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A systematic review of patient-reported outcome measures patients with chronic limb-threatening ischemia

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Abstract

Chronic limb-threatening ischemia (CLTI) causes significant morbidity with profound negative effects on health-related quality of life. As the prevalence of peripheral artery disease and diabetes

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continue to rise in our aging population, the public health impact of CLTI has escalated. Patient-reported outcome measures (PROMs) have become common and important measures for clinical evaluation in both clinical care and research. PROMs are important for the measurement of clinical effectiveness and cost effectiveness and for shared decision-making on treatment options. However, the PROMs used to describe the experience of patients with CLTI are heterogeneous, incomplete, and lack specific applicability to the underlying disease processes and diverse populations. For example, certain PROMs exist for patients with extremity wounds, and other PROMs exist for patients with pain, and still others exist for patients with vascular disease. Despite this multiplicity of tools, no single PROM encompasses all of the components necessary to describe the experiences of patients with CLTI. This significant unmet need is evident from both published reports and contemporary large-scale clinical trials in the field. In this systematic review, we review the current use of PROMs for patients with CLTI in clinical practice and in research trials and highlight the gaps that need to be addressed to develop a unifying PROM instrument for CLTI. (J Vasc Surg 2022;75:1762–75.)

Keywords

Peripheral artery disease; Chronic limb-threatening ischemia; Critical limb ischemia; Amputation; Patient reported outcome; Decision aid; Decision tool; Surgical decision; Surgical decision-making; Shared decision-making

Peripheral artery disease (PAD) is estimated to affect more than 200 million individuals around the globe, with an incidence increasing owing to aging, diabetes, lifestyle, and environmental factors.[1] The most severe manifestation of PAD is chronic limb-threatening ischemia (CLTI; also referred to as “critical limb ischemia” or CLI), where severe vascular insufficiency leads to disabling pain, wounds, and gangrene of the lower limb. CLTI incurs significant mortality, morbidity, and negative effects on physical function and health-related quality of life (HRQoL). Patients with CLTI often have other significant comorbidities and are at increased risk for both mortality and major amputation (each estimated at 22% at 1 year).[2,3] The management of these patients is multimodal, often requiring medical therapy, analgesics, wound care, revascularization, and associated surgical procedures such as minor and major amputation. Frequently multiple providers are involved in the care of patients with CLTI. Decision-making for individual patients with CLTI is a complex balance of estimated risks and benefits, inadequately informed by high-quality evidence. Recent and ongoing clinical trials are attempting to address this evidence gap, while contemporary practice guidelines promote greater standardization in evaluation and treatment.[4–8]

Patient-reported outcome measures (PROMs) have become an essential component of scientific evaluation of medical practice.[9,10] Although once limited to QoL instruments pursued only in the context of large clinical trials, PROMs now are commonplace in the treatment of many disease processes and have become a critical element of the evaluation of clinical practice and the value of care.[11–16] PROMs may be used to measure clinical and cost-effectiveness of treatment strategies, and to help guide shared decision-making. In certain treatment settings, such as transcatheter aortic valve replacement, the use of patient

decision support has been discussed as a necessary adjunct for payer reimbursement, and similar directions may lie ahead for PROMs.

However, no single validated PROM exists for patients with CLTI. Many different phenotypes exist within the spectrum of CLTI, such as neuropathic ulcers among patients with diabetes and varying degrees of PAD, in contrast with smokers with distal tissue loss specifically attributable to severe arterial insufficiency. Each patient has a different presentation, risk of limb loss, risk/benefit for treatment, and a different potential impact on their HRQoL. This clinical heterogeneity is the central tenet that underlies the challenge of developing a unifying PROM for CLTI. Other factors contribute to this challenge as well, including the complexity inherent in instrument development and the resource investment required by the stakeholders involved in the care of patients with CLTI.

To better understand the current landscape of PROMs for patients with CLTI, we conducted a systematic review of published studies in the field. This work involved first identifying each PROM and outlining the specific domains measured within the PROM. Second, we detailed how each PROM or group of PROMs has been used in studies of patients with CLTI over time. Finally, we outline how the frameworks created by these efforts may help point the way toward the development of a unified, validated PROM for CLTI.

METHODS

On January 14, 2019, a multidisciplinary group of clinicians, scientists, regulatory experts, and patients met in Washington, DC, convened by Vascular Cures (a 501(c)3 nonprofit foundation in Redwood City, CA) to discuss the current state of PROMs for patients with PAD. After these discussions, the group agreed that a contemporary review of the available PROMS for patients with CLTI was needed and a working group effort was launched.

We performed a systematic literature review of PROMs used in studies of patients with CLTI. A simple search strategy was designed and executed as outlined below. Our search spanned publications from 1990 to the end of calendar year 2020, and were limited to English articles on PUBMED with a searchable abstract.

Search terms.

- “critical limb ischemia” OR “chronic limb threatening ischemia” and
- “quality of life”

(any field, PUBMED, English language)

This search strategy was supplemented by abstract review and discussion among the authors of other studies known to have used a PROM in a population of patients with CLTI. A similar project convened by this group addressed claudication, and thus we limited this effort to critical limb ischemia.

Our initial search strategy initially identified 337 studies. Two authors reviewed the studies along with the HRQoL measures used within the study. Subsequently, members of the study team read each abstract identified in the search strategy. We kept only those studies that

(1) outlined a clinical series or group of patients with a CLTI diagnosis, and (2) had a QoL measure described within the abstract and body of the article. Studies that did not meet these criteria after review were not included (Appendix 1, online only). Studies that specifically commented on patients with critical limb ischemia, but also studied patients with claudication, were included with this review.

Once we had established our final study database, we took two key steps. First, we recorded the individual PROMs encountered across each study; these elements are outlined in Table I. Second, we then determined how these PROMs were used, individually and in combination, within the described research studies (Fig 1 and Appendix 2, online only).

A PRIMSA 2020 Checklist was completed after the conclusion of the systematic review, in accordance with *Journal of Vascular Surgery* guidelines. The review was registered with the PRISMA site at the National Institute for Health Research in the United Kingdom (PROSPERO Registration Number 265034). All participants at the VascularCures PROM-PAD working group reviewed the study goals and protocol (Appendix 3, online only).

RESULTS

Number of studies identified in our systematic review.

We identified a total of 337 studies for inclusion. After review, from these 337 studies we formed our final selection of 99 individual publications, with the criteria that each study evaluated patients with CLTI and reported a PROM or a HRQoL metric. These studies were published between 1992 and 2020 and used more than 20 different established or derived PROMs or QoL measures (Appendix 2, online only).

Components of current PROMs in CLTI.

Table I summarizes six of the most used PROM instruments for patients with CLTI. Many of these assessment tools consider some aspects of CTLI, and their impact on HRQoL. For example, the WOUND-QoL PROM, developed in 2014, is a short assessment tool designed to capture many of the aspects of QoL that are affected by chronic wounds and was compiled from a review of three other existing wound evaluation tools to simplify this difficult assessment process.[17] While it considers the effects of tissue loss and the pain associated with the wound, it is less precise in describing the effects on ambulatory function. There is a single question directly related to mobility (“Does the wound limit you in moving about?”), and similarly the impact of the wound on patient families and caregivers is only briefly explored. However, an advantage of WOUND-QoL when compared with its predecessors is that it is short—only 17 items in a short two-page questionnaire.

Other instruments have different characteristics. For example, the PADQOL instrument is longer, with 38 individual components, and includes domains related to fear or uncertainty.[18] Other measures are especially brief and focus only on function, such as the Walking Impairment Questionnaire, which has 14 components, and assesses only the individual’s perception of their walking ability,[19] The Walking Impairment Questionnaire has been broadly used in PAD research but most commonly in studies of intermittent claudication rather than CLTI.

Use of PROMs in CLTI studies over time.

Next, we examined the temporal patterns of PROM use in CLTI studies. As shown in Fig 1, the number of studies of patients with CLTI that report a PROM or QoL measure have increased exponentially in recent years. Studies of patients with CLTI reporting a PROM were uncommon in the 1990s and early 2000s, with fewer than five studies published per year before 2004. After 2004, the number of studies of patients with CLTI reporting a PROM increased and numbered nearly 10 studies per year for nearly all years from 2010 and thereafter.

Most studies in the early years, namely, between 1992 and 2002, used a single PROM (Appendix 2, online only). However, the number of studies which used multiple PROMs has increased over time, as shown in Appendix 2 (online only) and Fig 1. In Fig 1, we outline how commonly these measures were used over time, and how commonly multiple components were part of the scaling assessment effort for a PROM. The number of different PROMs used across the studies in each year is represented by the size of the circles in Fig 1 and conveys the increasing incidence of multiple PROM use apparent in review of Appendix 2 (online only). Although the size of the circles indicates the number of studies found which used a PROM, there is certainly heterogeneity in terms of how central the PROM element was in each study.

By 2020, 20 different studies using 10 different PROMs were published to communicate QoL information among patients with CLTI. The most commonly used PROMS were the World Health Organization Quality of Life BREF measure, the VascuQoL measure, the Short Form measures (SF-6, SF-8, SF-12, and SF-36), and the EQ-5D measures. These instruments have all been used collectively to describe the domains that affect patients with CLTI. There are other measures that are less commonly used, such as the Center for Epidemiological Studies Depression Scale, the Geriatric Depression Scale, and the Nottingham Health Profile. In total, more than 20 different measurement scales have been used to characterize PROMs for patients with CLTI.

Finally, there are several trials studying patients with CLTI which that either currently recruiting patients or have recently completed their enrollment (Table II). These trials generally have a limb-related primary outcome, such as major adverse limb event-free survival. However, all have incorporated QoL assessments in one form or another. BEST-CLI uses the EQ-5D measure, and BASIL-2 incorporates the European Quality of Life 5 level questionnaire, in addition to the SF-12, and other generic tools. Other studies, such as the Swedish Drug Elution Trial in Peripheral Artery Disease (SWEDEPAD-2), assess HRQoL with the VascuQoL-6, a disease-specific HRQoL instrument.

DISCUSSION

Summary of existing PROMs in CLTI.

Our comprehensive review demonstrates that the existing repository of PROMs for patients with CLTI is heterogeneous and lacks consistency, adequate validation, and complete coverage of all the domains of interest for CTLI patients. Unlike patients with claudication, where technology and patient avidity for HRQoL assessment for symptom abatement has

been a recent emphasis in both regulatory and other trials, PROMs in patients with CTLI have been much less well-studied. Given the inherent heterogeneity of CLTI and the challenges in measuring these outcomes in complex patients, a major task lies ahead in developing a uniform, validated approach for PROM collection in CLTI. Further, keeping the ability to make comparisons with broader, more generic measures may be helpful in contextualizing CLTI in comparison with other diseases. Our review demonstrates that this task still lies ahead for those who care for patients with CLTI, despite some progress in expanding the pool of potential instruments over the last two decades.

Generic QoL assessment tools, such as the EQ5-D and SF-12, are often used to characterize QoL and patient reported outcomes in CLTI (Fig 1; Appendix 2, online only). Simple, established measurement tools have certain advantages. The EQ-5D, developed in 1987, has been used in thousands of research studies, is short and efficient, and focuses on five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. However, although it has a long track record and it is simple, many researchers believe it lacks the specificity necessary to understand the treatment pathways encountered by patients with CLTI. This lack of specificity is not unique to the EQ-5D or the SF-12. This limitation also exists in vascular instruments such as the VascuQoL, which is not calibrated to the type of limitations experienced by patients with CLTI. Similar weaknesses are also present in other measures such as PADQOL. The growing realization that no one satisfactory CLTI measure exists, we believe, is the reason underlying the growth in the number of measures used over time as shown in Fig 1.

Why the current tools are too generic for use in CLTI.

As outlined elsewhere in this article, the gaps in existing PROMs for patients with CLTI are related to specificity and the spectrum of symptoms encountered by patients facing this disease. The need for discrimination in these PROMs is vital, because any of the new treatments that will be tested in CLTI require a careful assessment of any treatment effect. Such treatments include the full range of medical, biologic, regenerative, revascularization, and nonrevascularization interventions currently available or under development for CLTI. Capturing these treatment effects will be difficult, if not impossible, if the assessment tools are too general in nature and do not fully explore the domains of PROMs. Detecting a signal of a treatment effect will require more precise assessment of domains, and assessment of other domains not measured by these tools. By designing more precise and descriptive PROMs with more relevant domains calibrated to the treatment effects likely to be seen in these patients, we will both better understand individual treatment effects, as well as better evaluate existing and new therapies in clinical trials. A sample of currently enrolling trials studying patients with CLTI and incorporating PROMs is shown in Table II.

How stakeholders can work to advance PROMs in CLTI.

The VascularCures Foundation has a dedicated interest in partnering with researchers, patients, and investigators who are committed to a better understanding of treatment outcomes in PAD. By convening a multidisciplinary group of clinician-scientists, researchers, patients, regulatory experts, and industry partners to perform comprehensive

review, we hope to develop a broad foundation which will provide solid footing for the emergence of a widely applicable, validated set of PROMs in CLTI.

PROMs for patients with CLTI will need to inform decisions affecting individuals, groups, and, most important, patients with CLTI. These discussions will be beneficial to inform patient decision-making when individuals consider treatment options. Further, PROMs will be needed when treatments are compared across different groups in clinical trials.[20–23] Finally, the overall impact of systematic treatment of the comorbidities which often occurs concomitantly with CLTI, such as diabetes and smoking, may have small impact at the individual level. However, when examining small changes in QoL using accurate tools, differences may be detectable in large populations if the measures are precise and reproducible. Finally, ensuring that stakeholders contribute broadly from different populations will help to ensure that these new measures translate outcomes across race, ethnicity, sex, gender, and socioeconomic status.

The benefits of a unifying PROM for CLTI.

Despite the challenges of developing unifying PROMs for patients with CLTI, the benefits of a single systematic approach are obvious. Interoperability across research studies, ease of comparison of treatment effects, and clear clinical communication are only a few of the reasons why a single CLTI PROM would improve clinical care. However, achieving this goal would require a consistent definition of CLTI, and consistent measures to assess its impact, even across different patient populations.

In addition to having wounds with varying etiologies, patients with CLTI experience differing journeys that have a variable impact over time. Like congestive heart failure, CLTI is a chronic, disabling disease and recurrent exacerbations are common. Clinical events, often measured in survival analysis fashion, fail to fully capture the patient's trajectory. A patient with an ischemic ulcer will have severe pain and wounds, but these symptoms often abate rapidly after revascularization treatments. Another patient, such as one with a neuropathic ulcer, may have a more indolent course with fewer pain symptoms but frequent infections and recurrences. A facile and agile PROM for CLTI would reflect these changes over time and the impact of treatments on the overall course. It would enable researchers to better measure the burden of this chronic, disabling disease and the value of defined strategies of care.

PROMs for CLTI would help to raise public awareness for CLTI and its treatments.

Unlike many other disease processes such as cancer, heart disease, and obesity, CLTI remains poorly understood by the lay public.[24–26] Few messages exist to inform public awareness about CLTI. Moreover, given the complexity of the disease process and its predilection for affecting patients of lower socioeconomic status, there has been little interest in the dissemination of messages about the prevention and treatment of CLTI.[27,28] An important goal in the development of PROMs for patients with CTLI is to improve public awareness. A single PROM for CLTI would ease communication to the public and lay press and help to convey messages to support the development of treatments for all stages of the disease.

Potential domains measured in a novel PROM for CLTI.

The working group held extensive discussions and a brief Delphi processes to establish a preliminary list of key domains that would be considered in future work aimed at establishing a PROM specifically derived for assessment in patients with CLTI. This process included direct input from several patients. Several domains came to the fore: pain, mobility, wounds, patient and family support systems, psychological and mental health, and a patient-level experience measure related to overall social impact and QoL (Fig 2).[29–31] The group's consensus was that each of these domains contributed in a distinct way toward QoL for patients with CLTI, and a PROM focused on this effort would need to adequately capture these elements.[21,32–40] Finally, making certain a tool that could be completed accurately by a family member would also be a key contribution.

After extensive discussion to identify these domains, the group then discussed what steps would be next in formulating a validated and unifying CLTI instrument. As shown in Fig 3, the steps include initial data collection from focus groups, qualitative interviews to pilot survey design, and testing to final production and validation. Each of these steps can be a lengthy process involving patients at every juncture, a considerable task given the comorbidity profile of most patients with CLTI.

A pathway forward.

These qualitative experiments—further exploration of the domains in focus groups and qualitative interviews, construction of differing types of survey structures, and testing of the newly derived instruments for validity—will be the important next steps forward. Retrospective studies evaluating the literature and measures described to date, prospective studies collecting qualitative information and categorizing the domains precisely, and measure development and validation will need to be supported by pilot projects and grants, with the goal of arriving at a usable PROM for patients with CLTI to provide accurate patient-reported outcome assessment in both clinical and research settings.

We anticipate this process will evolve in a manner reflected by the US Food and Drug Administration Roadmap to Patient-Focused Outcome Assessment in Clinical Trials (Appendix 4, online only).[41] Divided into three parts, this outline describes how understanding the condition, conceptualizing the benefit, and assessing the treatment outcomes can be an effective pathway toward developing these measures. Key terminology and domains would also need to be defined a priori as part of this process. Although the focus of the US Food and Drug Administration efforts are measures to be used in clinical trials, these measures can also likely translate into real-world practice. The creation of a measure that can reflect quality would help to orient outcome assessment in variety of research and quality assessment forums.[42] An example in heart failure research is the Kansas City Cardiomyopathy questionnaire, which helped not only in clinical trial outcome assessment, but in quality comparisons across care systems as well.[43]

Choosing these pilot projects will be an effort undertaken by VascularCures and other stakeholders convened for this forum. Broader support from specialty societies and national funding agencies such as the Agency for Healthcare Research and Quality and the National

Institutes of Health is sorely needed. By collaborating with experts from vascular surgery, vascular medicine, podiatry, wound care, endocrinology, qualitative science, survey design, and clinical research, investigators will have a broad range of critique and insight to develop the best possible measures.

Potential barriers to design and implementation of PROMs in CLTI.

The group convened agreed that many challenges would be present in pursuing these tasks (Table III). These challenges will range from surmounting logistical challenges of PROM design with frail vascular patients to determining the optimal length and reproducibility of a survey instrument in both research and clinical settings. However, the group agreed that a single measure was the optimal goal, and that careful diligence toward this goal would be the primary pathway forward. Further, the group agreed that post-design assessment of feasibility, content validity, repeatability, and implementation would be necessary metrics of success. In other words, if the tool is ultimately so complex that it could not be used in practice, then this exercise would be in vain. As such, engagement with experts in implementation science would likely follow construction of the final PROM instruments to facilitate their dissemination.

CONCLUSIONS

The existing tools used to measure PROMs in patients with CLTI are limited, and a single better PROM for CLTI is needed. Unlike patients with intermittent claudication, where recent data have focused on more consistent measures of patient symptoms, patients with CLTI demonstrate different challenges and significant clinical heterogeneity. In patients with CLTI, there has been greater use of less precise measures, and many studies have resorted to a multiplicity of measures to evaluate patient reported outcomes. Development of a single, validated PROM for patients with CLTI will undoubtedly necessitate multidisciplinary efforts, time and investment from many stakeholders. We unequivocally aim for this measure to be a collaborative effort across all specialty groups who care for patients with CLTI. However, the return on this investment will be a more focused and precise way to measure treatment effects and progress in the care of the growing number of patients afflicted with CLTI.

In 2019 Vascular Cures convened the Working Group on Patient-Reported Outcome Measures in PAD to address shortcomings in outcomes measures in PAD and CLTI. A multidisciplinary group of clinicians, scientists, regulatory experts, payers, industry leaders and patients came together over two years to drive consensus on the current state of outcome measures in claudication and chronic limb-threatening ischemia and identify priority projects to meaningfully advance the field for the benefit of all stakeholders.

Vascular Cures is a national nonprofit organization committed to reducing death and disability from vascular diseases by advancing patient-centered research, catalyzing breakthrough collaborations and empowering individuals on their vascular health journeys. Vascular Cures would like to thank all Working Group participants for their contribution to the discussion and final articles and acknowledge the industry sponsors who made this important work possible: Abbott Vascular, Amgen, Bayer, Boston Scientific, Cook

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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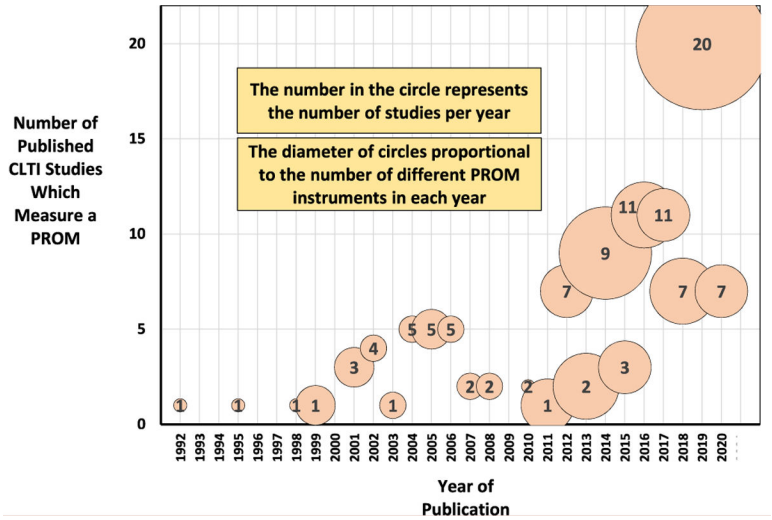

Fig 1.

Number of chronic limb-threatening ischemia (CLTI) studies reporting a Patient-reported Outcome Measure (PROM), by year.

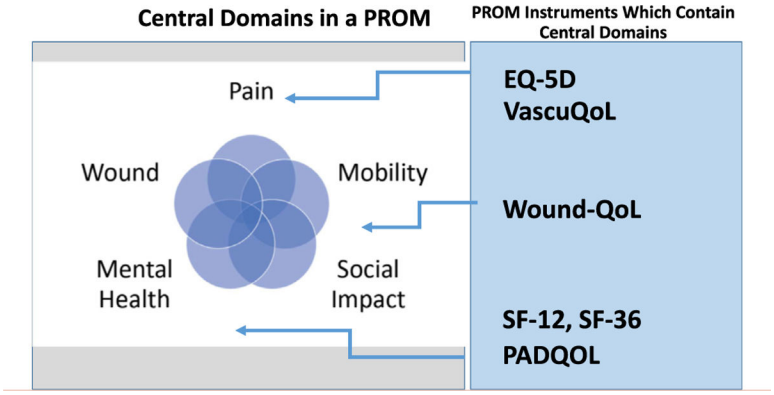

Fig 2.

Key terminology and domains in chronic limb-threatening ischemia (CLTI) Patient-reported Outcome Measure (PROM) development.

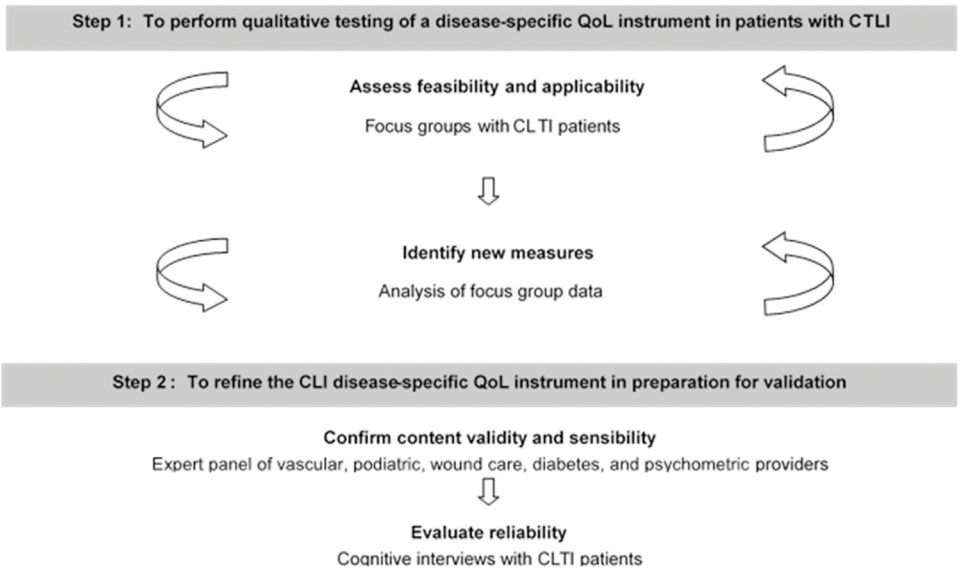

Fig 3.

Steps in developing a chronic limb-threatening ischemia (*CLTI*) Patient-reported Outcome Measure (PROM).

Table I.

Disease-specific quality of life (*QoL*) instruments used for the study of chronic limb-threatening ischemia

Instrument	No. of items	Scoring system	Domains/ subscales	Content validity	Construct validity	Internal consistency	Test-retest reliability	Sensitivity to change	Minimal clinically important difference	Time to administer	Self-administered vs interview-administered	Remarks	References
Vascu-QoL	25	1 to 7	Pain, symptoms, activities, emotional well-being, social well-being	Developed based on expert opinion and patient focus groups (Morgan)	IC/CLI. Correlations with Fontaine class, SF-36 (Morgan)	Alpha 0.7–0.8 for all items (Morgan)	ICC 0.94 (Morgan)	Statistically significant changes in score with clinical/ hemodynamic changes (Morgan, Mazari)	0.36 (Frans), 0.58 (Nordanstig), 0.87 for improvement and 0.23 for deterioration in IC population (Conijn)	10 min	Self-administered	Shorter version (VascuQoL-6) available	Morgan J Vasc Surg, 2001; Conijn Cardiovasc Intervent Radiol, 2015; Frans Eur J Vasc Endovasc Surg 2014; Nordanstig Health Qual Life Outcomes, 2012; Mazari J Vasc Surg, 2010
WIQ	14	0 to 100	Stair climbing, ambulation distance and speed	Unknown	IC. Statistically significant correlations with 6-min walk time and 4-m walk (McDermott)	Alpha 0.29 for pain subscale, other subscales 0.91–0.94 (Coyne)	ICC 0.68–0.83 (Coyne)	Responsiveness statistic 2.1–2.9 (Spertus)	0.11 for improvement and −0.03 for deterioration (Conijn)	6–8 min	Self-administered	Not true QoL measure, assesses only perception of walking	McDermott J Vasc Surg, 1998; Spertus Am J Heart, 2004; Coyne J Vasc Surg, 2003; Conijn Cardiovasc Intervent Radiol, 2015
Peripheral artery questionnaire	20	0 to 100	Physical limitation, symptoms, symptom stability, social limitation, QoL	Based on clinician and patient interviews (Spertus)	IC. Statistically significant correlation with domains of WIQ and SF-36 (Spertus)	Alpha 0.80–0.94 (Spertus)	ICC 0.70–0.90 (Spertus)	Responsiveness statistic 0.7 (treatment satisfaction); remainder were 1.9–4.1 (Spertus)	–	–	Self-administered	Includes unusual domains (eg, symptom stability)	Spertus Am Heart J, 2004

Instrument	No. of items	Scoring system	Domains/ subscales	Content validity	Construct validity	Internal consistency	Test-retest reliability	Sensitivity to change	Minimal clinically important difference	Time to administer	Self-administered vs interview-administered	Remarks	References
Peripheral artery disease quality of life	38	0 to 100	Self-concept and feelings, symptoms/ limitations in physical functioning, fear and uncertainty, positive adaptation	Based on patient interviews (Treat-Jacobson)	IC/CLI. Statistically significant correlation with domains of SF-36, POMS, WIQ (Treat-Jacobson)	Alpha 0.73–0.92 (Treat-Jacobson)	–	–	–	5–10 min	Self-administered	Includes unusual domains (eg, fear and uncertainty)	Treat-Jacobson Vasc Med, 2012
NeuroQoL	28		Painful symptoms, reduced feeling, diffuse sensorimotor symptoms, disruption of daily activities, interpersonal emotional burden, QoL	Based on clinician and patient interviews (Vileikyte)	Diabetic peripheral neuropathy. Used mediation studies to demonstrate construct validity, eg, NeuroQoL explained a greater portion of QoL than SF-12 (Vileikyte)	Alpha 0.88–0.95 (Vileikyte)	–	–	–	–	Self-administered		Vileikyte Diabetes Care, 2003
Questionnaire on quality of life with chronic wounds	17	0 to 4	Physical limitation, impaired mobility, daily life, leisure, social life, wound discharge, smell, appearance, psychological impairment, feeling disabled, expectation of wound course, being dependent, impairment owing to treatment, financial burden	Based on patient response to other instruments followed by expert consensus (Blome)	Adults with chronic wounds. Statistically significant correlation with domains of EQ-5D-3L, EuroQoL visual analog scale, and numerical rating scale for satisfaction with QoL	Alpha 0.71–0.91 (Blome)	ICC 0.79–0.86 (Sommer)	Correlation coefficients with domains of other tests weak to moderate (r = −0.12 to 0.51) (Blome)	–	–	Self-administered		Blome Wound Repair Regen, 2014; Sommer Wound Repair Regen, 2017

IC/CLI, Intermittent claudication/critical limb ischemia; *ICC*, intraclass correlation coefficient; *NeuroQol*, Quality of life in neurological disorders; *QoL*, quality of life; *SF-36*, Short Form 36; *Vascu-QoL*, King's College Hospital's vascular quality of life questionnaire; *WIQ*, Walking impairment questionnaire.

Table II.

Currently enrolling chronic limb-threatening ischemia (CLTI) trials

Study name	ClinicalTrials.gov identifier	Study status	Start of enrollment	PROMS
Exercise rehabilitation for patients with critical ischemia after revascularization	NCT03839953	Enrolling	2/15/2019	Vascu-Qol, SF-36
Administration of adipose-derived stem cells in patients with critical limb ischemia	NCT03968198	Enrolling	3/4/2020	Pain score (visual analogue)
Revascularization of stenosed vessels using optimized treatment of Rejuvenix for reversing endothelial dysfunction	NCT03041259	Not yet enrolling		Walking impairment questionnaire
Physician Initiated, Prospective, Non-randomized Single-centre, Single-arm Trial, Investigating the Safety and Efficacy of the Treatment With the Non-compliant Jade Balloon in TASC C and D Athero-occlusive Infrainguinal Disease in Patients With Chronic Limb Threatening Limb Ischemia From SingaporE (PINNACLE)	NCT04534192	Not yet enrolling		Walking impairment questionnaire
Safety and Efficacy Study Using Gene Therapy for Critical Limb Ischemia	NCT04274049	Enrolling	8/18/2019	Pain score (unspecified)
Safety and Efficacy Study Using Gene Therapy for Critical Limb Ischemia	NCT04275323	Enrolling	8/2/2019	Pain score (numerical rating scale), QoL (unspecified instrument)
Autologous Transplantation of BM-ECs With Platelet-Rich Plasma Extract for the Treatment of Critical Limb Ischemia	NCT02993809	Unknown	3/10/18	Pain score (visual analogue)
Intermittent Negative Pressure; Impact on Peripheral Artery Disease and Intermittent Claudication	NCT04100681	Terminated	8/19/2019	EQ-5D, VascuQoL-6, change in pain-free walking distance
Smartstep Smartphone PAD	NCT03479255	Enrolling	8/24/2018	SF-36, walking impairment questionnaire, 6-minute walk test
Recombinant SeV-hFGF2/dF Injection for PAOD	NCT03668353	Unknown	9/5/2018	Pain score (visual analogue), walking distance (unspecified)
Impact of Intravenous Iron Treatment of Preoperative Anemia in Patients With LEAD (IRONPAD)	NCT04083755	Enrolling	8/15/2019	SF-36
Leg Ischaemia Management Collaboration (LIMb)	NCT04027244	Enrolling	5/10/2019	Vascu-Qol, Barthel Index (disability), Hospital Anxiety and Depression Scale
RECCORD (Recording Courses of Vascular Diseases) Registry (RECCORD)	NCT03448029	Enrolling	1/1/2018	EQ-5D
Allogeneic Mesenchymal Stromal Cells for Angiogenesis and Neovascularization in No-option Ischemic Limbs (SAIL)	NCT03042572	Not yet enrolling		EQ-5D, Pain (visual analogue), pain-free walking distance, SF-36
BIO REsponse Adapted Combination Therapy Pilot Study	NCT03547986	Active, not enrolling	11/9/2018	EQ-5D, walking impairment questionnaire
ILLUMENATE Pivotal Post-Approval Study (PAS)	NCT03421561	Active, not enrolling	4/14/2017	EQ-5D, walking impairment questionnaire, walking distance
Autologous BMMNC Combined With HA Therapy for PAOD	NCT03214887	Unknown	1/17/2017	Pain (visual analogue), pain-free walking distance
Safety and Feasibility of Surmodics SUNDANCE™ Drug Coated Balloon (SWING)	NCT04107298	Not yet enrolling		EQ-5D, VascuQoL, walking impairment questionnaire

Study name	ClinicalTrials.gov identifier	Study status	Start of enrollment	PROMS
Stella Supera Siberia	NCT03951727	Enrolling	5/13/2019	EQ-5D
BEST-CLI	NCT02060630	Completed		EQ-54, VascuQol
Basil-2	ISRCTN:27728689	Enrolling		European Quality of Life questionnaire, SF-12
Basil-3	ISRCTN:27728689	Enrolling		European Quality of Life questionnaire, SF-12
Shifting Care and Outcomes for Patients with Endangered Limbs	NCT03171259	Enrolling		Peripheral Artery Questionnaire
SWEDEPAD-2 (The Swedish Drug Elution Trial in Peripheral Artery Disease)	NCT02051088	Enrolling		
Study period: 01/01/2017-09/10/2020 (3 full years + current year)				
Search: peripheral arterial disease, peripheral vascular disease, critical limb ischemia, chronic limb threatening ischemia				
“Primary outcome measures” and “Secondary outcome measures” analyzed for PROMs				

PROMS, Patient-Reported Outcomes; *SF-36,* Short Form 36; *Vascu-Qol,* King’s College Hospital’s vascular quality of life questionnaire.

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Table III.

Barriers to the design and implementation of Patient-Reported Outcomes (PROMs) for chronic limb-threatening ischemia (CLTI)

Challenge or barrier to measure development	Questions
Overall purpose	Are the measures clinically justified? Are the measures clinically applicable?
Measure format	Are the questions comprehensible and simple?
	Are the directions for usage clear?
	Is the survey thorough?
Face validity	Are the questions aimed at the right thing (ie, QoL)?
Content validity	Have important variables/questions been omitted?
	Have unsuitable variables/questions been included?
	Are appropriate score ranges used for questions?
Ease of use	How much time and effort are required to obtain and organize data (i.e., answer the survey)?