

MS SOPHIE E.R. HORBACH (Orcid ID : 0000-0002-3165-4774)

PROFESSOR PHYLLIS IRA SPULS (Orcid ID : 0000-0002-6035-2863)

Article type : Original Article

Development of an international core outcome set for peripheral vascular malformations (OVAMA project)

S.E.R. Horbach¹, C.M.A.M. van der Horst¹, F. Blei², C.J.M. van der Vleuten³, I. J. Frieden⁴, G.T. Richter⁵, S.T. Tan⁶, T. Muir⁷, A. Penington⁸, L.M. Boon⁹, P. I. Spuls¹⁰ on behalf of the OVAMA consensus group*

¹*Department of Plastic, Reconstructive and Hand Surgery, Academic Medical Center (AMC), University of Amsterdam, the Netherlands*

²*Department of Pediatrics, Lenox Hill Hospital, New York, USA*

³*Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands*

⁴*Department of Dermatology, University of California San Francisco, San Francisco, USA*

⁵*Department of Otolaryngology, Arkansas Children's Hospital, Arkansas, USA*

⁶*Wellington Regional Plastic, Maxillofacial and Burns Unit, Hutt Hospital, and Gillies McIndoe Research Institute, Wellington, New Zealand*

⁷*Department of Plastic and Reconstructive Surgery, James Cook University Hospital, Middlesbrough, UK*

⁸*Department of Paediatrics, University of Melbourne and Murdoch Children's Research Institute, Melbourne Australia*

⁹*Center for Vascular Anomalies, Division of Plastic and Reconstructive Surgery, Cliniques Universitaires Saint-Luc, Brussel, Belgium*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.16029

This article is protected by copyright. All rights reserved.

**Contributors of the OVAMA consensus project are listed in Appendix 4*

Corresponding author:

Sophie E.R. Horbach, MD

Department of Plastic, Reconstructive and Hand Surgery,

Academic Medical Center (AMC),

P.O. Box 22660, 1100 DD

Amsterdam, The Netherlands,

s.e.horbach@amc.uva.nl

T: +31 (0)20-5666679, F: +31 (0)20-691754

Short title: Core outcome set for vascular malformations

Funding statement: None. The authors did not receive financial support or funding for this study.

Disclosures: None declared. The authors have no other financial relationships relevant to this article to disclose.

- **What's already known about this topic?** There is a large heterogeneity in outcomes used in clinical trials on peripheral vascular malformations.
- This hampers the interpretation, comparison and aggregation of study data, and in turn the development of evidence-based treatment guidelines.
- Development of a 'core outcome set' (COS) may improve standardised outcome reporting.

What does this study add?

- International consensus was reached on the core outcome domains that should be measured in all therapeutic-efficacy studies in this field: *radiological assessment, physician-assessed signs, patient-reported pain, overall severity of symptoms, health-related QoL, patient satisfaction with treatment and outcome, and adverse events.*
- The next step is to reach consensus on how these domains should be measured (core outcome instruments).

SUMMARY

Background: An important limitation in vascular malformation research is the heterogeneity in outcome measures used for the evaluation of treatment outcome.

Objective: The Outcome measures for VAscular MAlformations (OVAMA) project aimed to reach international consensus on a core outcome set (COS) for clinical research on peripheral vascular malformations: lymphatic (LM), venous (VM) and arteriovenous malformations (AVM). In this consensus study, we determined what domains should constitute the COS.

Methods: Thirty-six possibly relevant outcome domains were proposed to an international group of physicians, patients and the parents of patients. In a 3-round e-Delphi process using online surveys, participants repeatedly rated the importance of these domains on a 5-point Likert scale. Participants could also propose other relevant domains. This process was performed for LM, VM and AVM separately. Consensus was pre-defined as 80% agreement on the importance of a domain amongst both the physician group and the patient/parent group. Outcomes were then reevaluated in an online consensus meeting.

Results: 167 physicians and 134 patients and parents of patients with LM (n=50), VM (n=71) and AVM (n=29) participated in the study. After three rounds and a consensus meeting, consensus was reached for all three types of vascular malformations on the core domains of radiological assessment, physician-reported location-specific signs, patient-reported severity of symptoms, pain, quality of life, satisfaction and adverse events. Vascular malformation type-specific signs and symptoms were included for LM, VM and AVM, separately.

Conclusion: It is recommended to measure at least these core outcome domains in therapeutic-efficacy studies on peripheral vascular malformations.

INTRODUCTION

Vascular malformations are developmental anomalies of the vascular system, classified by the International Society for the Study of Vascular Anomalies (ISSVA) by the type(s) of the vessels involved^{1,2}: lymphatic malformations (LM), venous malformations (VM), arteriovenous malformations (AVM) and capillary malformations (CM). In simple vascular malformations, a single vessel type is abnormally developed, whereas in combined vascular malformations multiple types of vessels are affected. Management of these congenital

anomalies is challenging, as they vary in clinical presentation, subtype, size and location.

Although many different treatment options are available in the literature, evidence-based treatment guidelines are not readily available. A main reason for the lack of these guidelines, is the variety of methods used to evaluate the efficacy of treatment in clinical research.³⁻⁵ Therefore, study results cannot be compared easily nor aggregated into meta-analyses. International standardization of outcome measures with a 'core outcome set' (COS) may help to address this deficiency. A COS is an agreed minimum set of standardised outcome measures adopted for evaluating treatment outcomes in a certain health condition.⁶ A COS should ideally represent *what* should be measured to assess treatment outcome (outcome domains) and *how* these measurements should be performed (measurement instruments).

OVAMA project

The aim of the Outcome measures for VAscular MAIformations (OVAMA) project is to develop an international COS for measuring treatment outcomes of all therapeutic interventions in adult and pediatric patients with peripheral vascular malformations. Three main categories of vascular malformations are approached separately: LM, VM and AVM. This project does not focus on solitary CM (port-wine stain) as these typically affect the skin only, in contrast to the other types of vascular malformation which can involve any tissues.

The OVAMA steering group, consisting of 11 internationally recognised experts in vascular anomalies or COS development, coordinates the project. In the OVAMA project, the steps of the HOME (Harmonizing Outcome Measures for Eczema) initiative roadmap are followed.⁷ This e-Delphi study represents the second step of the OVAMA project (*Figure 1*).

The goal of the present study is to reach an international consensus on *what* should be measured in studies to evaluate treatment outcome in vascular malformations, in other words, which *core outcome domains* should be included in the COS.

METHODS

Study design

This international consensus project consists of a 3-round e-Delphi study and a subsequent online consensus meeting (*Figure 2*).

As methodological guidelines for the development of COS have not yet been completely established⁸, the design of the e-Delphi study was based on general recommendations for Delphi methodology^{9,10} and the methods of other published COS studies^{8,11-16}. The results of this study were reported according to the Core Outcome Set-STAndards for Reporting (COS-STAR) checklist.¹⁷

The OVAMA project was registered at the Core Outcome Measures in Effectiveness Trials (COMET) Initiative^{18,19} and the Cochrane Skin Group - Core Outcome Set Initiative (CSG-COUSIN)²⁰, which also provided methodological advice for this study. The need for informed consent was waived by the institutional review board of the Academic Medical Center in Amsterdam.

Development of a list of outcome domains

A list of potentially relevant outcome domains was generated covering all outcomes encountered in published therapeutic-efficacy studies^{21,22} (*systematic review in draft*), group discussions with OVAMA steering group members and interviews with two patient

representatives. These outcomes were then classified into 9 domain categories, 36 outcome domains and 97 outcome domain items. Further definitions and descriptions of these outcomes can be found in *Appendix 1*. All outcomes were translated into Dutch and English using multiple forward-backward translations made by a team of two independent native Dutch speaking translators and a bilingual native English speaking translator.²³ Discrepancies in the translations were resolved by consensus.

Participant recruitment

There is no official consensus on the number of participants that should be enrolled in a Delphi study.²⁴ Since we aimed to develop a globally applicable COS, we recruited as many international stakeholders as possible. Two major stakeholder groups were invited: physicians with proven expertise in the management of vascular malformations and patients or parents of patients with peripheral vascular malformations (LM, VM, AVM or combined vascular malformations).

Physicians were contacted through contact lists of the the International Society of the Study for Vascular Anomalies (ISSVA), the Vascular Anomalies Special Interest Group in the United Kingdom (VASIG-UK), corresponding authors of relevant literature on vascular malformations in the last five years (PubMed search is shown in *Appendix 2*) and personal networks of the OVAMA steering group.

Patients and the parents of patients could participate if they had a peripheral VM, LM or AVM (or a combination of these), classified according to the ISSVA classification². Patients with any other types of vascular anomalies or vascular malformations located in the central nervous system (e.g., intracranial vascular malformations) were excluded. Patients/parents were contacted through three patient organisations: the Vascular

Birthmark Foundation (United States), the Birthmark Support Group (United Kingdom) and HEVAS (The Netherlands). Personalised e-mail invitations were sent and a weblink to the survey was placed on the websites of the patient organisations.

e-Delphi survey procedure

The 36 outcome domains were incorporated into English and Dutch surveys (SurveyMonkey Inc., San Mateo, California, USA) in lay language. A 3-round e-Delphi survey procedure was performed in which all participants repeatedly rated the importance of each outcome domain (*Figure 2*). Outcome items that belonged to a certain domain (e.g., ‘frequency of pain episodes’ as an item belonging to the domain *pain*) were shown to illustrate the domain, but only the importance of the overall domain was rated. Physicians rated separately for LM, VM and AVM, patients/parents only rated for their own type(s) of vascular malformation. In each e-Delphi survey, the importance was rated on a 5-point Likert scale from 0 to 4, corresponding to ‘not at all important’, ‘slightly important’, ‘moderately important’, ‘very important’ or ‘crucial’, respectively. Similar Likert scales have been used in other Delphi surveys.^{9,10,15,25} Consensus was reached when there was at least 80% agreement on the ‘importance’ (score 3 or 4 on the Likert scale) in both stakeholder groups.⁹ Consensus on ‘non-importance’ was defined as 80% of agreement on score 1 or 2 on the Likert scale in both stakeholder groups. In the first two survey rounds, participants had the option to propose new outcome domains that were not in the initial predefined list.

In the second and third e-Delphi rounds, all participants received feedback on the consensus scores of the previous round in both the physician group and the patient/parent group..Subsequently, all outcome domains on which consensus had not been reached, were

re-rated. Participants who completed the first e-Delphi round were invited for the second and the third e-Delphi round.

After three e-Delphi rounds, outcome domains were classified as 'provisionally excluded' (no consensus on the importance or consensus on non-importance in both stakeholder groups), 'undecided' (consensus on the importance in only one stakeholder group) or 'provisionally included' (consensus on the importance in both stakeholder groups).

Consensus meeting

The e-Delphi results were discussed in an online consensus meeting (AnyMeeting Inc., Huntington Beach, CA, USA). Participants who completed at least two e-Delphi rounds (n=143) were invited to join the meeting. The meeting was chaired by a member of the OVAMA steering group (Ph.I.S.). The e-Delphi ratings of each outcome domain were discussed separately for LM, VM, and AVM. The primary goal of the meeting was to discuss the 'undecided' domains and to hold a final IN/OUT vote. For 'provisionally excluded' and 'provisionally included' domains, a vote was only held if at least five participants strongly argued that the outcome of the e-Delphi rounds for that domain should be reconsidered.

The IN/OUT vote was held separately for patients/parents and physicians. Whenever more than 50% of the participants in both stakeholder groups voted IN, the domain was included in the COS. Outcomes of the consensus meeting that are in conflict with the results of the e-Delphi rounds will be discussed again in a separate face-to-face meeting around the time of the ISSVA conference 2018 (Amsterdam, the Netherlands).

Data analyses

Data were analyzed using the Statistical Package for Social Sciences (SPSS Statistics, v.22, IBM Corporation, Armonk, NY, USA). Categorical data were presented in numbers and percentages. Percentages of agreement on the importance in each Delphi round were calculated for all outcome domains, separately for each type of vascular malformation. For the consensus meeting, absolute numbers of IN and OUT votes were presented. All results were presented separately for the physician and the patient/parent groups.

RESULTS

Participant characteristics

A total of 167 physicians from around the world participated in the first round. The majority of the physicians were specialists in interventional radiology (25%), dermatology (23%) or plastic surgery (14%). Most physicians (89.2%) are members of multidisciplinary vascular anomalies teams. A total of 134 patients and parents of patients with 150 vascular malformations (50 LM, 71 VM and 29 AVM) were enrolled. This included patients with combined lymphatic-venous malformations (LVM), who participated in both the LM and VM questionnaires, and patients with 2 or more vascular malformations of different types.

Participant characteristics of round 1 are presented in *Table 1*.

e-Delphi rounds

Table 2 provides a summary of the results of the e-Delphi procedure. Numbers of participants and response rates for each e-Delphi round are shown in *Table 3*. On average, approximately 75% of participants participated in all three rounds. Detailed scores of both stakeholder groups in all e-Delphi rounds can be found in *Appendix 3*.

For **LM**, the participants proposed to add the domains *recurrence* and *impact on family* to the list. Consensus was reached for *recurrence, radiological assessment, overall severity of symptoms, pain, location-specific signs and infections, overall health-related quality of life (QoL)* and QoL domains *Activities of Daily Living (ADL) emotional well-being* and *mobility*, all satisfaction domains and the majority of the adverse event domains.

For **VM**, the domains *recurrence, coagulation parameters, sleep disturbances* and *venous thromboembolism* were added to the list. Consensus was reached for the domains *recurrence, radiological assessment, overall severity of symptoms, pain, location-specific signs, localised thrombosis* as assessed by physician, *overall health-related QoL*, QoL domains *mobility, work/study, ADL, confidence* and *emotional well-being*, all satisfaction domains, and most adverse events domains.

For **AVM**, *cardiac function, amputations, mortality* and *recurrence* were additionally proposed by the participants. Consensus was reached for *recurrence, radiological assessment, overall severity of symptoms, pain, appearance as assessed by the physician, location-specific signs*, physician-reported signs of *bleeding* and *cardiac function, overall QoL*, QoL domains *ADL, confidence, mobility* and *work/study*, the satisfaction domains and *most adverse events (including amputations and mortality)*.

None of the domains reached consensus on 'non-importance'. Eleven domains remained 'undecided' and were brought forward to the consensus meeting.

Consensus meeting

Thirty-one physicians and eight patients/parents participated and voted in the online consensus meeting (*Appendix 4*). Outcome of the consensus meeting and discussion points raised by the participants are presented in *Table 4*. Of the 11 'undecided' domains (LM, n=4; VM, n=3; AVM, n=4), 8 were voted IN and 3 were voted OUT.

Despite the fact that *appearance as assessed by the physician* was provisionally excluded for LMs and VMs in the e-Delphi rounds, it was voted IN during the consensus meeting. The domain *appearance assessed by the patient/parent* was also reconsidered for VM and AVM, but was voted OUT. The voting results in the domain category *appearance* were in contradiction with the outcome of the e-Delphi rounds and require further discussion at a separate face-to-face meeting.

Two QoL domains were provisionally excluded for one malformation type but included for the other two types: *work/study* for LM and *emotional well-being* for AVM. These domains were voted IN to harmonise the COS for all types of vascular malformations. However, during the consensus meeting, participants agreed that *overall health-related QoL* should be the only QoL core outcome domain and all other QoL domains for which consensus was reached should be considered as essential subdomains.

Similarly, participants argued that all domains describing types of adverse events should be included as one regrouped core outcome domain labelled '*adverse events*'.

A vote was held for the provisionally excluded domain *coagulation parameters*, but it was voted OUT by majority. More research was deemed necessary to determine the role of coagulation parameters in evaluating treatment outcome.

The provisionally included domain '*cardiac function*' was reconsidered by the participants, as high output failure is a rare complication of AVM and should perhaps not necessarily be measured in all AVMs. However, due to the severity of this disease complication participants decided that it should remain in the COS.

Lastly, '*recurrence*' was provisionally included based on the e-Delphi. Yet, the general opinion during the consensus meeting was that the definition of *recurrence* requires further clarification as it may overlap with the other included domains (e.g., radiologic recurrence, symptom recurrence).

Core outcome domain set

The final core domain set (*Table 5*) consists of six domain categories, comprising eight outcome domains for all types of vascular malformations: *radiological assessment of the vascular malformation* (e.g., size, depth/extent and flow), *physician-assessed location-specific signs* (caused by compression of adjacent body structures by the malformation, e.g., swallowing and respiratory difficulties), *patient-reported pain*, *overall severity of symptoms*, *overall health-related QoL*, *patient satisfaction with treatment and outcome*, and *adverse events*. Additional type-specific core domains are included separately for each vascular malformation type. For LM, *physician-reported signs of infections* and *lymphatic fluid leakage* are included. For VM *localised thrombosis* and for AVM *cardiac function* and *signs and symptoms of bleeding*. Furthermore, *recurrence* and *appearance* are recommended

outcome domains for all vascular malformation types, but require further face-to-face discussion before inclusion in the COS.

DISCUSSION

This study identified the core outcome domains for peripheral vascular malformations, according to a large group of international experts, patients and parents. Eight core outcome domains were included in the COS for all types of peripheral vascular malformations. For each distinct vascular malformation type, several additional core domains on type-specific signs (assessed by the physician) and/or symptoms (reported by the patient) were included. These core outcome domains represent the minimum that should be measured in therapeutic efficacy studies in this field. However, this does not preclude measurement of additional outcomes which may be relevant depending on the study objective. Although this COS was primarily developed for clinical research, it may form the basis for a more concise COS that can be implemented in clinical practice. Prioritisation of core outcome domains is warranted to further define the COS and enhance its feasibility in clinical practice.

It is noteworthy that appearance (e.g., size, color and shape/texture of the vascular malformation and distortion of bodily or facial features) did not achieve consensus in the e-Delphi rounds, since most published studies used size reduction based on the clinical appearance of the vascular malformation, as a primary outcome measure. In a meta-analysis on bleomycin sclerotherapy,⁴ size reduction of the vascular malformation was

measured in 24 of 27 included studies, and in most of these studies (n=20) evaluation of size reduction was based on the appearance of the vascular malformation on physical examination.

In only 4 of the studies included in the abovementioned review,⁴ radiological imaging was performed to measure the exact size reduction. Radiological assessment was included in the COS, however, in the next steps of the OVAMA project, it is needed to determine whether follow-up imaging to evaluate treatment outcome is feasible in all cases (e.g., due to financial or hospital restrictions) and what the optimal timing and imaging modality is.

Strengths and limitations

The strength of this study is its international scope, including an international patient population and many well-known experts in the field. Nevertheless, most participants were from Europe or the U.S., which may limit the COS' transcultural applicability. The study methods were based on those of other study groups such as the HOME initiative (Atopic eczema)²⁶ and OMERACT (Rheumatoid Arthritis)^{16,27}, who have laid the foundation for COS development methodology. Furthermore, recommendations of the COS initiatives COMET and CSG-COUSIN were followed.

Although COS development is a fast-growing field, many methodological aspects are not yet clearly defined. We encountered several methodological issues while conducting this study. First, we noticed a ceiling effect: participants' responses on the Likert scale were negatively skewed toward the higher scores. A 7-point or 9-point Likert scale might therefore appear more appropriate, however, negative skewness is also observed in Likert

scales with a higher number of scale points.²⁸ Two e-Delphi rounds might have been sufficient for determining the most important domains, especially when considering that the (expected) drop in responses in round 2 and 3 makes it statistically less difficult to come to an agreement. To assure that all outcome domains were rightfully included in the e-Delphi rounds, we asked participants to critically re-appraise all provisionally included domains in the consensus meeting. Nevertheless, the participants agreed that none of the domains could be omitted from the core set. It was challenging to determine if outcomes were domain categories, outcome domains or domain items. Several aspects of QoL and types of adverse events were initially listed as separate outcome domains but were considered as subdomains by the study participants and thus regrouped into the domains 'overall health-related QoL' and 'adverse events'. Other domains, such as impairment in mobility, fit in multiple categories (e.g. QoL or patient-reported symptom). The COMET initiative is currently working on a standard list of 'general' outcome domains, which will be of great value to COS researchers.

In this study, it was not feasible to organize a face-to-face consensus meeting, as the study participants were geographically dispersed and there were no upcoming international conferences. The online consensus meeting was ideal for voting, however, a face-to-face meeting may set off a more elaborate in-depth (small and whole group) discussion. This may also enhance patient and parent engagement, which is an essential part of COS development.^{29,30} As the discussion about the domains 'recurrence' and 'appearance' was too complex to manage online, we chose to bring this discussion forward to a face-to-face meeting.

Future perspectives

The next step of this project is to select outcome instruments that should be used to measure the core outcome domains. To inform this decision, we will perform systematic reviews to determine which outcome measurement instruments are available for each core domain and how well these instruments are validated, as per the HOME Roadmap.

Acknowledgements

We thank all physicians, patients and parents for their valuable contributions to this study.

Furthermore, we thank the members of the multidisciplinary working group of Vascular Anomalies in the Academic Medical Center (Dr. J.H. Sillevius Smitt, Dr. M.A. Middelkamp Hup, Prof. J.A. Reekers and Dr. M.A. Koelemay), Dr. D.T. Ubbink and Prof. H.C. Williams for their valuable feedback during the initial development of the study protocol.

REFERENCES

- 1 Dasgupta R, Fishman SJ. ISSVA classification. *Semin. Pediatr. Surg.* 2014; **23**: 158-61.
- 2 Wassef M, Blei F, Adams D *et al.* Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics* 2015; **136**: e203-e14.
- 3 Horbach SE, Lokhorst MM, Saeed P *et al.* Sclerotherapy for low-flow vascular malformations of the head and neck: A systematic review of sclerosing agents. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2015.
- 4 Horbach SE, Rigter IM, Smitt JH *et al.* Intralesional Bleomycin Injections for Vascular Malformations: A Systematic Review and Meta-Analysis. *Plastic and reconstructive surgery* 2016; **137**: 244-56.
- 5 Langbroek GB, Horbach SE, van der Vleuten CJ *et al.* Compression therapy for congenital low-flow vascular malformations of the extremities: A systematic review. *Phlebology / Venous Forum of the Royal Society of Medicine* 2016: 268355516684694.
- 6 Prinsen CA, Vohra S, Rose MR *et al.* How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. *Trials* 2016; **17**: 449.

- 7 Schmitt J, Apfelbacher C, Spuls PI *et al.* The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. *The Journal of investigative dermatology* 2015; **135**: 24-30.
- 8 Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. *PLoS medicine* 2011; **8**: e1000393.
- 9 von der Gracht H. Consensus measurement in Delphi studies. *Technological forecasting & social change : an international journal* 2012; **79**: 1525-37.
- 10 Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. *Information & Management* 2004; **42**: 15-29.
- 11 Coulman KD, Hopkins J, Brookes ST *et al.* A Core Outcome Set for the Benefits and Adverse Events of Bariatric and Metabolic Surgery: The BARIACT Project. *PLoS medicine* 2016; **13**: e1002187.
- 12 Thorlacius L, Ingram JR, Garg A *et al.* Protocol for the development of a core domain set for hidradenitis suppurativa trial outcomes. *BMJ open* 2017; **7**: e014733.
- 13 McNair AG, Whistance RN, Forsythe RO *et al.* Core Outcomes for Colorectal Cancer Surgery: A Consensus Study. *PLoS medicine* 2016; **13**: e1002071.
- 14 Potter S, Holcombe C, Ward JA *et al.* Development of a core outcome set for research and audit studies in reconstructive breast surgery. *The British journal of surgery* 2015.
- 15 Eleftheriadou V, Thomas K, van Geel N *et al.* Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment cell & melanoma research* 2015.
- 16 Boers M, Kirwan JR, Wells G *et al.* Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *Journal of clinical epidemiology* 2014; **67**: 745-53.
- 17 Kirkham JJ, Gorst S, Altman DG *et al.* Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. *PLoS medicine* 2016; **13**: e1002148.
- 18 Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: Its Role in Improving Cochrane Reviews. *The Cochrane database of systematic reviews* 2012; **5**: Ed000041.
- 19 Gargon E, Williamson PR, Altman DG *et al.* The COMET Initiative database: progress and activities update (2015). *Trials* 2017; **18**: 54.
- 20 Schmitt J, Deckert S, Alam M *et al.* Report from the kick-off meeting of the Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN). *The British journal of dermatology* 2016; **174**: 287-95.
- 21 Balakrishnan K, Bauman N, Chun RH *et al.* Standardized Outcome and Reporting Measures in Pediatric Head and Neck Lymphatic Malformations. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* 2015.
- 22 Alomari AI, Karian VE, Lord DJ *et al.* Percutaneous sclerotherapy for lymphatic malformations: a retrospective analysis of patient-evaluated improvement. *Journal of vascular and interventional radiology : JVIR* 2006; **17**: 1639-48.
- 23 Guidelines for best practice in cross-cultural surveys. In. Ann Arbor, U.S.A.: Survey Research Center, Institute for Social Research, University of Michigan 2010.
- 24 Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. *Int. J. Nurs. Stud.* 2001; **38**: 195-200.
- 25 Al Wattar BH, Tamilselvan K, Khan R *et al.* Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study. *BJOG* 2016.
- 26 Schmitt J, Langan S, Stamm T *et al.* Core outcome domains for controlled trials and clinical recordkeeping in eczema: international multiperspective Delphi consensus process. *The Journal of investigative dermatology* 2011; **131**: 623-30.

- 27 Toupin-April K, Barton J, Fraenkel L *et al.* Development of a Draft Core Set of Domains for
Measuring Shared Decision Making in Osteoarthritis: An OMERACT Working Group on
Shared Decision Making. *The Journal of rheumatology* 2015.
- 28 Dawes JG. Do data characteristics change according to the number of scale points used? An
experiment using 5 point, 7 point and 10 point scales. 2012.
- 29 Jones JE, Jones LL, Keeley TJ *et al.* A review of patient and carer participation and the use of
qualitative research in the development of core outcome sets. *PLoS One* 2017; **12**:
e0172937.
- 30 Kearney A, Williamson P, Young B *et al.* Priorities for methodological research on patient and
public involvement in clinical trials: A modified Delphi process. *Health expectations : an
international journal of public participation in health care and health policy* 2017.

Supporting information

Appendix 1. Definitions of the outcome categories, domains and items.

*Appendix 2. PubMed search strategy used for the identification of physician experts in the
field of vascular malformations.*

*Appendix 3. Complete results of Delphi rounds 1, 2 and 3, specified per vascular
malformation type and stakeholder group.*

*Appendix 4. A list of OVAMA contributors: participating physicians in the e-Delphi rounds
and participants in the online consensus meeting.*

Figure legends

*Figure 1. Overview of the steps of the OVAMA project, following the methodological
framework of the Harmonising Outcome Measures for Eczema (HOME) roadmap⁷.*

Figure 2. Overview of the e-Delphi procedure and the online consensus meeting.

Characteristics Physicians	N (%)	Characteristics Patient/Parents	N (%)
Total group	167 (100%)	Total group	134 (100%)
Specialty (top 5)		Patients	54 (40.3%)
Interventional radiology	41 (24.6%)	Parents/caregivers	80 (59.7%)
Dermatology	39 (23.4%)	Educational level	
Plastic surgery	24 (14.4%)	Primary school	2 (1.4%)
Pediatrics	14 (8.4%)	High school	10 (7.5%)
Pediatric surgery	13 (7.8%)	College (no degree)	44 (32.8%)
Other*	11 (6.6%)	College/University (Bachelor degree)	48 (35.8%)
Years of experience		Graduate school (Master's degree)	30 (22.4%)
0-<5 years	15 (9.0%)	Age of patient	
5-<10 years	35 (21.0%)	0-<5 years	30 (22.4%)
10-<15 years	30 (18.0%)	5-<10 years	18 (13.4%)
15-<20 years	43 (25.7%)	10-<18 years	21 (15.7%)
>20 years	44 (26.3%)	18-<35 years	29 (21.6%)
Country of employment (top 5)		35-<50 years	22 (16.4%)
Unites States	41 (24.6%)	>50 years	14 (10.4%)
United Kingdom	29 (17.4%)	Country of residence (top 5)	
The Netherlands	15 (9.0%)	The Netherlands	57 (42.5%)
Canada	9 (5.4%)	Unites States	43 (32.1%)
France	9 (5.4%)	United Kingdom	14 (10.4%)
Other*	64 (38.3%)	Germany	4 (3.0%)
Type of hospital		Australia	3 (2.2%)
University hospital	139 (83.2%)	Canada	3 (2.2%)
Urban hospital	24 (14.4%)	Other*	10 (7.9%)
Suburban or rural hospital	3 (1.8%)	Type of vascular malformation	
Private clinic	14 (8.4%)	CM (in addition to LM, VM or AVM)	17 (12.7%)
Member of multidisciplinary working group	149 (89.2%)	LM^	50 (37.3%)
Number of new patients visiting annually		VM^	71 (53.0%)
0-20	15 (9.0%)	AVM	29 (21.6%)
20-100	76 (45.5%)	Location of vascular malformation	
100-200	36 (21.6%)	Head and neck	97 (72.4%)
200-400	28 (16.8%)	Trunk	47 (35.1%)
>400	12 (7.2%)	Pelvic region and buttocks	38 (28.4%)
Number of patients treated annually		Upper extremities	19 (14.2%)
0-20	30 (18.0%)	Lower extremities	44 (32.8%)
20-100	89 (53.3%)	Previous therapies	
100-200	31 (18.6%)	Compression garments	33 (24.6%)
200-400	12 (7.2%)	Surgery	61 (45.5%)
>400	5 (3.0%)	Sclerotherapy	55 (41.0%)
Types of vascular malformations treated		Embolization	38 (28.4%)
LM	163 (97.6%)	Laser	32 (23.9%)
VM	166 (99.4%)	Oral medication	7 (5.2%)
AVM	143 (85.6%)	Other#	6 (4.5%)
Combined vascular malformations	159 (95.2%)	Syndromes diagnosed	
		None	111 (82.8%)
		Klippel Trenaunay syndrome	16 (11.9%)
		Proteus syndrome	1 (0.01%)
		Other**	6 (0.06%)

Table 1. Characteristics of the participants in e-Delphi round 1. *Full list can be found in Appendix 4. ^ One patient with a LVM participated in both the LM and VM questionnaires. # lymphatic drainage or lymphosuction (n=4), radiotherapy (n=2) **Suspected PIK3CA-related overgrowth syndrome unclassified (n=2), lymphangiomatosis with lymphatic malformation (n=2), PHACE (posterior fossa, hemangioma, arterial anomaly, cardiac anomaly, eye anomaly) syndrome with AVM in head/neck area (n=2).

Domain category	Domain	Physicians rating very important or crucial (%) in last round			Patients/parents rating very important or crucial (%) in last round			Consensus after e-Delphi		
								Consensus in round 1		
								Consensus in round 2		
								Consensus in round 3		
		LM	VM	AVM	LM	VM	AVM	LM	VM	AVM
Anatomy	Radiological assessment	84.2	82.6	92.0	85.7	93.8	93.1	●	●	●
Appearance	Appearance as assessed by physician	62.2	57.9	85.7	77.8	65.5	83.3	-	-	●
	Appearance as assessed by patient/parent	71.7	47.6	61.1	86.7	78.2	77.8	?	-	-
Signs (physician)	Bleeding	35.4	36.5	97.6	77.8	78.2	83.3	-	-	●
	Lymphatic fluid leakage	61.4	5.6	2.4	84.4	36.4	22.2	?	-	-
	Infections	79.6	9.5	13.5	80.0	69.1	66.7	●	-	-
	Localized thrombosis	15.7	88.9	5.6	57.8	94.5	44.4	-	●	-
	Signs associated with localization	98.5	93.2	95.5	83.3	84.4	88.9	●	●	●
Symptoms (patient)	Overall severity of symptoms	97.7	89.1	88.3	95.2	81.7	86.2	●	●	●
	Pain	87.4	89.1	86.5	88.0	84.5	86.2	●	●	●
	Fatigue	11.0	9.5	15.9	37.8	43.6	44.4	-	-	-
	Bleeding	31.5	36.5	97.6	51.1	67.3	77.8	-	-	?
	Lymphatic fluid leakage	62.2	4.8	3.2	55.6	29.1	33.3	-	-	-
QoL	Itching	3.9	3.2	2.4	26.7	21.8	33.3	-	-	-
	Overall Quality of Life	88.0	90.9	88.3	86.0	84.5	93.1	●	●	●
QoL	Activities of Daily Living	91.7	93.7	94.7	83.3	89.1	88.9	●	●	●
	Mobility	97.0	96.2	94.7	85.7	87.5	100	●	●	●
Physical well-being	Work/study	71.7	82.6	80.3	73.3	81.3	88.9	-	●	●
	Sports	18.9	15.1	8.7	37.8	49.1	44.4	-	-	-
	Leisure/playing	22.0	17.5	16.7	57.8	61.8	61.1	-	-	-
QoL	Confidence/self-esteem	77.2	80.2	81.7	84.4	90.9	94.4	?	●	●
	Body image	59.8	63.5	62.7	71.1	83.6	61.1	-	?	-
	Social functioning	70.1	78.6	68.3	84.4	90.9	66.7	?	?	-
	Emotional well-being	85.0	80.2	77.8	93.3	94.5	77.8	●	●	-
	Sexual well-being	18.9	16.7	18.3	26.7	34.5	27.8	-	-	-
Satisfaction	Patient satisfaction with outcome	95.5	96.2	86.5	85.7	87.5	89.7	●	●	●
	Patient satisfaction with treatment	95.5	93.9	82.8	92.9	85.9	86.2	●	●	●
Adverse events	Systemic complications	91.7	97.6	92.1	81.0	85.5	61.1	●	●	?
	Bleeding-related complications	70.1	88.9	97.6	66.7	69.1	66.7	-	?	?
	Wound-related complications	94.5	95.5	95.2	86.7	82.8	66.7	●	●	?
	Nerve-related complications	97.0	96.2	87.7	88.1	82.8	82.8	●	●	●
	Major complications	100	98.5	94.5	90.5	89.1	86.2	●	●	●
Practical issues	Burden of treatment	75.6	65.9	58.7	77.8	70.9	61.1	-	-	-
	Number of treatment procedures	37.8	34.9	40.5	48.9	58.2	66.7	-	-	-
	Economic issues (costs for health insurer)	6.3	7.1	7.1	24.4	30.9	55.6	-	-	-
	Financial issues (costs for patient)	7.1	8.7	7.1	26.7	38.2	44.4	-	-	-
Proposed by participants	*Recurrence	93.7	88.6	87.9	97.8	82.8	83.3	●	●	●
	*Coagulation parameters	n/a	47.6	n/a	n/a	56.4	n/a	n/a	-	n/a
	*Sleep disturbances	n/a	11.1	n/a	n/a	40.0	n/a	n/a	-	n/a
	*Venous Thrombo-Embolism (VTE)	n/a	96.0	n/a	n/a	87.3	n/a	n/a	●	n/a
	*Cardiac function (high output failure)	n/a	n/a	97.6	n/a	n/a	83.3	n/a	n/a	●
	*Amputations	n/a	n/a	90.9	n/a	n/a	83.3	n/a	n/a	●
	*Mortality	n/a	n/a	98.4	n/a	n/a	83.3	n/a	n/a	●
	*Impact on family	20.5	n/a	n/a	42.2	n/a	n/a	-	n/a	n/a

Table 2. Results of e-Delphi rounds. Last scores before reaching consensus or scores of last round are presented. Scores 80% or higher are displayed in red. * = proposed in 1st round, n/a not applicable, - <80% agreement in both stakeholder groups (no consensus), ? ≥80% agreement in one stakeholder group (undecided), ● ≥80% agreement in both stakeholder groups (consensus). n/a = not applicable.

	Number of participating physicians			Number of participating patients/parents		
	Round 1	Round 2 (response rate)*	Round 3 (response rate)*	Round 1	Round 2 (response rate)*	Round 3 (response rate)*
LM	167	133 (80%)	127 (76%)	50	42 (84%)	45 (90%)
VM	165	132 (80%)	126 (76%)	71	64 (90%)	55 (77%)
AVM	163	132 (81%)	126 (77%)	29	18 (62%)	17 (59%)

Table 3. Participant numbers and response rates in e-Delphi round 1, 2 and 3. *Relative to round 1

Domain category	Outcome domain	LM			VM			AVM			Remarks from consensus meeting
		e-Delphi	Vote IN/OUT	Meeting	e-Delphi	Vote IN/OUT	Meeting	e-Delphi	Vote IN/OUT	Meeting	
Anatomy	Radiological assessment	●		IN	●		IN	●		IN	
	Appearance as assessed by physician	-	Pat 7/1 Phys 25/3	IN*	-	Pat 5/2 Phys 27/2	IN*	●		IN	<i>Recommended by majority despite e-Delphi results. Needs further discussion. Voted IN for LM, no consensus for VM & AVM</i>
Appearance	Appearance as assessed by patient/parent	?	Pat 6/2 Phys 22/7	IN	-	Pat 3/5 Phys 18/10	OUT*	-	Pat 2/5 Phys 21/9	OUT*	
	Bleeding	-		OUT	-		OUT	●		IN	
	Cardiac function (high output failure)	-		OUT	-		OUT	●	Pat 5/2 Phys 23/6	IN*	<i>Measuring high output failure in AVM is crucial because of its severity, despite rarity</i>
Signs assessed by physician	Lymphatic fluid leakage	?	Pat 5/2 Phys 26/4	IN	-		OUT	-		OUT	
	Infections as assessed by physician	●		IN	-		OUT	-		OUT	
	Localized thrombosis	-		OUT	●		IN	-		OUT	
	Signs associated with localization	●		IN	●		IN	●		IN	
	Overall severity of symptoms	●		IN	●		IN	●		IN	
Symptoms reported by patient	Pain	●		IN	●		IN	●		IN	
	Fatigue	-		OUT	-		OUT	-		OUT	
	Bleeding	-		OUT	-		OUT	?	Pat 5/2 Phys 26/4	IN	
	Lymphatic fluid leakage	-		OUT	-		OUT	-		OUT	
	Itching	-		OUT	-		OUT	-		OUT	
QoL	Overall health-related Quality of Life	●		IN	●		IN	●		IN	<i>All subdomains of health-related QoL should fall under domain QoL</i>
QoL	Activities of Daily Living	●		IN	●		IN	●		IN	<i>Included for uniformity</i>
Physical well-being	Mobility	●		IN	●		IN	●		IN	
	Work/study	-	Pat 7/0 Phys 23/5	IN*	●		IN	●		IN	
	Sports	-		OUT	-		OUT	-		OUT	
	Leisure/playing	-		OUT	-		OUT	-		OUT	
QoL Psychological well-being	Confidence/self-esteem	?	Pat 5/1 Phys 29/2	IN	●		IN	●		IN	<i>Included for uniformity</i>
	Body Image	-		OUT	?	Pat 1/7 Phys 3/23	OUT	-		OUT	
	Social functioning	?	Pat 2/6 Phys 2/27	OUT	?	Pat 1/6 Phys 3/23	OUT	-		OUT	
	Emotional well-being	●		IN	●		IN	-	Pat 7/0 Phys 26/3	IN*	
	Sexual well-being	-		OUT	-		OUT	-		OUT	
Satisfaction	Patient satisfaction with outcome	●		IN	●		IN	●		IN	
	Patient satisfaction with treatment	●		IN	●		IN	●		IN	
Adverse events	Systemic complications	●		IN	●		IN	?	Pat 7/0 Phys 28/1	IN	
	Bleeding-related complications	-	(No vote)	OUT	?	Pat 7/0 Phys 20/9	IN	?	Pat 6/0 Phys 27/0	IN	<i>All types of adverse events should be included in COS and fall under domain</i>
	Wound-related complications	●		IN	●		IN	?	Pat 7/0 Phys 29/0	IN	

	Nerve-related complications	●	IN	●		IN	●	IN	<i>adverse events.</i>
	Major complications/SAE	●	IN	●		IN	●	IN	
	Amputations	-	OUT	-		OUT	●	IN	
	Mortality	-	OUT	-		OUT	●	IN	
	Venous Thrombo-Embolism (VTE)	-	OUT	●		IN	-	OUT	
Practical issues	Burden of treatment	-	OUT	-		OUT	-	OUT	<i>Recommended but needs further specification</i>
	Number of procedures required	-	OUT	-		OUT	-	OUT	
	Economic issues	-	OUT	-		OUT	-	OUT	
	Financial issues	-	OUT	-		OUT	-	OUT	
	Recurrence	●	IN	●		IN	●	IN	
Proposed by participants	Impact on family	-	OUT	n/a		n/a	n/a	n/a	
	Coagulation parameters	n/a	n/a	-	Pat 4/3 Phys14/15	OUT*	n/a	n/a	
	Sleep disturbances	n/a	n/a	-		OUT	-	OUT	

Table 4. Results of online consensus meeting. *Pat* = patient/parent group, *Phys* = physician group. *LM* = lymphatic malformation, *VM* = venous malformation, *AVM* = arteriovenous malformation '●' = provisionally included, '?' = undecided '-' = provisionally excluded. * Although these domains were already provisionally included or excluded based on the e-Delphi results, a vote was proposed by the participants (n≥5) due to new insights generated by the discussion in the consensus meeting. n/a = not applicable.

Domain category	Core outcome domains included in COS			
	For all vascular malformation types	Specific for LM	Specific for VM	Specific for AVM
Anatomy of the vascular malformation	Radiological assessment (size, flow characteristics etc.)			
Physician-reported signs	Location-specific signs	- Infections - Lymphatic fluid leakage	Localized thrombosis	- Bleeding - Cardio-vascular health issues
Patient or parent-reported symptoms	- Pain - Overall severity of symptoms			
Quality of Life	- Overall health-related QoL, including (sub)domains: - Work - Activities of Daily Living - Mobility - Emotional well-being - Confidence			
Satisfaction	- Patient satisfaction with treatment - Patient satisfaction with outcome			
Adverse events	All		Venous thrombo-embolism	- Mortality - Amputation
Outcome domains recommended but requiring further discussion*				
Recurrence	Recurrence in general	Needs further specification; may be left out if it overlaps with other included domains		
Appearance	- Appearance as assessed by the physician - Appearance as assessed by the patient or parent (so far only consensus for LMs)	Needs further discussion; contrasting results of e-Delphi surveys and online consensus meeting		

Table 5. List of proposed core outcome domains. *Requires further discussion during the ISSVA conference 2018 in Amsterdam, the Netherlands.