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REVIEW ARTICLE

Health-related quality-of-life questionnaires for deep vein thrombosis and pulmonary embolism: A systematic review on questionnaire development and methodology

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Abstract

To improve the quality and accuracy of the patient-reported outcome measures that assess health-related quality of life (HRQoL), guidelines have been developed to standardize the development and validation process. Considering the increasing importance of HRQoL questionnaires in research, we set out to review the literature and evaluate whether existing questionnaires developed for deep vein thrombosis (DVT) and pulmonary embolism (PE) fulfill state-of-the-art requirements. The literature search was conducted in March 2019 and updated in September 2020. Seven databases were searched. No time limit was set for the search to include all available questionnaires. The inclusion criteria were original publications describing the development of disease-specific HRQoL questionnaires specific to DVT or PE in adults and available in English. The questionnaires were assessed to determine whether they fulfill the requirements in the latest guidelines. A total of 3826 references were identified. After the exclusion process, 15 papers were reviewed in full, of which 7 were included. Four questionnaires were developed for chronic venous disease, two were specific to DVT, and one was specific to PE. Most questionnaires we found in this review, fulfilled some but none fulfilled all recommendations in existing guidelines. Because the development of current available HRQoL questionnaires specific to DVT or PE do not fulfil all recommendations of existing guidelines, there is room for improvements within this field. Such improvements could likely enhance the quality associated with the use of these end points in clinical trials and practice.

KEYWORDS
embolism and thrombosis, patient-reported outcome measures, pulmonary embolism, quality of life, surveys and questionnaires, thrombosis, venous thrombosis

Essentials

- Deep vein thrombosis and pulmonary embolism impact quality of life.
- Guidelines exist for the development of quality-of-life questionnaires.
- None of the seven questionnaires found fulfilled the guideline requirements.
- A new questionnaire developed according to guidelines may improve usefulness.

1 | INTRODUCTION

Using patient-reported outcome measures (PROMs), for example, symptom measurement and health-related quality of life (HRQoL), has become increasingly common in clinical research. In deep vein thrombosis (DVT) and pulmonary embolism (PE), which are collectively known as venous thromboembolism (VTE), a growing understanding of their chronic nature and potential lifelong consequences has highlighted PROMs as relevant end points.[1,2] A PROM is a measure of the patient's health condition that collects information directly from the patient without interpretation of a clinician, and may be used to assess any aspect of a patient's health, from generic to disease-specific.[3,4] While generic questionnaires may be applied to any population including healthy populations and can be used for comparing different populations, disease-specific questionnaires may provide better sensitivity to disease-specific variations and may have greater relevance for patients with specific diseases or conditions.[5]

Following the increased interest in and the importance of PROMs, guidelines have been developed by the European Organization for Research and Treatment of Cancer (EORTC), the Food and Drug Administration (FDA) and others regarding quality standards for their development and use.[6,7] The EORTC guidelines present a modular development guide with four phases: (i) generation of relevant HRQoL issues; (ii) conversion of the issues into a set of items; (iii) pretesting the item list; and (iv) large-scale international field testing. Phases 1 and 2 require the involvement of at least three countries and languages; phase 3 should include a wider range of countries and is recommended to include at least six countries, while phase 4 should include as many countries as possible.[6] Patient participation in the form of qualitative interviews has been highlighted as the most important step to ensure high content validity, that is, appropriateness of a measure's content for its target population.[8]

To ensure the quality of a questionnaire, the development should be guided by current guidelines. However, whether or not existing questionnaires in VTE fulfill guideline recommendations is unknown. Moreover, given the plethora of questionnaires, researchers and clinicians not experienced in this field can potentially use PROMs in research or in the clinical setting that have not been developed according to the recommended methodology, consequently limiting interpretation, validity, and usefulness.

Due to the lack of a gold standard to validate the results of questionnaire development, the whole process of development and psychometric validation together provide the basis for validity of a questionnaire. In this review, we set out to review the literature and evaluate if existing questionnaires developed for DVT and PE fulfill state-of-the-art requirements, with a particular focus on the development phase before psychometric validation.[6,7] To avoid the misconception where a questionnaire is declared valid based only on the results from psychometric analysis, we opted not to include this in our review, as it would be of less concern if the development is not done optimally. Additionally, a systematic review published by Robert Launois, evaluates the psychometric validation for the most commonly used questionnaires, namely, Venous Insufficiency Epidemiological and Economic Study–Quality of Life (VEINES-QOL) and Chronic Venous Insufficiency Questionnaire (CIVIQ) as well as Specific Quality of Life and Outcome Response–Venous (SQOR-V).[9]

2 | MATERIALS AND METHODS

The current review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[10] An information specialist (HS) planned and performed systematic literature searches in MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), Health and Psychosocial Instruments (Ovid), Cumulative Index of Nursing and Allied Health Literature (EBSCO), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Epistemonikos. Search terms were identified in collaboration between the authors (HSW, EA, and HS). The search consisted of a combination of subject headings, where applicable, and text words in title, abstract, and keywords. See Appendix S1 for full search strategies in all databases. Searches were performed on March 3, 2019, and updated on September 20, 2020.

No time limit was set for the search to include all available questionnaires.

The inclusion criteria were original publications describing the development of disease-specific HRQoL questionnaires specific to DVT or PE in adults. Furthermore, publications and questionnaires had to be available in English. Questionnaires developed for chronic venous disease are often used for the DVT population and were consequently included in the current review. Questionnaires developed specifically for other chronic venous diseases such as varicose veins or ulcers were excluded.

Duplicates were removed and all identified articles transferred to RAYYAN, a web application to help authors screen references.[11] Two authors (HSW and EA) performed an independent assessment of titles and abstracts. Upon completion, both authors' individual assessments were accessible, and any cases of discrepancies were discussed and reconciliated. In case of disagreement, consensus was achieved by the involvement of the remaining co-authors.

In addition, to identify potentially relevant papers not identified in the database searches, we scrutinized the reference lists of review papers. These did not yield any additional results.

In the included articles, questionnaire development was assessed systematically on the basis of existing guidelines by the EORTC and FDA (Table 1).[6,7] Three essential criteria were formulated based on the main phases of development as described in the EORTC guidelines (Table 1). This includes the inclusion of patients for obtaining the relevant issues, pretesting, and item reduction as well as international cooperation.

A questionnaire was deemed not developed according to current guidelines if any of the criteria listed in Table 1 were not fulfilled.

3 | RESULTS

The search yielded 3826 papers after removal of duplicates, of which 3806 were excluded on the basis of title and abstract (Figure 1). Of the remaining papers, five were excluded due to unavailability in English.[12–16] Fifteen papers were reviewed in full, of which seven were included and analyzed further.[17–23] Six of the eight excluded papers were review papers.[9,24–28] The questionnaire developed by Mathias et al[29] was excluded, as neither the questionnaire itself nor the items comprising it have been published. The questionnaire Assessment of Burden in Chronic–Venous Disease was excluded due to the questionnaire being a burden-of-disease questionnaire and not a HRQoL questionnaire.[30] Screening of the review articles on this topic and the references of the included studies did not reveal any questionnaires that had not already been identified.

Of the questionnaires included, four were developed for chronic venous disease, two were specific to DVT, and one was specific to PE. Following is a description of the identified questionnaires:

3.1 | CIVIQ and CIVIQ-14

CIVIQ, published in 1996, was the first questionnaire to assess HRQoL for patients with chronic venous disease.[17] The questionnaire was developed in France, and its original language is French. During its development, the questionnaire was modified and thus named CIVIQ-2 to distinguish it from its predecessor. Based on 20 semistructured individual interviews with 20 patients, 188 items were generated. These were eventually reduced to 20 items divided into four dimensions: physical, psychological, social, and pain. The questionnaire has been used in DVT studies but has not been through psychometric validation for this population.[31,32] During the assessment of the construct validity (demonstrating that the measure assesses its intended concept), the authors found that some of the items did not perform well.[33] This problem was amplified when implemented internationally. To amend this issue, the authors developed a new questionnaire, the CIVIQ-14, by removing six items and combining the social dimension with the physical dimension.[18]

This questionnaire fulfills patient participation criteria as well as item reduction and pretesting, but there was no international cooperation during development.

3.2 | Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms

The Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms (VEINES-QOL/Sym) questionnaire was developed as part of the Venous Insufficiency Epidemiological and Economic Study for the chronic venous disease population and published in 2003.[20] This questionnaire was developed in English through international collaboration, and items were generated by literature review, existing measures, and expert opinions. This process resulted in the formation of a 26-item questionnaire divided into four dimensions: symptoms, psychological, limitation in daily activities, and change over the past year. The questionnaire was modeled after the Short Form-36 with similar format and response scales. Two scores can be calculated from the questionnaire. One question, regarding the time of day that leg problems are most severe is descriptive and not included in the scores. The VEINES-QOL score is based on 25 questions, while the symptoms dimension that contains 10 of the questions can be used separately to produce a symptom severity score, the VEINES-SYM score. The VEINES-QOL/Sym has

TABLE 1 Assessment of HRQoL questionnaires in DVT and PE for the fulfillment of the essential criteria based on current guidelines

	CIVIQ	VEINES-QOL/Sym	SQOR-V	DVTQOL	VT-QOL	PEmb-QoL
1. Involvement of the target population in obtaining relevant issues is clearly described and the method is appropriate	+	−	−	+	−	+
2. The process of pretesting and item reduction is clearly described and the method is appropriate	+	−	−	+	−	−
3. International cooperation during the development that includes at least 3 different countries with 3 different languages	−	+	−	−	−	−

Note: The assessment is based on whether the method used in the development of the questionnaire is appropriate and whether the developers provide adequate information.

Abbreviations: CIVIQ, Chronic Venous Insufficiency Questionnaire; DVT, deep vein thrombosis; DVTQOL, Deep Vein Thrombosis Quality of Life; HRQoL, health-related quality of life; PEmb-QoL, Pulmonary Embolism Quality of Life; SQOR-V, Specific Quality of Life and Outcome Response–Venous; VEINES-QOL/Sym, Venous Insufficiency Epidemiological and Economic Study–Quality of Life/Symptoms; VT-QOL, Venous Thrombosis–Quality of Life.

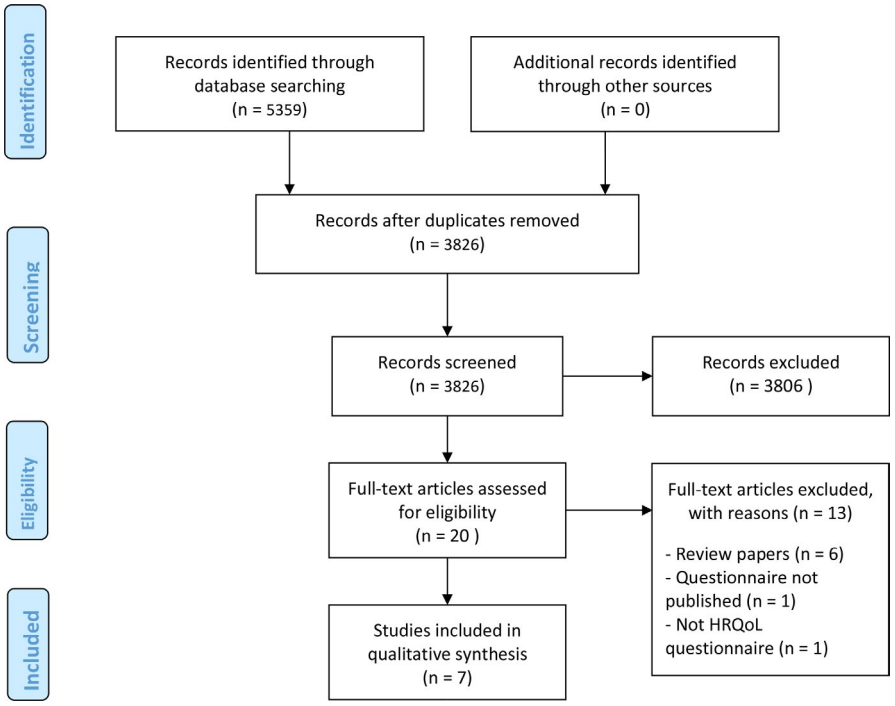

FIGURE 1 Citation retrieval and handling process. HRQoL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses

been through psychometric validation for the DVT population and translated into many languages. It is the most widely used questionnaire for the measurement of HRQoL in DVT.[34–38]

VEINES-QOL/Sym fulfills the international cooperation criteria, but not the patient involvement for item generation, item reduction or pretesting criteria.

3.3 | SQOR-V

The SQOR-V questionnaire was developed in France for chronic venous disease patients and published in 2007.[19] Item generation was based on a literature search and an expert panel who constructed a 46-item questionnaire in English that was translated into French before further development. The questionnaire is divided into five dimensions: discomfort, appearance, restriction of movements, risk, and emotional problems. The SQOR-V differentiates between the lower extremities by allowing patients to score each lower extremity separately. To our knowledge, this questionnaire has not been used or psychometrically validated specifically for the DVT population.

In this questionnaire patient involvement for item generation, item reduction, pretesting or international criteria are not fulfilled.

3.4 | Deep Vein Thrombosis Quality of Life

Deep Vein Thrombosis Quality of Life (DVTQOL) was published in 2004 and was developed and psychometrically validated for patients with proximal DVT treated with warfarin for at least 4 weeks.[21] This questionnaire was developed in Sweden, with Swedish as the original language. Items were generated by interviews with patients with DVT, consulting experts, and a review of the literature. The final questionnaire consisted of 29 items in six dimensions: emotional distress, symptoms, limitation in physical activity, hassle with monitoring, sleep disturbance, and dietary problems related to warfarin. To our knowledge, this questionnaire has not been used outside the original study.

DVTQOL fulfills patient participation criteria as well as item reduction and pretesting, but there was no international cooperation during development.

3.5 | Venous Thrombosis–Quality of Life

Venous Thrombosis–Quality of Life (VT-QOL) was published in 2004 and was developed and psychometrically validated as a disease-specific HRQoL questionnaire for patients with DVT.[22] VT-QOL was developed in English with patients from the United States and consists of 25 items in four dimensions: physical functioning, social functioning, general mental health, and thrombosis repercussions. The method of development was somewhat unclear. The authors highlight that questionnaire development was based on previous questionnaires, as well as on interviews with patients. However, no detailed description of these interviews is available in the publication.[22] To our knowledge, this questionnaire has not been used outside the original study.

In this questionnaire, patient involvement for item generation, item reduction, pretesting, or international criteria are not fulfilled.

3.6 | Pulmonary Embolism Quality of Life

Published in 2009, Pulmonary Embolism Quality of Life (PEmb-QoL) is the only questionnaire found that was developed specifically for the PE population and psychometrically validated.[23,39] It was originally developed in Dutch and later translated into English. Item generation was done by interviewing 10 patients, which resulted in 40 items covering six dimensions: frequency of complaints, activities of daily living limitations, work-related problems, social limitations, intensity of complaints, and emotional complaints. The methodology does not mention any process of item reduction following interviews, and there is no description of the process between interviews and the final questionnaire. PEmb-QoL has been translated to other languages and has been used in other studies.[40–43]

PEmb-QoL fulfills patient involvement in item generation criteria, but not the item reduction, pretesting, and international cooperation during development criteria.

Details concerning the analyses of the different questionnaires are summarized in Table 1. Overall, three questionnaires presented clear evidence of patient involvement[17,21,23]; two describe pretesting and item reduction adequately,[17,21] and only one fulfills the international cooperation criteria.[20]

4 | DISCUSSION

In this systematic review of disease-specific HRQoL questionnaires used in DVT or PE populations, development of the seven questionnaires identified did not fulfill all rigorous recommendations in current guidelines. Of note, most fulfilled one or more guideline recommendations. The lack of full guideline adherence may be explained by the fact that all the questionnaires found were developed before the introduction of the current guidelines.

Guidelines have been developed by the FDA, EORTC, and professional societies such as the International Society for Quality of Life Research and International Society for Pharmacoeconomics and Outcomes Research.[6–8,44] The aforementioned organizations agree on the importance of patient involvement and the core concepts of questionnaire development.

Patient involvement in the form of qualitative interviews is the most important step in the development of a questionnaire to ensure the appropriateness of a measure's content for its target population.[8] This step is crucial to avoid irrelevant, missing, ambiguous, or badly worded questions, as no statistical adjustment can compensate for poor item generation. CIVIQ, DVTQOL, and PEmb-QoL included patients for the purpose of item generation.[17,21,23]

The process of pretesting and item reduction are important to identify relevant issues, remove duplicates/irrelevant issues, identify the dimensions of the questionnaire, and construct the final refined questionnaire to be validated. CIVIQ and DVTQOL are the only questionnaires with an adequate description of pretesting and item reduction.[17,21]

The modular development model by EORTC requires the collaboration of at least three countries with three different languages during the initial development.[6] This is to account for cultural and language differences that may lead to different interpretations of HRQoL as well as the different lifestyles. The importance of these criteria is underlined by the results from CIVIQ 2. While patients were included in the item generation and the questionnaire meets most of the criteria, due to the lack of international collaboration, the questionnaire was not applicable outside its country of origin and original language.[33] International cooperation in the development phase is missing for all questionnaires except for the VEINES-QOL/Sym.[20]

Treatment options for patients with DVT and PE have also evolved since the development of these questionnaires. Before introduction of the new direct oral anticoagulants, patients were treated with vitamin K antagonists that required careful monitoring and change in eating habits.[45] This is reflected in DVTQOL, which includes hassle with monitoring and dietary problems as separate dimensions.[21] It is also possible that these restrictions will have affected the results in the psychological dimensions. After the introduction of the new direct oral anticoagulants and their use by the majority of VTE population in many countries, monitoring and dietary restrictions became less relevant.[46]

Of note, occasionally the developer may not be able to rely mainly on patients for item generation or may be limited due to a low number of available patients.[47,48] No such limitations apply for the DVT or PE populations, and therefore the best available options should be chosen during the development of questionnaires for these populations.

Overall, our study demonstrated that although most of the available questionnaires fulfill one or more requirement, none fulfills all guideline recommendations. Moreover, several other methodological or practical limitations are applicable. This in turn may limit interpretation, validity, and usefulness of PROMs in this field.

An issue encountered during this review was the lack of information or ambiguity in the publications. Several publications did not include a clear description of the steps of development in the methodology, and the results section was often lacking in information. Many aspects of the questionnaires, their development, and testing results were omitted. This may have been due to the lack of clear reporting guidelines during the time of development of those questionnaires. In addition, restricting the inclusion criteria to English language and adults may have limited the scope of the review. Another limitation may have been the lack of evaluation of the translation process to other languages as well as mapping the availability of questionnaires in different languages. On the other hand, the comprehensive search in several databases as well as the individual assessment of the papers by two of the authors and the review of other overview articles and their references strengthen the review.

5 | CONCLUSION

Because the development of current available HRQoL questionnaires specific to DVT or PE do not fulfill all recommendations of current guidelines for development of HRQoL questionnaires, there

is room for improvements within this field. Such improvements could likely enhance the quality associated with the use of these end points in clinical trials and practice.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception or design of the work. The search was performed by HS, who also contributed greatly to the methodology and Appendix S1. EA and HSW performed the assessment of the search results. All authors contributed to drafting the work or revising it critically for important intellectual content and approved this version for submission.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest. WG reports personal fees from Novartis, personal fees from Amgen, grants and personal fees from Bayer, grants and personal fees from Pfizer/BMS, personal fees from Sanofi, personal fees from Principia, and personal fees from MSD, outside the submitted work.

OPEN RESEARCH BADGES

This article has earned an Open Data, Open Materials, and Preregistered Badge for making publicly available the digitally shareable data necessary to reproduce the reported results. The data are available at https://doi.org/10.17605/OSF.IO/PN46B and https://doi.org/10.17605/OSF.IO/ABHE8.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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