the instrument should detect **(119)**. This final approach can overlap with aspects of criterion validity, especially if there is no other measurement tool available to compare its score to the new instrument and the external criterion to examine responsiveness is clinical hypotheses presented by clinicians. ePAQ-VAS require further assessment of its responsiveness in future studies with emphasis on both the internal and external responsiveness.

10.7 Acceptability

ePAQ-VAS was developed so that it can be completed online before the outpatient clinic. However, the response rate was only 24.2% of the patients invited to complete the questionnaire online. There are several reasons for this low response rate for the online questionnaire. The survey was designed for research purposes only, and consequently, there were no personal incentives for the respondents in relation to their own care **(31)**. Furthermore, lower levels of computer literacy in an elderly population or lack of access to a computer or internet may explain the low response rate. Additionally; vascular patients also are more likely to suffer from a severe disability, and this is likely to adversely affect their ability to complete the questionnaire online. Several attempts were made to overcome these issues, and provisions were developed so the patients could complete the online questionnaire with the help of a researcher or on their own using an electronic tablet or laptop computers.

The acceptability of ePAQ-VAS was assessed by examining the completeness of data within the scales attempted by the patients. ePAQ-VAS showed good acceptability, with 350 responses missing from 56,238 (0.62%).

In the research protocol, there were plans to examine the impact of the routine use of ePAQ-VAS on the duration of the clinic appointment. There were also plans to assess the acceptability of the instrument by asking the patients and the clinicians to complete the QQ10 questionnaire **(120)**. However, ePAQ-VAS was not adopted for routine clinical use during the research phase, and these studies are potential future research topics if the instrument is integrated into the routine care of vascular patients.

For further information on the development and validation of ePAQ-VAS, including the psychometric testing and analysis, please see the next chapter, which is the final paper of this PhD by publication.

Chapter Eleven: Paper 6 "Electronic personal assessment questionnaire for vascular conditions (ePAQ-VAS): development and validity."

Electronic personal assessment questionnaire for vascular conditions (ePAQ-VAS): development and validity

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Background: This paper describes the development and validation of an electronic personal assessment questionnaire for vascular conditions (ePAQ-VAS) that captures the symptomatology, quality of life and clinically relevant data of patients presenting to vascular services.

Methods: A two-stage survey was conducted in patients attending a tertiary vascular department. Patients completed the ePAQ-VAS remotely online, or on site using an electronic tablet. In the first stage of the survey, the responses were used to perform confirmatory factor analysis to assess the construct validity and remove redundant items. The internal reliability of disease-specific scales was investigated. In the second stage of the survey, the acceptability, known-group validity, test–retest reliability, and responsiveness of ePAQ-VAS was assessed.

Results: In total, 721 patients completed ePAQ-VAS. Their mean(s.d.) age was 63·5(15·7) years and 468 (64·9 per cent) were men. Some 553 patients (76·7 per cent) completed the questionnaire in clinic and the remainder completed the questionnaire online. The results of the confirmatory factor analysis confirmed the conceptual model for ePAQ-VAS structure and eliminated six items. Internal reliability was acceptable for all the scales (Cronbach's α greater than 0·7). The test–retest reliability measured by the intraclass correlation coefficient ranged from 0·65 to 0·99. The results showed that the instrument was responsive over time with the standardized response mean ranging from 0·69 to 1·60.

Conclusion: ePAQ-VAS is a holistic data-collection process that is relevant to vascular service users and has potential to contribute to patient-focused care and the collection of aggregate data for service evaluation. A demonstration version of the final version of ePAQ can be viewed at http://demo-questionnaire.epaq.co.uk/home/project?id=VASC_1.7&page=1.

[Correction added on 16 April 2020, after first online publication: link to questionnaire has been corrected]

Introduction

Clinical outcomes in patients undergoing procedures for vascular diseases have been the focus for evaluation of vascular services in the UK[1]. These clinical outcomes, including technical measures such as vessel or bypass patency and pressure indices, or functional issues such as walking distance, may be a poor proxy for the effect of a condition on a patient. The use of these outcomes reflects only the impact of vascular disease and treatment on the small proportion of patients who develop adverse clinical outcomes[2]. They do not measure the impact of vascular disease and treatment among many other patients, including those treated conservatively[2,3].

In response to this problem, several condition-specific and generic patient-reported outcome measures (PROMs) have been developed for use in specific vascular conditions. These include condition-specific PROMs that can capture aspects of disease important to patients and provide a picture about the impact of the disease on health-related quality of life[4,5], and generic measures can be used to capture benefits across different conditions and treatments[5]. PROMs can be used for diagnosis, monitoring and measurement of treatment effects, especially when integrated into an electronic patient record[6]. Increasingly, PROMs are being used to calculate quality-adjusted life-years for use in cost-effectiveness analysis of health and care interventions.

The routine use of PROMs in clinical practice can guide treatment choice, shared decision-making and self-management. Evidence also suggests that clinicians can provide improved patient-centred care when PROMs are integrated into disease registries, where outcomes are tracked over time[6].

However, use of these measures to assess the impact of vascular conditions is limited to clinical studies, and rarely for patients' assessment and service evaluation[7-11]. This is in part because most vascular patients present with overlapping symptoms or mixed conditions; logistically, it is difficult to use paper-based PROMs to monitor patients with chronic and recurrent vascular conditions[12-15].

As part of the National Institute for Health Research (NIHR) programme considering the configuration and monitoring of vascular services, a new vascular PROM was developed. This new electronic tool followed the successful models in which electronic PROMs were used for patients' diagnosis, assessment and long-term monitoring[16].

The electronic patient assessment questionnaire for vascular patients (ePAQ-VAS) was developed in line with internationally recognized standards and guidelines[17-19]. It captures the impact of five main vascular conditions: abdominal aortic aneurysm (AAA), peripheral arterial disease (PAD), carotid artery disease (CAD), varicose veins (VV) and venous leg ulcers (VLU). The decision to include only these conditions was based on systematic reviews and a clinicians' consensus exercise[7-11,20]. The advantages of this electronic tool are that it can be integrated into an electronic patient record and facilitate focused consultations, as patients can complete the questionnaire before the clinic appointment. Patients can complete the questionnaire on mobile phones or computers, and remote completion can facilitate virtual clinics. The electronic data generated by patients can help long-term monitoring of disease, service evaluation, and linkage to other data. Lastly, this electronic tool incorporates skipping rules, removing the need for patients to complete irrelevant sections.

The aim of this paper is to present the steps taken to develop and validate the ePAQ-VAS.

Methods

The conceptual framework for the ePAQ-VAS questionnaire was developed from three distinct sources to identify the key issues, symptoms and impact of AAA, PAD, CAD, VLU and VV on patients with these conditions. First, systematic literature reviews of existing outcome measures and qualitative evidence were conducted[7-11,21-24]. Second, clinicians involved in the care of vascular patients were invited to list the key issues, symptoms and impact

of these conditions[20]. Third, semistructured interviews were conducted with five vascular patient groups (PAD, AAA, CAD, VLU and VV). Users of vascular services attending the vascular department of Sheffield Vascular Institute (SVI) at Sheffield Teaching Hospitals NHS Foundation Trust were recruited for the study. Purposive sampling techniques ensured a range of participants of different ages, sex and stages of treatment. Patients were asked about their symptoms and the impact of the condition on their functioning and lifestyle. Framework analysis was used to study the qualitative data from the interviews and six overarching themes were identified for patients with PAD, AAA, CAD, VLU and VV. These were symptoms (including pain), impact on physical function, social impact, psychological impact, financial impact and lifestyle[25].

The themes identified above were used by the ePAQ-VAS steering committee to generate items (questions) for the initial item pool (*Table S1*, supporting information).

The list of items was presented first to 13 clinicians involved in the care of vascular patients; they were invited to score the relevance of items in the provisional version of ePAQ-VAS and suggest new items[20]. Second, to ensure face validity, interviews were conducted with 19 patients, purposefully sampled from vascular populations described above. Inputs from clinicians and service-users were used to revise the questionnaire by deleting 59 items, adding five items and rephrasing 12 items.

The resulting ePAQ-VAS had 114 items; these were divided into sections, including a generic section asking about common vascular symptoms, relevant medical conditions, medications, clinically relevant questions (such as smoking, weight, diabetes) and screening questions, to ensure only relevant questions were presented to the patients based on their specific vascular complaint. There were three disease-specific sections, including AAA, CAD and lower-limb sections. In these disease-specific sections there were eight scales with 55 items. The eight scales were CAD-related anxiety, impact of CAD on activities of daily living (ADL), AAA-related anxiety, impact of AAA on activities of ADL, PAD symptoms, VLU symptoms, VV symptoms, and impact of lower-limb vascular disease on ADL. *Fig. 1* provides an overview of the development process.

Item reduction and internal reliability

To reduce the burden of ePAQ-VAS, statistical analysis of the results of a survey was done to delete questions from ePAQ-VAS that were redundant. Consecutive patients attending outpatient clinics run by SVI between June 2017

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Fig. 1 Diagram showing development of the ePAQ-VAS
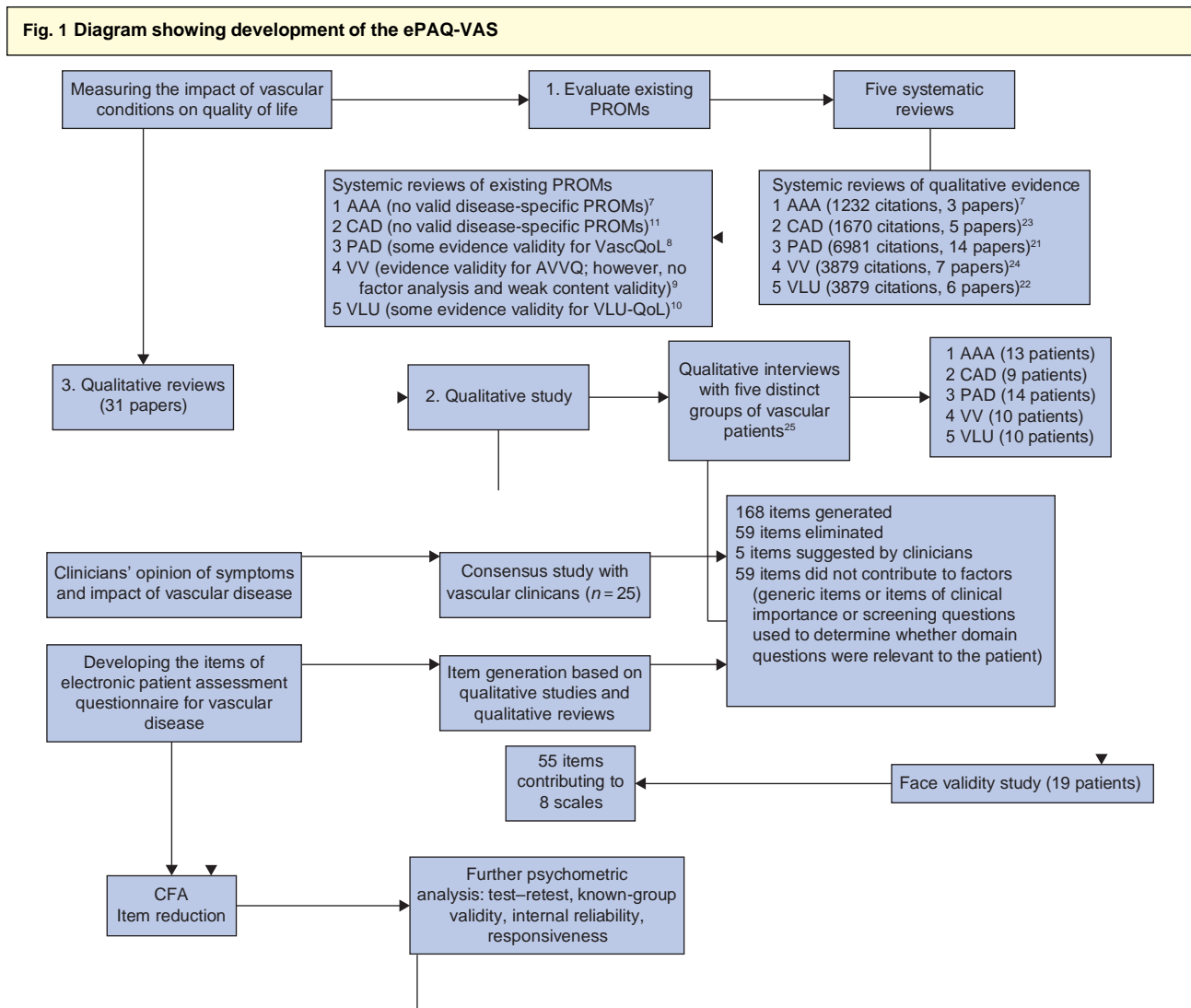
PROM, patient-reported outcome measure; AAA, abdominal aortic aneurysm; CAD, coronary artery disease; PAD, peripheral arterial disease; VascQoL, King's College Vascular quality-of-life-questionnaire; VV, varicose veins; AVVQ, Aberdeen Varicose Vein Questionnaire; VLU, venous leg ulcers; VLU-QoL, venous leg ulcer quality of life; CFA, confirmatory factor analysis.

and June 2018 were invited to complete the questionnaire online before their clinic appointment, or on site using electronic devices. On site, patients could complete questions and ask for technical help from researchers. The five key vascular conditions identified (AAA, CAD, PAD, VLU and VV) were all represented in the sample.

Sample-size calculation was based on previous studies[26,27] suggesting a required ratio of between four and ten respondents per item to enable factor analysis and internal reliability calculations. Based on 55 items within ePAQ-VAS contributing to eight scales, up to 550 patient completions were considered necessary.

Item reduction

A one-factor confirmatory factor analysis (CFA) model for ordinal data[28] was fitted to each of the eight scales to test whether the empirical data supported the eight scales identified in the conceptual framework. The results of the analysis were also used to reduce the number of items. Appropriateness of the CFA model for each scale was assessed by examining the comparative fit index (CFI) and the root mean square error of approximation (RMSEA), where CFI greater than $0·95$ and RMSEA below $0·08$ were regarded as an appropriate fit[29]. Furthermore, item factor loadings (above $0·4$), model residual correlations and modification indices were considered to examine local

dependence within domains[29]. For these three indices, their magnitude was evaluated in comparison with other items in the scale; when the modification index (MI) was greater than 100 and residual correlation (RC) was above 0·10, this was taken as indicating lack of fit and the item was removed from the scale[29]. Redundant items were removed using the results from the CFA.

Mplus© version 8.2 (Muthén and Muthén, Los Angeles, California, USA) was used for the statistical analyses[30].

Internal consistency

To assess whether each scale in ePAQ-VAS was measuring what was intended, Cronbach's α coefficient was calculated to measure the reliability of internal consistency. Cronbach's α of at least 0·70 was considered acceptable; however, scores exceeding 0·92 were taken to indicate that items in the scale may be redundant[18,31].

Acceptability, validity, reliability and responsiveness of ePAQ-VAS

The results of relevant items from the above survey and an additional survey were used to validate the measure by examining acceptability, test–retest reliability, construct validity, and the responsiveness of the measure.

All consecutive patients invited to outpatient clinics run by the SVI from June 2018 to January 2019 were asked to participate. For test–retest reliability, patients were asked to complete a second questionnaire 3–7 days later, provided there was no change to their health status. Only patients with AAA, PAD, VLU and VV were included in this survey, as patients with CAD were only available before vascular procedures. To assess responsiveness, patients completed the ePAQ-VAS before and 6 weeks after PAD and VV procedures. The second survey for test–retest reliability and responsiveness was completed over the telephone by one of the researchers.

Acceptability

Acceptability of the ePAQ-VAS was measured by examining the completeness of the data. Good level of acceptability was confirmed when 80–95 per cent of the data was completed by the patients[31]. Additionally, the mean and median of time taken to complete this instrument online or in clinic was calculated.

Scoring

A summative score for each of the eight scales in ePAQ-VAS was calculated and standardized to a 0–100 scale, where 0 indicated the best and 100 the worst outcome. Skipped items were allocated a score of zero, as

the questionnaire allows skipping of sections and individual questions that are not of relevance.

Test–retest reliability

Intraclass correlation coefficients (ICCs) were used to assess test–retest reliability. ICCs exceeding 0·7 are generally regarded as indicating reliability for population-based research, and ICCs exceeding 0·9 are considered to indicate reliability for use clinically with individuals[32].

Known-group validity

Known-group validity was examined using hypothesis testing to examine whether the scales correlated well with expected clinical group differences. Correlations are considered low when r is less than 0·30, moderate when r is 0·30–0·49, and high when r is 0·50 or above[15]. Hypotheses were stated *a priori*, including the postulated direction[17,33]. The clinical hypotheses proposed that the CAD anxiety and ADL scale scores would be higher (worse) for patients with stroke than in those presenting with a transient ischaemic attack. The AAA scale score would be higher with patients with a larger aneurysm, and patients with ulceration or rest pain and PAD would have a worse score than those with PAD and claudication. A list of these hypotheses for each condition can be found in *Table S2* (supporting information).

Responsiveness

Responsiveness was measured using standardized effect size, calculated as the change of score between the postoperative patient score and the preoperative score divided by the standard deviation at baseline. An effect size of 0·30–0·50 is regarded as small, 0·50–0·80 as moderate, and 0·80 and above as large[33]. The standardized response mean was also calculated as the mean difference between baseline and postintervention values divided by the standard deviation of the change, and classified using the same criteria.

Statistical analyses were performed using SPSS® version 24 (IBM, Armonk, New York, USA).

Results

The response rate for patients invited to complete the questionnaire online before attending their clinic appointment was 24·2 per cent. In total, 721 patients completed the ePAQ-VAS. Their mean(s.d.) age was 63·5(15·7) years. Some 468 patients were men (64·9 per cent); 553 patients (76·7 per cent) completed the questionnaire in a clinical environment (clinic or ward) and the remainder completed the questionnaire online. The mean time to complete the ePAQ-VAS in the clinic was 12·51 (median

Table 1 Number of respondents and mean score for each scale of the ePAQ-VAS

Scale	No. of respondents	Mean(s.d.) score (of 100)
AAA		
Related anxiety	121	23·74(21·84)
Impact on ADL	121	17·41(20·82)
CAD		
Related anxiety	50	44·17(29·61)
Impact on ADL	50	32·40(30·29)
PAD		
Symptoms	308	47·08(26·86)
Impact on ADL*	308	50·28(30·88)
VLU		
Symptoms	122	34·97(24·37)
Impact on ADL*	122	55·46(30·91)
VV		
Symptoms	248	36·86(18·91)
Impact on ADL*	248	28·52(26·69)

*Measured by the lower-limb vascular disease impact on the activities of daily living (ADL) scale in the ePAQ-VAS. AAA, abdominal aortic aneurysm; CAD, coronary artery disease; PAD, peripheral arterial disease; VLU, venous leg ulcers; VV, varicose veins.

9·14) min, and the mean online before the clinic appointment was 36·51 (median 30·44) min. The difference in completion time is likely due to the availability of help from researchers in the clinic. ePAQ-VAS showed good acceptability, with 350 item responses missing from 56 238 (0·6 per cent). The final scores were calculated for each scale (*Table 1*).

Item reduction

The eight scales in the condition-specific sections of the ePAQ-VAS were identified through qualitative evidence from patients and clinicians. The responses of patients from the first survey were used in the CFA models to examine whether this structure was supported empirically. In the CAD section, two scales were modelled and all items within CAD-related anxiety supported the latent factor. However, two items were dropped from the impact of CAD on ADL domain. The first was a generic item about the impact of CAD diagnosis on enjoyment of life; this item had high MI and RC with other items in the same scale. The other item deleted from this scale asked about impact on mood, and this had low factor loading. In the AAA section, only one item asking about the impact of AAA on enjoyment of life was deleted; this item had high MI and RC with items in the same scale. A similar item asking about the impact of lower-limb symptoms on enjoyment of life was also dropped because of high MI and RC with other items

in the same scale. In the lower-limb section, two further items asking about cold feet and VLU symptoms were dropped from the final version of ePAQ; both items had low factor loading. *Tables S3– S8* (supporting information) provide further details of the results of the CFA models, factor loading and other parameters.

Internal reliability

After dropping six items based on the results from the CFA, the internal consistency of each scale was examined; all scales had a Cronbach α coefficient of at least 0·70, and none exceeded 0·92 (*Table S8,* supporting information).

Test–retest reliability

For the test–retest survey, 150 patients (60 with PAD, 39 with VLU, and 51 with VV) completed the relevant sections of a second questionnaire after 3– 7 days. Test – retest results were calculated for the symptom scale and impact of lower-limb vascular disease on ADL for patients with PAD, VLU and VV separately. The ICC ranged from 0·65 for VV symptoms to 0·98 for the PAD and lower-limb ADL symptoms, and 0·99 for VLU symptoms (*Table S8,* supporting information).

Known-group validity

The correlation between AAA size and AAA-related anxiety was significant. There was a significant correlation between rest pain and PAD symptoms and the impact of PAD on ADL. The presence of ulcer had a statistically significant correlation with the PAD ADL score.

Ulcer recurrence had a significant correlation with the VLU symptom scale score. The presence of VV in both legs had a significant correlation only with VV symptoms, and no strong correlation with the VV ADL score. Correlations between the proposed clinical hypotheses and CAD ADL and CAD anxiety scores were low, ranging from −0·089 to 0·094 (*Table 2*). This could be due to the small sample size (50 patients) in the CAD group.

The results of known-group validity were mixed, with some being in line with proposed clinical hypotheses, for instance the larger the size of AAA the greater the anxiety caused by the condition, and the presence of rest pain or ulcer significantly impacting on the score of PAD scales. However, some clinical hypotheses, particularly in CAD scale scores, were not in line with what was proposed (*Table 2*).

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Table 2 Known-group differences in the intraclass correlation coefficient for condition-specific scales in the ePAQ-VAS

	ICC	
Hypothesis	Anxiety or symptom scale*	ADL scale
CAD		
Patient presented with stroke	−0.089	−0.089
Patient presented with multiple TIAs	−0.105	0.094
AAA		
Size of aneurysm	0.234	0.159
Surveillance *versus* preoperative patient	0.158	0.116
PAD		
Rest pain	0.668	0.479
Ulcer with PAD symptoms	0.101	0.153
VLU		
Ulcer recurrence	0.541	0.133
VV		
VVs in both legs	0.500	0.068
Presence of VLU	0.450	−0.215

*Anxiety scale for coronary artery disease (CAD) and abdominal aortic aneurysm (AAA); symptom scale for peripheral arterial disease (PAD), venous leg ulcers (VLU) and varicose veins (VV). ICC, intraclass correlation coefficient; ADL, activities of daily living; TIA, transient ischaemic attack.

Table 3 Effect size for measuring responsiveness of the ePAQ-VAS

	No. of patients	Standardized effect size	Standardized response mean
PAD			
Symptoms	37	0.69	0.74
Impact on ADL	37	0.85	0.69
VV			
Symptoms	55	1.48	1.60
Impact on ADL	55	0.82	0.78

PAD, peripheral arterial disease; ADL, activities of daily living; VV, varicose veins.

Responsiveness

A total of 92 patients completed the responsiveness survey; of these, 55 patients had VV procedures and 37 had lower-limb revascularization procedures for PAD. These patients completed the ePAQ-VAS before surgery, and once more at least 6 weeks after the operation. All patients included in the analysis had successful outcomes from the procedure. Effect size and standardized response mean values were determined for all the relevant scales of the ePAQ-VAS to examine whether it could pick up the difference in health status following a successful intervention.

The effect size was moderate for PAD symptoms and large for the remaining scales (*Table 3*). The results for the standardized response means were all moderate, apart from those for VV being large.

Discussion

Systematic reviews[7–11] of condition-specific vascular PROMs identified a lack of adequately validated tools for most vascular conditions. The use of validated PROMs is limited, and the data generated are rarely used in clinical decision-making or monitoring of patients[9]. TheePAQ-VAS is a tool that covers the five main vascular conditions of AAA, PAD, CAD, VV and VLU. It has been developed in line with US Food and Drug Administration, consensus-based standards for the selection of health measurement instruments (COSMIN), and other international guidelines[17–19]. The items in this multisectional tool were developed based on the views of vascular patients experiencing the conditions and clinicians treating them. ePAQ-VAS was evaluated for its acceptability, reliability, validity and responsiveness in a large study involving 721 patients. The results of this study show that it has robust content and face validity, and good acceptability, internal consistency and responsiveness. Many of the scales in the ePAQ-VAS exhibited good test–retest reliability and known-group validity.

The main advantages of the ePAQ-VAS are that it is a single instrument covering most patients treated by vascular services. This is particularly important for patients presenting with mixed symptoms or multiple conditions, thereby facilitating a focused, as well as a holistic, approach to treat the causes of their symptoms. The electronic format of this tool makes it easier to monitor patients over time, especially those with chronic conditions and those treated with lifestyle modification or conservatively. The questionnaire can be completed before the clinic or at the clinic before meeting the clinician, and can help shared decision-making and enable focused consultations. The data collected cover clinical and quality-of-life information, and can be added to the patient electronic record. This can help to assess the service over time if adopted locally and nationally. Evidence suggests that when electronic tools such as the ePAQ-VAS are included in disease registries they can facilitate patient-centred care[6]. Another strength of the ePAQ-VAS is that it generates detailed descriptions of the quality of life for people with different vascular conditions. The EQ-5D™ (EuroQol Group, Rotterdam, the Netherlands) is a generic outcome measure with five dimensions (mobility, self-care, usual activity, pain, anxiety and depression) that can be used to generate

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quality-adjusted life-years, a composite measure of the length and quality of life, and is recommended for use in economic evaluation[34]. Therefore, if the EQ-5D™ is used alongside the ePAQ-VAS, utility values can be generated for the different vascular health states, which in turn can be used in economic evaluation in research settings and ser- vice evaluation in clinical settings. The disease-specific data and utility values may also be used in the future to consider the relationship between such generic measures and the more detailed symptomatic and disease-specific description of vascular conditions provided by ePAQ-VAS.

There are several limitations to this study. The survey for validating this tool was conducted in a single centre. Patients who completed the questionnaire were aware that they were completing it for research purposes only and that the results would not be used in their clinical con- sultation or management. This could be one of the rea- sons for the low completion rate of the ePAQ-VAS before the clinic appointments. Previous experience with elec- tronic personal assessment questionnaires used in other disease areas suggests that patients are more likely to com- plete outcome measures before their clinic appointment when they are in routine clinical use and assist in their management[6,35]. Future studies are warranted to examine response rates and the discrepancy between response rates online before the clinic and those at the clinic before meet- ing clinicians. Furthermore, the online nature of the ques- tionnaire meant that younger patients, or those with family support, were more likely to complete the ePAQ-VAS com- pared with older patients and those less familiar with online technology.

The discrepancy in completion times for patients com- pleting the questionnaire online before the clinic appoint- ment and those completing it in the clinic before their appointment could have arisen because patients completing online were unsupervised and unsupported. Completion times may have been affected by variables such as internet connection speeds as well as interruptions or distractions, which were not measured. The presence of researchers in the clinics could have introduced bias to the results of com- pletion time, reducing it for patients who completed the questionnaire in the clinic.

The sample size for some of the statistical analyses was small, particularly for patients presenting with CAD and AAA. This was due to resource limitations of the research team and patient availability compared with other dis- ease groups, such as PAD and VLU. The access to cer- tain patient groups, especially after surgery, was limited. In addition, the follow-up data for test– retest and respon- siveness were collected by telephone, with the answers recorded by an interviewer. The presence of an interviewer

could have introduced bias to the results and reduced com- pletion time. Further studies could explore ways in which to improve data collection for follow-up. Another area of val- idation of this instrument is the predictive validity, which can be important for examining the ability of the question- naire to monitor the impact of chronic vascular conditions on quality of life and the symptom changes over time.

This research has resulted in the development of a new electronic instrument for the collection of patient-reported outcome data, the ePAQ-VAS, which captures symptoma- tology, quality-of-life and other clinically relevant data such as experience with the National Health Service (NHS) and co-morbidities, experienced by most patients pre- senting to vascular services. Such data may contribute to electronic patient records and be invaluable in the management of individual patients and in the collection of aggregate data for service evaluation and research. A demonstration version of the final version of ePAQ can be viewed at http://demo-questionnaire.epaq.co.uk/home/ project?id=aaa_1.0&page=1.

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31 Lamping DL, Schroter S, Marquis P, Marrel A, Duprat-Lomon I, Sagnier PP. The community-acquired pneumonia symptom questionnaire: a new, patient-based outcome measure to evaluate symptoms in patients

Chapter Twelve. Discussion

This PhD by publication is a combination of six peer-reviewed papers that contributed to the development and validation of ePAQ-VAS, a PROM for use with adult vascular patients with AAA, PAD, CAD, VLU and VVs. I am the first author of five of the papers and the second author in one. This commentary provides details on the rationale for each step in the development of this new tool and provides more information about my role in modifying the methods, data collection, recruitment, analysis of data and the writing of these papers. I contributed to most of the workstreams that fed into the development of ePAQ-VAS, including systematic reviews to identify validated PROMs for the following conditions: CAD, VVs and VLU, as well as qualitative reviews for CAD, PA, VVs and VLU; the data from these qualitative reviews contributed to the content validity of ePAQ-VAS. I also performed a Clinicians' consensus study, and I significantly contributed to the development of the conceptual framework of ePAQ-VAS. I assisted in the recruitment of the patients for the survey. I also performed the analysis on the survey data, including data cleaning, producing summative scores for each scale within ePAQ-VAS and more importantly, performed the psychometric analysis of ePAQ-VAS. All the changes to the methods were approved by senior members in the group, who also reviewed the analysis.

The initial stage in developing ePAQ-VAS was to identify the most valid, reliable and responsive PROMs for patients with AAA, PAD, CAD, VLU and VVs. The findings from these reviews served as the background for the work needed to develop ePAQ-VAS. The first and second papers of this PhD were designed to identify all the papers that described the development and validation of PROMs for patients with VVs and VLU **(35, 36)**. The aim of these reviews was to assess the robustness of the psychometric evidence for each PROMs and decide whether a tool can be directly included in ePAQ-VAS. These two reviews were planned to be a single review with the same methodology but to identify PROMs for patients with chronic venous disease. However, it was decided to divide the review into two; this was appropriate as the chronic venous disease is a broad description and can include several conditions that affect veins in the human body, including post-thrombotic disease. Furthermore, the titles generated from the searches were large and difficult to manage. Therefore, after consultation with the senior members of the group and the chief investigator,

instead of one review, two reviews were performed. One of the main features of these reviews was the use of psychometric criteria developed specifically to assess the evidence of PROMs validation. The criteria were based on published recommendations as well as international checklists such as COSMIN and US FDA PROMs guidance **(53, 55)**. The main limitation that could affect the generalisability of the results of these reviews was the heterogeneity of the patients included in the studies as well as the different protocols for administering the PROMs. The differences in the methodology of the included studies, patient population and treatment pathway could have influenced the reported results. There was also a scarcity of information on important aspects of developing the PROMs, including how missing data were dealt with when validating the PROMs.

The most valid tool for use in patients with VVs tool was AVVQ. This PROMs was developed by Garratt *et* al., and data from the systematic review reported that this instrument had good test re-test reliability, construct and criterion validity, and responsiveness. However, the evidence for the content validity was poor, as the items were developed by a researcher and confirmed by two vascular surgeons **(35)**. The most appropriate outcome measure for patients with VLU was VLU-QoL. This instrument that was developed by Hareendran *et* al. had good content validity, construct validity, criterion validity, and internal consistency. However, evidence for its responsiveness was poor **(36)**.

The data from these two reviews suggested that none of the VVs and VLU outcome measures could be included directly in ePAQ-VAS. However, the results from these two papers as well as three other systematic reviews to identify validated PROMs for patients with PAD, AAA, and CAD was used to inform other aspects of developing ePAQ-VAS; for example, the scales of the identified tools were used to develop the conceptual framework of ePAQ-VAS. The items from the most valid PROMs were used for triangulation studies in the next two papers in this study.

The third and fourth papers of this PhD were systematic qualitative evidence synthesis performed to examine the impact of PAD and CAD on quality of life **(37-38)**. These two reviews identified all themes from the primary studies for PAD and CAD. These were then mapped against the items of the outcome measures identified in previous studies **(73-74)**. The mapping was performed to find the PROMs that captured the most important issues to patients with the respective conditions. In this PhD, two peer-reviewed qualitative evidence synthesis reviews are included. The first paper examined the impact of PAD on quality of life.

The strength of this review was that the included studies had patients with varying severity of PAD. The inclusion in the review of patients with intermittent claudication and critical limb ischemia and amputation ensured the variety of impacts on quality of life was captured. In the triangulation study reported in this paper, it was reported that the PROMs used for patients with PAD **(47)** only cover some of the theme identified in the qualitative review **(37)**. This study identified that a comprehensive measure is needed to examine the outcomes of patients with PAD at different stages of the disease. This is important for monitoring outcomes for this patient group. The main limitation of this paper was the lack of detail in some of the included studies about the severity PAD in the study population. Also, the primary qualitative data were limited, and it was impossible to explore the primary data from the patients in detail **(37)**. The fourth paper in this PhD identified and analysed all the primary qualitative data relating to patients with CAD in a comprehensive systematic review. The review included data from patients at different stages of their care pathway and patients with symptomatic and asymptomatic CAD. This helped provide a comprehensive overview of all the issues that impact the quality of life of patients with CAD. The triangulation subsection of this paper reported that there were no PROMs that covered the themes generated from the qualitative review and that there was a need for a new comprehensive outcome measure for patients with CAD.

The data from these two papers and three other similar qualitative reviews for AAA, VVs and VLU **(37-38, 46, 84-85)** were used to develop the conceptual framework and content of ePAQ-VAS. The evidence from these qualitative reviews was important to overcome the limitations of the primary qualitative study **(83)**. The reviews ensured that a variety of perspectives were included. The qualitative evidence synthesis ensured that all relevant qualitative data for patients with AAA, CAD, PAD, VVs and VLU was available to develop ePAQ-VAS conceptual framework. The data from these reviews also ensured that the disease-specific sections were developed based on the views of the relevant patients and that the HRQoL of these patients can be measured based on how they expressed the impact of the disease and treatment process on their wellbeing and activities of daily living. The conceptual framework of all the sections within ePAQ-VAS was developed using qualitative data of patients and to less extent input from vascular specialists. This was a necessary step to identify all the domains relevant to the HRQoL of patients with AAA, CAD, PAD, VVs and VLU.

The fifth paper of this PhD presented the steps taken to develop the conceptual framework of ePAQ-VAS **(39)**. This study reported how the results of the systemic reviews, the primary qualitative study and a consensus study with clinicians were used in an iterative process to develop the framework of ePAQ-VAS. The results from the triangulation studies were used to develop items for each disease category, and the scales of PROMs identified in the systematic reviews were used to help develop the sections and scales of ePAQ-VAS. Input from clinicians ensured clinically relevant questions were added, including the five questions suggested by them. In the face validity study, the patients had the opportunity to examine the appropriateness of the instrument and the items within it. The results of the face validity study were used to modify the questionnaire, including the rephrasing of 12 questions. ePAQ-VAS was divided into sections, including a generic section asking about common vascular symptoms, relevant medical conditions, medications, clinically relevant questions (e.g. smoking, weight, diabetes) and screening questions to ensure only relevant questions are presented to the patients based on their specific vascular complaint. There were three disease-specific sections, including AAA, CAD and lower limbs sections. In these disease-specific sections, there were eight scales. These were CAD-related anxiety, the impact of CAD on activities of daily living (ADL), AAA related anxiety, impact of AAA on ADL, PAD symptoms, VLU symptoms, VV symptoms and impact of lower limb vascular disease on ADL. The major strengths of this paper were the strong as well as large qualitative evidence base supporting ePAQ-VAS and the systematic involvement of patients and clinicians in developing this new instrument. There were no mixed vascular focus group discussions, and the qualitative data from the face validity study were from semi-structured face to face interviews. The evidence from the consensus study would have been more useful if patients, as well as clinicians, were invited to participate. This would have ensured that consensus could have been reached over what items to include in ePAQ-VAS. One of the other limitations was the ePAQ-VAS developmental group did not include patients as members.

In the final and sixth paper of this PhD, the results of a large psychometric survey in which ePAQ-VAS was administered to vascular patients were presented. The analysis in the paper evaluated the acceptability, reliability, validity and responsiveness of ePAQ-VAS. In summary, the reported results showed that ePAQ-VAS has good content validity, acceptability, internal consistency, and responsiveness. Most of the scales within the ePAQ-VAS exhibit good test-retest reliability and known group validity. There were several limitations to this study. First,

the participants in the survey were recruited from a single centre; future surveys to re-examine the evidence in this paper should consider recruiting patients from multiple centres as ePAQ-VAS is adopted as a clinical tool for routine use. The patients completing the questionnaire were aware that they are completing it for research purposes and that the results would not be of direct benefit to them. There was a low response rate for online completion of ePAQ-VAS prior to the clinic appointment, and further studies in the future should examine the difference between response rates online before the clinic and at the clinic. An important limitation of this study was the small sample size for some of the analyses, particularly for patients with CAD and AAA.

These six papers present important steps taken to develop and validate ePAQ-VAS. The electronic instrument covers the five main vascular conditions of AAA, PAD, CAD, VVs and VLU; and it has been developed in line with the FDA, other published guidance **(50, 52)**. The items were developed based on the views of vascular patients experiencing these conditions. Extensive qualitative reviews were undertaken to ensure content validity for this instrument. ePAQ-VAS was evaluated in a large survey of patients, and the results of the psychometric evidence report that this electronic PROMs has good evidence for internal construct validity, content validity, internal consistency, and responsiveness. Further research is needed to examine other aspects of this outcome measure, including predictive validity. This examines the ability of the questionnaire to monitor the impact of chronic vascular conditions on quality of life and the symptom change over time.

ePAQ-VAS is a multi-dimensional measure developed for use in AAA, PAD, CAD, VVs and VLU. It is a single electronic tool covering most vascular conditions. The electronic format may make it easier to monitor patients over time, especially those with chronic conditions and those treated with lifestyle modification or conservatively. However, the electronic nature of the instrument may reduce access to a group of patients particularly the elderly and those with disabilities that have no access to the appropriate technology to access the questionnaire. The items in ePAQ-VAS can capture information about disease symptoms, quality of life, co-morbidities, medical history and other relevant healthcare issues. This type of information can aid communication between healthcare professionals and patients and support shared-decision making. This instrument also collects information on clinically relevant data such as experience with NHS services. Data collected by ePAQ-VAS can contribute to electronic

patient records and be invaluable in the management of patients and collection of aggregate data for service evaluation and research.

ePAQ-VAS is now available on http://demo-questionnaire.epaq.co.uk/home/project?id=aaa_1.0&page=1 . It has satisfactory psychometric properties and more importantly it comes with the electronic infrastructure to collect data, provide real-time feedback to increase its usefulness in clinics. Mixed methods approach was used to develop ePAQ-VAS with the unique use of data from systematic reviews. The content and face validity confirm that such reviews are important and that they should be factored in when developing new PROMs.

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