Development of an international standard set of outcome measures for patients with venous thromboembolism

an International Consortium for Health Outcomes Measurement consensus recommendation

Gwozdz, Adam M; de Jong, Cindy M M; Fialho, Luz Sousa; Likitabhorn, Theerawich; Sossi, Frieda; Jaber, Paula Blancarte; Højen, Anette Arbjerg; Arcelus, Juan I; Auger, William R; Ay, Cihan; Barco, Stefano; Gazzana, Marcelo B; Bayley, Julie; Bertoletti, Laurent; Cate-Hoek, Arina ten; Cohen, Alexander T; Connors, Jean M; Galanaud, Jean Philippe; Labropoulos, Nicos; Langlois, Nicole; Meissner, Mark H; Noble, Simon; Nossent, Esther J.; de León Lovatón, Paula Ponce; Robert-Ebadi, Helia; Rosovsky, Rachel P; Smolenaars, Noa; Toshner, Mark; Tromeur, Cécile; Wang, Kang Ling; Westerlund, Eli; de Wit, Kerstin; Black, Stephen A; Klok, Frederikus A.

Published in:
The Lancet Haematology

DOI (link to publication from Publisher):
10.1016/S2352-3026(22)00215-0

Publication date:
2022

Document Version
Accepted author manuscript, peer reviewed version

Development of an international standard set of outcome measures for patients with venous thromboembolism: an International Consortium for Health Outcomes Measurement (ICHOM) consensus recommendation

[1,2]Adam M. Gwozdz, MBBS[*]; [3]Cindy de Jong, MD[*]; [4]Luz Sousa Fialho, PhD; [5]Theerawich Likitabhorn, MD; [4]Frieda Sossi, MSc; [4]Paula Blancarte Jaber, MD; [6]Anette Arbjerg Højen, PhD; [7]Juan I. Arcelus, MD; [8]Prof William R. Auger, MD; [9]Prof Cihan Ay, MD; [10,11]Stefano Barco, MD; [12]Marcelo Basso Gazzana, PhD; [13]Julie Bayley, PhD; [14]Prof Laurent Bertoletti, MD; [15]Arina ten Cate-Hoek, MD; [16]Alexander T. Cohen, MD; [17]Jean M. Connors, MD; [18]Jean-Philippe Galanaud, MD; [19]Prof Nicos Labropoulos, MD; [20]Nicole Langlois, MSc; [21]Mark H. Meissner, MD; [22]Prof Simon Noble, MD; [23]Esther J. Nossent, MD; [24]Paula Ponce de León Lovatón, MD; [25]Helia Robert-Ebadi, MD; [26]Rachel P. Rosovsky, MD; [27]Noa Smolenaars, BSc; [28]Mark Toshner, MD; [29]Cécile Tromeur, MD; [30]Kang-Ling Wang, MD; [31]Eli Westerlund, PhD; [32,33]Kerstin de Wit, MBChB; [1]Prof Stephen A. Black, MD[‡]; [3]Prof Frederikus A. Klok, MD[‡]

[‡*]contributed equally

[1]Academic Department of Vascular Surgery, Section of Vascular Risk and Surgery, School of Cardiovascular Medicine and Science, St Thomas' Hospital, King's College London, London, United Kingdom

[2]Academic Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, London, United Kingdom; Department of Vascular Surgery, Imperial College Healthcare NHS Trust, London, United Kingdom

[3]Department of Medicine - Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

[4]International Consortium for Health Outcomes Measurement, London, United Kingdom

[5]International Consortium for Health Outcomes Measurement, Boston, Massachusetts, United States

[6]Aalborg Thrombosis Research Unit, Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

[7]Department of Surgery, University of Granada Medical School, Granada, Spain

[8]Department of Pulmonary Medicine, University of California, San Diego, California, United States

[9]Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[10]Department of Angiology, University Hospital Zurich, Zurich, Switzerland

[11]Center for Thrombosis and Hemostasis, Johannes Gutenberg University Mainz, Mainz, Germany

[12]Serviço de Pneumologia e Cirurgia Torácica, Hospital Moinhos de Vento; ANAHP, Porto Alegre, Rio Grande do Sul, Brazil

[13]Lincoln Impact Literacy Institute, University of Lincoln, Lincoln, United Kingdom

[14]CHU de St-Etienne, Service de Médecine Vasculaire et Thérapeutique; INSERM, UMR1059, Université Jean-Monnet; INSERM, CIC-1408, CHU de Saint-Etienne ; INNOVTE, CHU de Saint-Etienne ; all in F-42055, Saint-Etienne, France

[15]Heart and Vascular Center, Maastricht University Medical Centre, Maastricht, The Netherlands

[16]Department of Hematological Medicine, Guy's and St. Thomas' Hospital; King's College London, London, United Kingdom

[17]Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States

[18]Department of Medicine, Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Canada

[19]Division of Vascular Surgery, Department of Surgery, Stony Brook Hospital, Stony Brook, New York, United States

[20]Department of Medicine, Ottawa Hospital Research Institute, Ottawa, Canada

[21]Department of Surgery, University of Washington, Seattle, Washington, United States

[22]Marie Curie Palliative Care Research Centre, Cardiff University, Cardiff, United Kingdom

[23]Department of Pulmonary Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC location Vrije Universiteit Amsterdam, Boelelaan 1117, Amsterdam, The Netherlands

[24]Clínica San Felipe - Red SANNA, Jesús María, Peru

[25]Division of Angiology and Hemostasis, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[26]Division of Hematology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States

[27]Department of Industrial Design, University of Technology Eindhoven, Eindhoven, The Netherlands

[28]Heart Lung Research Institute, Department of Medicine, University of Cambridge, Cambridge, United Kingdom

[29]Département de Médecine Interne et Pneumologie, CHU Brest; GETBO, Université de Bretagne Occidentale; F-CRIN INNOVTE, Saint Étienne, France

[30]General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan

[31]Department of Clinical Sciences, Karolinska Institutet; Danderyd Hospital, Danderyd, Sweden

[32] Department of Emergency Medicine, Queen's University, Kingston, Ontario, Canada

[33]Departments of Medicine and HEI, McMaster University, Hamilton, Ontario, Canada

Corresponding author:

Frederikus A. Klok

Department of Medicine - Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands; Albinusdreef 2, 2333 ZA, Leiden, the Netherlands

Phone: +31-715269111

Email: f.a.klok@lumc.nl

Word count: 3189

Word count summary: 150

References: 39

Number of tables: 2

Number of figures: 3

Supplementary material: Appendix A-B

SUMMARY

The International Consortium for Health Outcomes Measurement (ICHOM) assembled an international working group of venous thromboembolism (VTE) experts and patient representatives to develop a standardised minimum set of outcomes for integration into clinical practice and potentially research, supporting clinical decision-making, and benchmarking of quality of care. A total of 15 core outcomes important to patients and healthcare professionals were selected and categorised into four domains: patient-reported outcomes, long-term consequences of the disease, disease-specific complications, and treatment-related complications. The outcomes and outcome measures were designed to apply to all VTE patients ≥16 years old. A minimum number of items, part of the outcome measures and instruments in the core set to be measured at predefined time points, capture all core outcomes. Additional measures are introduced by a cascade opt-in system that allows for further assessment if required. This set will facilitate implementation of the use of patient-centered outcomes in daily practice.

Keywords

Venous thromboembolism; deep vein thrombosis; pulmonary embolism; patient-centered outcomes; patient-reported outcome measures; value-based health care

Search strategy and selection criteria

During the development process of the standardised set of outcomes, literature searches were performed using appropriate medical subject heading (MeSH) terms and search terms. Potentially relevant outcome domains and clinical and patient-reported outcomes were identified through a literature search of PubMed, performed on March 8th 2021, with search terms capturing "Venous Thromboembolism", combined with terms covering "Patient Reported Outcome Measures" (as well as terms with "patient relevant") and "Treatment Outcome", in "Adults" and "Adolescents" (children were excluded from the scope of the project). Papers published in English and published in the past ten years were reviewed. Original research papers in which clinical and patient-reported outcomes were reported in a population of patients with pulmonary embolism and/or deep vein thrombosis were included for full-text review to identify outcomes. Separate outcome-specific literature searches were performed to identify potentially relevant (patient-reported) outcome measures.

INTRODUCTION

Venous thromboembolism (VTE) comprising of deep vein thrombosis (DVT) and pulmonary embolism (PE) affects 1-3% of the population and has an annual incidence of 1-2/1000 in the Western World.[1-3] Approximately 60% of all VTE cases present as DVT with the other 40% presenting as PE with or without DVT.[4] The management of VTE involves anticoagulation and may be complicated by sequelae which include recurrent VTE, anticoagulant therapy associated bleeding, post-thrombotic syndrome (PTS), and post-PE syndrome (PPES), the latter two affecting 40-50% of all VTE survivors.[5-8] VTE has a significant negative impact on patients' lives, causing a reduced quality of life, a higher prevalence of unemployment, and emotional distress including anxiety and post-thrombotic panic syndrome.[9-14]

The management of VTE around the globe is inconsistent and highly diverse. Not only are there differences in healthcare systems, availability of resources, and socio-religious circumstances, but recent guidelines also differ regarding recommendations on risk stratification, management of VTE, and long-term follow-up, and little consideration to the patients' perspective or values with recommended use of patient-reported outcomes is provided. Along this, there are major differences in treatment outcomes, e.g., mortality[15-17], loss of quality of life adjusted life-years[18], and chronic thromboembolic pulmonary hypertension (CTEPH)[19] across countries and continents. Other differences involve use of healthcare resources measured by rate of hospital admissions[20,21], duration of hospitalisation[21], and use of interventional techniques. Moreover, work-related disability and psychosocial consequences such as persisting anxiety and depression, which are of considerable importance to the individual patient, as well as society as a whole, receive minimal attention in current VTE patient pathways.[11-14]

There is increasing recognition of the importance of integrating all aspects of healthcare to focus on the delivery of value-based healthcare. The 'value' in value-based healthcare is derived from measuring health outcomes against the cost of their delivery, and value-based approaches lead to improved health outcomes for patients with fewer clinical visits, medical tests, and procedures.[22] Thus, rather than a system within which providers are paid based on the number of healthcare services they deliver,[23] a shift to a value-based approach for VTE would drive providers to be rewarded for helping patients improve their health, reduce the

effects and incidence of chronic disease, and live healthier lives in an evidence-based way. A fully standardised approach for value-based healthcare would include both clinical and patient-reported outcome measures (PROMs), assessed at fixed time points, using well-defined instruments and definitions.

To support improvements in care for patients with VTE globally via a value-based healthcare approach, the International Consortium for Health Outcomes Measurement (ICHOM) assembled a geographically diverse working group of 27 clinical and/or scientific VTE experts and patient representatives from 13 countries in Europe, North America, Latin America and Asia Pacific. ICHOM is a not-for-profit organisation that has previously developed 40 standard sets of value-based outcomes covering different disease states. The aim of this project was to propose a broadly applicable and easy to use standardised minimum set of outcomes for VTE patients, including PROMs as well as clinical outcomes and case-mix factors. The ICHOM-VTE set serves three specific goals: (i) to standardise and improve the care for individual patients with VTE, (ii) to facilitate standardisation of outcomes to make meaningful comparisons across institutions and countries and, (iii) to empower patients to manage their disease and seek optimal care focused on their individual needs.

STRATEGY

A project team (FAK, SAB, CDJ, AMG, FS, PBJ, TL and LF) guided the working group's efforts over 13 months. The working group convened via nine videoconferences between January 2021 and February 2022, following a structured process which involved professionals and patients in all meetings. The development of the standard set involved several phases: defining the scope of the project; prioritising and defining outcome domains; evaluating and selecting appropriate outcome measurement tools; and selecting and defining relevant case-mix variables and timepoints.

Identification of potential outcomes and case-mix variables

The project team performed a systematic literature review, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[24] to identify potentially relevant outcome

domains, clinical and patient-reported outcomes, (treatment-related) complications and case-mix variables. Appropriate medical subject heading (MeSH) terms and free word searches were used (Online Appendix A). The literature search resulted in 1004 articles. Two reviewers (CDJ, AMG) independently screened the articles and included original research papers in which clinical and patient-reported outcomes were reported in a population of patients with pulmonary embolism and/or deep vein thrombosis. Any disputes were resolved by a third reviewer (FS). This resulted in 188 articles being included for full-text review. Patient representatives from the working group participated as a patient advisory group in an additional separate breakout session to explore their perspectives on the importance of various outcomes identified from the literature, and what affected them the most during their day-to-day activities. The predefined criteria by which outcomes were assessed for inclusion in the set were: (i) frequency of the outcome, (ii) impact on the patients, (iii) potential for modifying the outcome, and (iv) feasibility of measuring the outcome. Variables to be used as case-mix factors, which take the effects of different risk profiles that impact outcomes into account and allow standardised risk adjustment across different populations, were assessed on: (i) relevance, (ii) independence, and (iii) measurement feasibility. All potentially relevant outcomes and case-mix variables were discussed during the videoconferences and put to vote in a three-round modified Delphi process.

Selection of (patient-reported) outcome measures and definitions

We mapped the standard set outcomes to corresponding PROMs and definitions identified from the literature review. We applied widely used definitions by scientific organisations, in guidelines or applied in studies to define the clinical outcomes. If multiple were found, all were put to vote in the Delphi. We identified original and validation studies on relevant PROMs and evaluated psychometric quality (i.e., validity, reliability, and sensitivity to change), domain coverage, and feasibility of measurement and implementation. Feasibility considerations included the availability of translations and potential costs associated with the wide implementation of the individual instruments.

Modified Delphi process and open review

Outcome selection was performed in an online three-round modified Delphi process. Following each working group videoconference, all working group members were required to vote. The consensus process followed the RAND/University of California (Los Angeles) methodology to achieve consensus on which outcomes should be included.[25] The results of each vote were reviewed by the working group during the subsequent videoconference. Inclusion in the standard outcome set required that at least 80% of the working group voted an item as 'essential', 'best instrument' or 'relevant case-mix variable' (represented by a score 7-9 on a 9-point Likert scale) in either voting round. Outcomes and case-mix variables were excluded if at least 80% of the working group members voted an item as 'not recommended' (score 1-3). All inconclusive outcomes were voted on in the final third round with 70% consensus required to be ultimately included; if the 70% majority was not met, the outcome was left out of the final set. For the PROMs and case-mix variables, 70% agreement was required to be included. Based on the discussion with the working group, a tool-package (i.e. combination of instruments to measure the outcomes) with cascade opt-in system was proposed and included after the voting round following the videoconference.

In order to allow for input from patients and professional stakeholders outside of the formal working group, an open review period in the English language was held prior to the last working group videoconference. The project team contacted English-spoken patients and professional stakeholders outside the project's working group via email and social media. They were shown an overview of the set and asked to provide independent feedback and to rate the importance of outcomes following a 9-point Likert scale, using an online survey. The results of this survey were presented to the working group during the final videoconference.

CONSENSUS RECOMMENDATIONS

Question 1: What is the target population for the ICHOM set and should patient subgroups be considered?

The outcomes and measures included in the VTE standard set were defined for a target population of patients of 16 years and older, diagnosed with VTE; including patients with incidental VTE. While the working group initially decided that subcategories for patients with cancer-associated VTE, pregnant women with VTE and

VTE patients at the end of life should be considered, these subgroups were later de-selected since we could not identify any subgroup-specific outcomes not already covered in the overarching set. Of note, separate ICHOM sets are available for pregnancy and several cancer types.[26,27] The working group considered these complementary to the VTE set in relevant patients.

Question 2: What are the core outcomes in the ICHOM-VTE set?

After consolidating the literature review findings and focus group meetings, a proposed list of 87 outcomes was identified for discussion and voting, of which the working group selected 15 core outcomes crucial to patients and health professionals (Figure 1; Table 1). The results of the Delphi process regarding the selection of outcomes are summarised in Online Appendix B.

The outcomes were categorised into four domains: (i) patient-reported outcomes, (ii) long-term consequences of the disease, (iii) disease-specific complications, and (iv) treatment-related complications. The working group recommended specific patient-reported outcomes in all the following sub-domains be captured: disease-specific and general quality of life, functional limitations including the ability to work, pain, dyspnea, satisfaction with treatment, psychosocial wellbeing including anxiety, depression, and post-thrombotic panic syndrome, as well as changes in life view. The outcome domain focussing on long-term consequences of VTE was recommended to consist of the following sub-domains: healthcare resource utilisation (e.g., hospitalisations, diagnostic tests, and visits to medical professionals such as physiotherapists), chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic pulmonary disease (CTEPD), and post-thrombotic syndrome (PTS). Survival, VTE recurrence, bleeding, and procedure-related complications were considered relevant disease-specific or treatment-related complications.

Question 3: Which set of instruments would be optimal to capture these outcomes?

The working group decided on a measurement tool package that captures all of these core outcomes. Since several of the optimal instruments identified by the working group involve partly overlapping questions and

domains, a cascade opt-in system was adopted to ensure that a minimum number of items would capture all core outcomes (Figure 2). The measurement tools for the core set include the PROMIS short form Global Health[28], PEmb-QoL[29], VEINES-QOL[9], and the single item Post-VTE Functional Status Scale[30] (PVFS) along with a single question on treatment satisfaction, and changes in life view. If patients indicated the presence of pain, dyspnea, anxiety, depression or treatment dissatisfaction (all single questions in the core set of instruments), the cascade opt-in system proposed additional instruments to acquire relevant dimensions and details via PROMIS short form Pain Intensity[31], PROMIS short form Dyspnea Severity[32], Patient Health Questionnaire-9 (PHQ-9)[33], Generalized Anxiety Disorder-7 (GAD-7)[34], and the Anti-Clot Treatment Scale (ACTS)[35].

Long-term consequences of disease and complications are healthcare professional-reported. Definitions were primarily derived from the International Society on Thrombosis and Haemostasis (ISTH) set of common data elements for VTE research and can be found in detail in the online Reference Guide.[36]

Question 4: Which baseline characteristics and case-mix variables are relevant for the ICHOM set?

The working group selected important baseline characteristics and case-mix variables to allow standardised risk adjustment across different populations. The working group identified several patient demographics, measures of baseline health status, and treatment-related factors that impacted the outcomes included in the core standard set (Table 2). The demographic risk-adjustment factors selected for inclusion were age, sex, race, ethnicity, and level of education. The clinical risk-adjustment factors (baseline and treatment-related) include body mass index, comorbidities according to the Self-Administered Comorbidities Questionnaire[37], history of VTE, high-risk/massive PE, phlegmasia, unprovoked VTE, actual use of antithrombotic medication, and specific interventions for treatment of VTE.

FINAL SET

The final ICHOM standard set of patient-centered outcome measures for VTE patients including relevant timepoints is shown in Figure 3 and can be found on: https://connect.ichom.org/patient-centered-outcome-

measures/venous-thromboembolism/. Of the recommended patient-reported outcome measures, quality of life, treatment satisfaction, and changes in life view are not to be captured at baseline. The PVFS scale can be used to assess the pre-VTE functional status for comparison.

This set was subjected to open review by people with lived-experience and expert professionals. A total of 22 patients and 29 healthcare professionals completed the survey. Most patients who participated were in the age 46-60 years, 27% of patients had experienced PE, 23% DVT, and 50% both PE and DVT. The professionals were mostly physicians (90%); 7% were researchers and 3% were healthcare administrators. Agreement rates among patients and professionals (i.e., the proportion of patients and professionals rating the importance of outcomes as essential) were at least 65% for 12 of the 15 core outcomes in the standard set. For the other three outcomes, there was discrepancy between patients and professionals. The outcomes CTEPH and CTEPD were rated as essential by 50% and 45% of patients, respectively, while 83% and 79% of professionals rated these outcomes as essential. In contrast, the outcome changes in life view was rated as essential by 48% of professionals, while 70% of patients considered this outcome to be essential. A vast majority (95%) of the patients felt that the proposed outcomes broadly captured all the important aspects that matter most for people with VTE, and that applying the set and collecting the information would be helpful to support patient care. Healthcare professionals were asked to provide feedback on the entire set. Agreement rates between professionals for the included PROMs, clinical outcome measures and case-mix variables were 92%-100%, and 88-100% for the timepoints proposed to measure the outcomes and variables. In addition, four professionals who completed the survey responded on the extensiveness of the set, and commented that the set might have too many instruments and measurements. After discussion and consideration by the working group during the final videoconference, all outcomes were considered crucial to be captured at the proposed timepoints, with the core set of selected instruments and additional instruments via the cascade opt-in system.

Several limitations of the set need to be acknowledged. Despite considerable efforts to engage VTE experts from Asia and Africa, and despite the nationality, cultural and religious diversity of our team, the majority of the working group members currently live in Europe and North America which may have

influenced the decision making process. Furthermore, the PROMs included in the standard set were developed in Europe or North America and mostly lack country- or region-specific validation, which is a major limitation of this and other standard outcome sets.

IMPLEMENTATION

The final set is now available online for use within clinical practice and potentially research. Whilst we have drawn on publicly accessible tools where possible, to implement the set, colleagues must first assess the technology, informatics, and access infrastructures available within an individual healthcare institution or regional healthcare system. We advise preparing an implementation plan in context, with a 'roll out' phase consisting of pilot data collection and refinement of the workflow, ahead of implementing the full set for all patients within our stated scope. From here data can be collected on every patient according to the defined timepoints for measurement of the outcomes. The Data Dictionary (part of the online Reference Guide) provides all details to guide data collection and supports implementation of outcomes measurement as consistently as possible, which is crucial to be able to make comparisons across institutions and countries.

Beyond this, embedding PROMs into electronic health records would ease cross-care integration and enhance routine measurement of patient-reported outcomes into clinical practice. Furthermore, in recognition of the time challenges in practice of completing PROMs, incorporating these as digital measures could provide the necessary flexibility to automatically direct patients and providers to relevant questions (via the cascade opt-in system), shortening the time needed to complete the tools. We are cognisant of the need to collect minimal data to limit burden on both healthcare providers and patients, but at the same time recognise the need to encompass all important outcomes for meaningful comparisons. Feasibility of measurement and implementation were important considerations during the working group discussions and selection of outcome measures, in addition to comprehensiveness with the realities of being a patient or provider in VTE. Notably, so far, ICHOM has developed 40 standard sets, which are implemented in 271 institutions (i.e. the number of institutions implementing at least one ICHOM set) across 51 countries, highlighting the success of existing ICHOM standard sets. A map with areas across the globe where ICHOM

Sets of Patient-Centered Outcome Measures have been implemented, is shown on: https://www.ichom.org/global-set-implementation/. Implementation studies have been performed for different ICHOM sets, showing the feasibility of implementing ICHOM sets. Help and support with implementation as well as with application of the PROMs is provided in the by ICHOM. Of note, in the current era, the questionnaires can be easily included in an online survey that will also facilitate the correct post-processing and interpretation of the PROMs.

Whilst the aim is to achieve a globally adopted standard set, we recognise that there are different resources, digital infrastructures and healthcare contexts in low-, middle-, and high-income countries that may affect the speed and success of implementation. Training and education, commitment and enabling attitude of healthcare professionals are believed to facilitate implementation[38], which can help offset more structural challenges within the system. Notably, the PROMs suggested in our standard set do not require a fee or license, can be completed on paper and can be implemented with minimum resources. Nonetheless, implementation in resource-poor regions and countries poses more challenges than in most Western countries. ICHOM and the working group will continuously keep promoting global use of the standard set, and provide help to local institutions where possible. Also, if a desired translation is not available, ICHOM provides guidance in translating PROMs following a defined process in accordance with the ISPOR Principles of Good Practice.[39]

CONCLUSIONS

Based on the principles of evidence-based medicine integrating patients' values, best available evidence and medical expertise, we have developed a consensus recommendation for a standardised minimum set of outcomes that are deemed to cover all important aspects of VTE treatment and clinical course that matter most to patients and healthcare professionals (the so-called 'must-haves'): ICHOM-VTE. As with all ICHOM sets, the process of development is unique through the extensive engagement of patient representatives in all steps and decisions. Following the focus groups, several outcomes that had not been previously studied

in VTE were considered relevant and therefore were included in the final set, e.g., changes in life view. The working group targets integration of the standard set into routine clinical practice and potentially research. The high level of patient involvement in the development phase of the set is expected to improve compliance to completing the instruments in daily practice. We anticipate that the introduction of this set will contribute significantly towards learning how to increase value in VTE care. Healthcare professionals and policy makers will be able to use these measures to identify effective, high-value practices in the therapeutic management and follow-up of VTE patients, which in turn, helps to better target efforts towards quality improvement. Moreover, and importantly, implementation of this set will empower VTE patients to actively participate in their care, and together with involved professionals, make better-informed decisions about healthcare options.

Declaration of interests

AAH reports research grants from The Danish Heart foundation and The Novo Nordisk Foundation, consulting fees from Bayer and The Bristol-Myers Squibb-Pfizer Alliance, speaker bureaus from Bayer, The Bristol-Myers Squibb-Pfizer Alliance and MSD.

JIA reports honoraria from Sanofi and Rovi for educational activities, and research funding from Sanofi and Bayer AG.

WRA reports consultation agreements with Bayer and Janssen PH; payment or honoraria from Bayer Pharmaceuticals, support for attending meetings and/or travel from Bayer Pharmaceuticals, participation on (Data Safety Monitoring or Advisory) Board of Janssen PH.

CA received personal fees for lectures and participation in advisory boards from Bayer, BMS, Daiichi-Sankyo, Pfizer and Sanofi.

SB reports grants or contracts from Bayer, INARI, Boston Scientific, Medtronic, Bard, SANOFI, and Concept Medical; consulting fees or honoraria from INARI, Bayer, Boston Scientific, and Concept Medical; and support for attending meetings and/or travel from Bayer and Daiichi Sankyo.

LB reports personal fees and non-financial support from Aspen, personal fees and non-financial support from Bayer, personal fees and non-financial support from BMS-Pfizer, personal fees and non-financial support from Leo-Pharma, grants, personal fees and non-financial support from MSD, personal fees and non-financial support from Johnson and Johnson, outside the submitted work.

ATC reports grants or contracts from Alexion Pharmaceuticals, Bayer Pharma AG and PMS/Pfizer, and consulting fees and payments or honoraria from Alexion Pharmaceuticals, Bayer Pharma AG and PMS/Pfizer, all fees paid to his company.

HRE reports speaker's honoraria from Bayer and Daichi-Sankyo, and support for attending meetings and/or travel from Bayer.

RPR reports consulting fees from BMS, Janssen, Inari, Penumbra, Abbott, and research grants paid to her institution from BMS and Janssen, all outside the scope and unrelated to this project.

CT reports payment or honoraria from Riche Bayer, Astra Zeneca, Actelion and Janssen.

KLW reports honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer for CME lectures.

SAB reports consulting fees and payment or honoraria from BSCI, Gore, BD, Cook, Phillips, Vesper, Veryan, Vetex, Medtronic; research grants from Boston Scientific and Medtronic that are paid to his institution; advisory board for Philips, Medtronic, Gore, and Boston Scientific.

FAK reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Leo Pharma, Daiichi-Sankyo, Actelion, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe Program, all outside the submitted work and paid to his institution.

AMG, CdJ, LSH, TL, FS, PBJ, MBG, JB, AtCH, JMC, JPG, NicosL, NicoleL, MHM, SN, EJN, PPdLL, NS, MT, EW, KdW report no conflicts related to this project.

Acknowledgements

This project was supported from unrestricted grants from Bayer, Boston Scientific, Dutch Thrombosis Association, Leiden University Medical Center, Leo Pharma and King's College London. The European Society

for Vascular Surgery, the North American Thrombosis Forum, the Swiss Society of Angiology, and the Italian Society of Hemostasis and Thrombosis expressed written support of the project or accepted the project as a formal society's project. JB and NS were the patient representatives of our working group.

Authors' contributions

The manuscript was drafted by AMG, CDJ and FAK. All authors contributed to the working group discussions and online voting, provided important intellectual content, reviewed and edited the manuscript, and all have approved the manuscript's final version.

Source of funding

The project was supported from unrestricted grants from Bayer, Boston Scientific, Dutch Thrombosis Association, Leiden University Medical Center, Leo Pharma and King's College London.

REFERENCES

1. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. *Nature reviews Disease primers* 2018; **4**: 18028.

2. Wolberg AS, Rosendaal FR, Weitz JI, et al. Venous thrombosis. *Nature reviews Disease primers* 2015; **1**: 15006.

3. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *Journal of thrombosis and haemostasis : JTH* 2007; **5**(4): 692-9.

4. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016; **41**(1): 3-14.

5. Rabinovich A, Kahn SR. The postthrombotic syndrome: current evidence and future challenges. *J Thromb Haemost* 2017; **15**(2): 230-41.

6. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *The European respiratory journal* 2021; **57**(6).

7. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood reviews* 2014; **28**(6): 221-6.

8. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2014; **130**(18): 1636-61.

9. Kahn SR, Ducruet T, Lamping DL, et al. Prospective evaluation of health-related quality of life in patients with deep venous thrombosis. *Archives of internal medicine* 2005; **165**(10): 1173-8.

10. Klok FA, van Kralingen KW, van Dijk AP, et al. Quality of life in long-term survivors of acute pulmonary embolism. *Chest* 2010; **138**(6): 1432-40.

11. Hunter R, Noble S, Lewis S, Bennett P. Long-term psychosocial impact of venous thromboembolism: a qualitative study in the community. *BMJ Open* 2019; **9**(2): e024805.

12. Hunter R, Lewis S, Noble S, Rance J, Bennett PD. "Post-thrombotic panic syndrome": A thematic analysis of the experience of venous thromboembolism. *British journal of health psychology* 2017; **22**(1): 8-25.

13. Tran A, Redley M, de Wit K. The psychological impact of pulmonary embolism: A mixed-methods study. *Research and practice in thrombosis and haemostasis* 2021; **5**(2): 301-7.

14. Jorgensen H, Horvath-Puho E, Laugesen K, Braekkan S, Hansen JB, Sorensen HT. Risk of a permanent work-related disability pension after incident venous thromboembolism in Denmark: A population-based cohort study. *PLoS medicine* 2021; **18**(8): e1003770.

15. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. *The Lancet Respiratory medicine* 2020; **8**(3): 277-87.

16. Barco S, Valerio L, Ageno W, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. *The Lancet Respiratory medicine* 2021; **9**(1): 33-42.

17. Barco S, Valerio L, Gallo A, et al. Global reporting of pulmonary embolism-related deaths in the World Health Organization mortality database: Vital registration data from 123 countries. *Research and practice in thrombosis and haemostasis* 2021; **5**(5): e12520.

18. Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. *Circ Res* 2016; **118**(9): 1340-7.

19. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. *Pulmonary circulation* 2021; **11**(1): 2045894020977300.

20. van der Wall SJ, Hendriks SV, Huisman MV, Klok FA. Home treatment of acute pulmonary embolism: state of the art in 2018. *Current opinion in pulmonary medicine* 2018; **24**(5): 425-31.

21. Klok FA, Huisman MV. When I treat a patient with acute pulmonary embolism at home. *Hematology American Society of Hematology Education Program* 2020; **2020**(1): 190-4.

22. Stowell C AC. Better Value in Health Care Requires Focusing on Outcomes. 2015. https://hbr.org/2015/09/better-value-in-health-care-requires-focusing-on-outcomes (accessed 9 May 2022.

23. Porter ME. What is value in health care? *N Engl J Med* 2010; **363**(26): 2477-81.

24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.

25. Fitch K. The RAND/UCLA Appropriateness Method User's Manual. *Santa Monica, CA: RAND* 2001.

26. Ong WL, Schouwenburg MG, van Bommel ACM, et al. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer: The International Consortium for Health Outcomes Measurement (ICHOM) Initiative. *JAMA Oncol* 2017; **3**(5): 677-85.

27. Nijagal MA, Wissig S, Stowell C, et al. Standardized outcome measures for pregnancy and childbirth, an ICHOM proposal. *BMC Health Serv Res* 2018; **18**(1): 953.

28. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res* 2009; **18**(7): 873-80.

29. Klok FA, Cohn DM, Middeldorp S, et al. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. *Journal of thrombosis and haemostasis : JTH* 2010; **8**(3): 523-32.

30. Boon G, Barco S, Bertoletti L, et al. Measuring functional limitations after venous thromboembolism: Optimization of the Post-VTE Functional Status (PVFS) Scale. *Thrombosis research* 2020; **190**: 45-51.

31. Cella D, Choi SW, Condon DM, et al. PROMIS(®) Adult Health Profiles: Efficient Short-Form Measures of Seven Health Domains. *Value Health* 2019; **22**(5): 537-44.

32. Choi SW, Victorson DE, Yount S, Anton S, Cella D. Development of a conceptual framework and calibrated item banks to measure patient-reported dyspnea severity and related functional limitations. *Value Health* 2011; **14**(2): 291-306.

33. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**(9): 606-13.

34. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**(10): 1092-7.

35. Cano SJ, Lamping DL, Bamber L, Smith S. The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in venous thromboembolism patients. *Health Qual Life Outcomes* 2012; **10**: 120.

36. Le Gal G, Carrier M, Castellucci LA, et al. Development and implementation of common data elements for venous thromboembolism research: on behalf of SSC Subcommittee on official Communication from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH* 2021; **19**(1): 297-303.

37. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003; **49**(2): 156-63.

38. Moore L, Britten N, Lydahl D, Naldemirci Ö, Elam M, Wolf A. Barriers and facilitators to the implementation of person-centred care in different healthcare contexts. *Scand J Caring Sci* 2017; **31**(4): 662-73.

39. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; **8**(2): 94-104.

Tables and Figure legends

Table 1: Summary of ICHOM venous thromboembolism standard set of outcomes.

Table 2: Case-mix variables included in the ICHOM set of patient-centered outcome measures for venous thromboembolism.

Figure 1: Development of the ICHOM set of patient-centered outcome measures for venous thromboembolism through a structured working group process.

Figure 2: Overlap between the patient-reported outcomes and patient-reported outcome measures. By introducing a cascade option (core set versus optional set), relevant overlap is mostly avoided. The PROMIS short forms Pain Intensity and Dyspnea Severity are triggered by PROMIS short form Global Health (GH) and PEmb-QoL, respectively. The Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) are triggered by PROMIS short form Global Health. The Anti-Clot Treatment Scale (ACTS) is triggered by the single question on satisfaction with treatment.

Figure 3: The final ICHOM standard set of outcome measures for patients with venous thromboembolism (VTE) including relevant timepoints. Of the recommended patient-reported outcome measures, quality of life, treatment satisfaction and changes in life view are not to be captured at baseline. The PVFS scale can be used to assess the pre-VTE functional status for comparison.

Table 1: Summary of ICHOM venous thromboembolism standard set of outcomes.

Domain	Outcome	Details*	Timing	Data source
Patient-reported outcomes	Quality of life	(1) Measured using the PROMIS Scale v1·2 - Global Health, PEmb-QoL, and VEINES-QOL questionnaires	3 months and 6 months; 1 year and then annually**	Patient
	Functional limitations (including ability to work)	(2) Measured using the Post-VTE Functional Status Scale	Index event; 3 months and 6 months; 1 year and then annually**	Patient
	Pain (including symptom severity)	(1) and if required (3) measured using the PROMIS Short Form v2·0 - Pain Intensity - 3a	Index event; 3 months and 6 months; 1 year and then annually**	Patient
	Dyspnea (including symptom severity)	(4) Measured using the Pemb-QoL and PROMIS Short Form v1·0 - Dyspnea Severity - 10a	Index event; 3 months and 6 months; 1 year and then annually**	Patient
	Psychosocial wellbeing	(1) and if required (7) measured using the PHQ-9 and GAD-7 questionnaires	Index event; 3 months and 6 months; 1 year and then annually**	Patient
	Satisfaction with treatment	(5) Measured through the question: "Are you satisfied with your VTE treatment?" and if required (6) measured using the Anti-Clot Treatment Scale	3 months and 6 months; 1 year and then annually**	Patient
	Changes in life view	(8) Measured through the question: "Have you experienced a change in your expectations, aspirations, values, or perspectives on life opportunities since the diagnosis of VTE?"	3 months and 6 months; 1 year and then annually**	Patient

Long-term consequences of disease	Healthcare resource utilization	- Number of hospitalizations, and length of stay - Number of emergency room visits - Number of non-hospital activities (including general practice, outpatient clinic visits, home healthcare, and rehabilitation)	Index event; 3 months and 6 months; 1 year and then annually**	Clinician
	Chronic thromboembolic pulmonary hypertension	Clinical diagnosis	3 months and 6 months; 1 year and then annually**	Clinician
	Chronic thromboembolic pulmonary disease	Clinical diagnosis	3 months and 6 months; 1 year and then annually**	Clinician
	Post-thrombotic syndrome	Villalta Score	3 months and 6 months; 1 year and then annually**	Clinician
Disease-specific complications	Recurrence	Has the patient had recurrent VTE according to the ISTH definition? - Yes/No	Index event; 3 months and 6 months; 1 year and then annually**	Clinician
	Survival	Death regardless of cause	Index event; 3 months and 6 months; 1 year and then annually**	Clinician
Treatment-related complications	Bleeding	Did the patient have any bleeding that was worrisome to the patient or the clinician, impacted daily activities or required medical treatment? - Yes/No	Index event; 3 months and 6 months; 1 year and then annually**	Clinician
	Procedure-related complications	Has the patient experienced an undesirable and/or unintended outcome that is a direct result of a procedure? - Yes/No	Index event; 3 months and 6 months; 1 year and then annually**	Clinician

VTE: venous thromboembolism, PHQ-9: Patient Health Questionnaire-9, GAD-7: Generalized Anxiety Disorder-7, ISTH: International Society on Thrombosis and Haemostasis.

*The numbers in parentheses are reported along with the measurement tools to be used to measure the outcomes. The tool(s) to be used to measure the outcome are written out in full with a number in parentheses, when reported for the first time. After the first mention, the number in parentheses refers to the measurement tool(s) as introduced along with that specific number.

**For as long as the patient is under care.

Table 2: Case-mix variables included in the ICHOM set of patient-centered outcome measures for venous thromboembolism.

Variable	Details	Timing	Reporting source
Demographic Factors			
Year of birth	Year of birth as YYYY	Index event	Clinical, patient-reported or administrative data
Sex	Sex at birth	Index event	Clinical, patient-reported or administrative data
Race	The biological race of the person	Index event	Patient-reported
Ethnicity	The cultural ethnicity of the person that they most closely identify with	Index event	Patient-reported
Level of education	Highest level of education completed based on local standard definitions of education levels; to consult the International Standard Classification of Education	Index event	Patient-reported
Baseline Health Status			
BMI	Calculated in kg/m^2: weight in kilograms divided by height in meters squared	Index event; 1 year and annually*	Clinical
Previous history of VTE	Yes/No	Index event	Clinical
Comorbidities	Based on the Self-Administered Comorbidities Questionnaire	Index event; 1 year and annually*	Patient-reported
High-risk/Massive PE	Yes/No	Index event	Clinical
Phlegmasia	Yes/No	Index event	Clinical
Unprovoked VTE	Yes/No	Index event	Clinical
Treatment-related Factors			
Antithrombotic treatment	Yes/No; generic name of the drug; dose; medical indication; drug class	Index event; 3 months and 6 months; 1 year and annually*	Clinical
Underwent interventional treatment for VTE	Yes/No	Index event; 3 months and 6 months; 1 year and annually*	Clinical

BMI: Body Mass Index, VTE: venous thromboembolism, PE: pulmonary embolism.

*For as long as the patient is under care.

Figure 1: Development of the ICHOM set of patient-centered outcome measures for venous thromboembolism through a structured working group process.

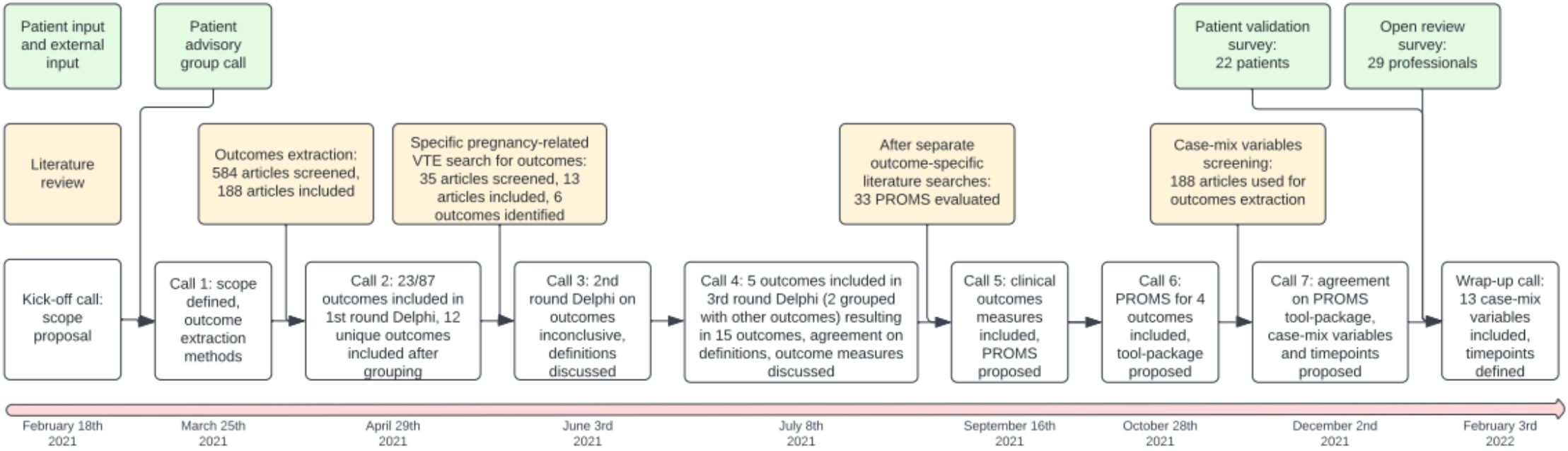


Figure 2: Overlap between the patient-reported outcomes and patient-reported outcome measures. By introducing a cascade option (core set versus optional set), relevant overlap is mostly avoided. The PROMIS short forms Pain Intensity and Dyspnea Severity are triggered by PROMIS short form Global Health (GH) and PEmb-QoL, respectively. The Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) are triggered by PROMIS short form Global Health. The Anti-Clot Treatment Scale (ACTS) is triggered by the single question on satisfaction with treatment.

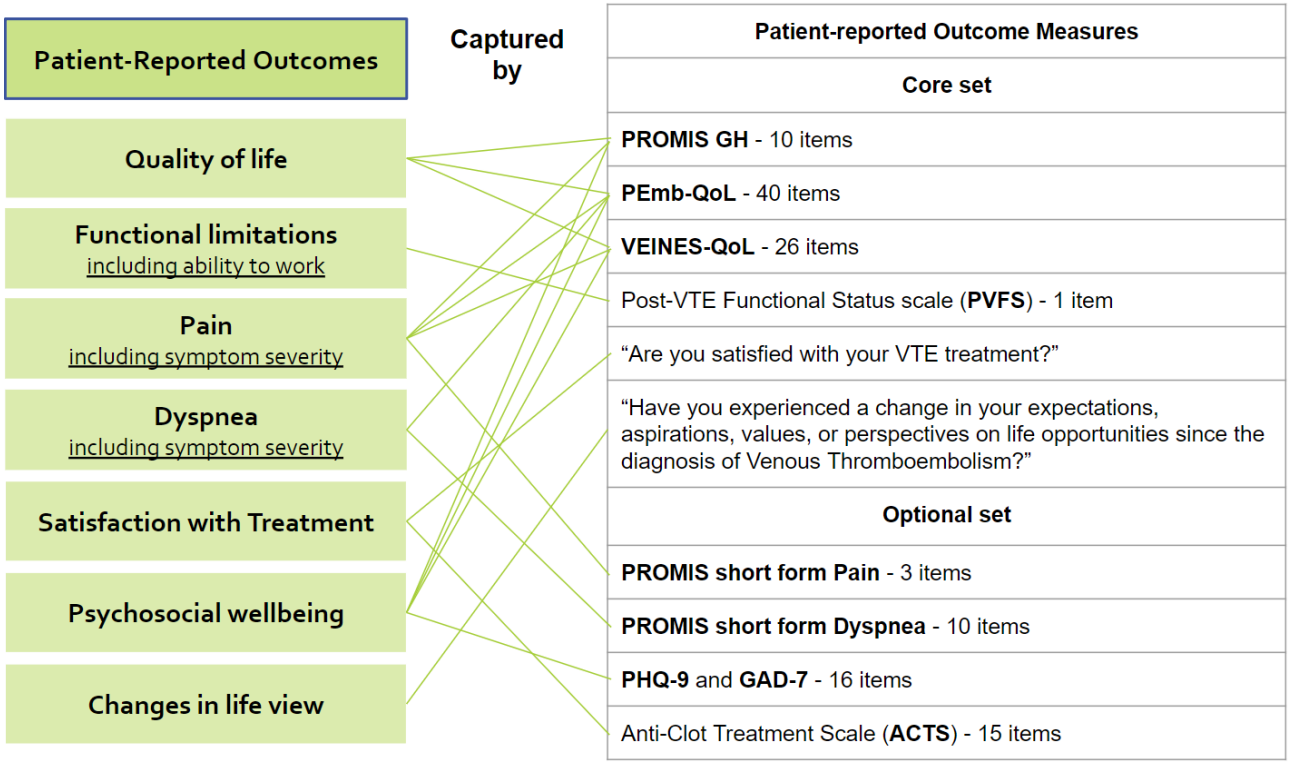
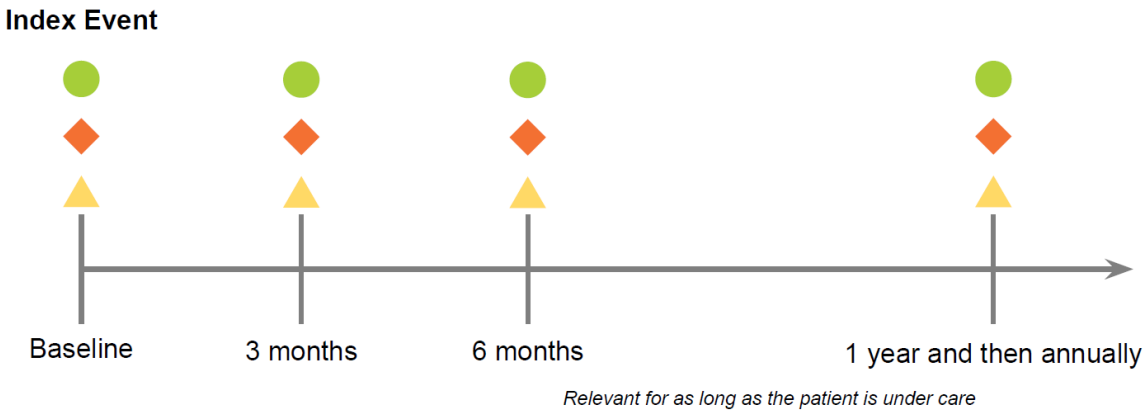


Figure 3: The final ICHOM standard set of outcome measures for patients with venous thromboembolism including relevant timepoints. Of the recommended patient-reported outcome measures, quality of life, treatment satisfaction and changes in life view are not to be captured at baseline. The PVFS scale can be used to assess the pre-VTE functional status for comparison.



Index Event = Date of the VTE diagnosis
Baseline = Data collection date

Note: 1) Data collection starts at the time of diagnosis
2) A new timeline should be triggered if the patient suffers a recurrent VTE event
3) More details about patient-reported outcome measures, clinical outcome measures, and case-mix variables can be found in the ICHOM VTE Reference Guide