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

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- **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 MAlformations (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 established[8], 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 classification[2]. 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.



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**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) roadmap[7].*

*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<br>*Consensus in round 1*<br>*Consensus in round 2*<br>*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 | - | - | - |
| | Itching | 3.9 | 3.2 | 2.4 | 26.7 | 21.8 | 33.3 | - | - | - |
| **QoL** | Overall Quality of Life | 88.0 | 90.9 | 88.3 | 86.0 | 84.5 | 93.1 | ● | ● | ● |
| ***QoL* Physical well-being** | 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 | ● | ● | ● |
| | 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* Psycho-logical well-being** | 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

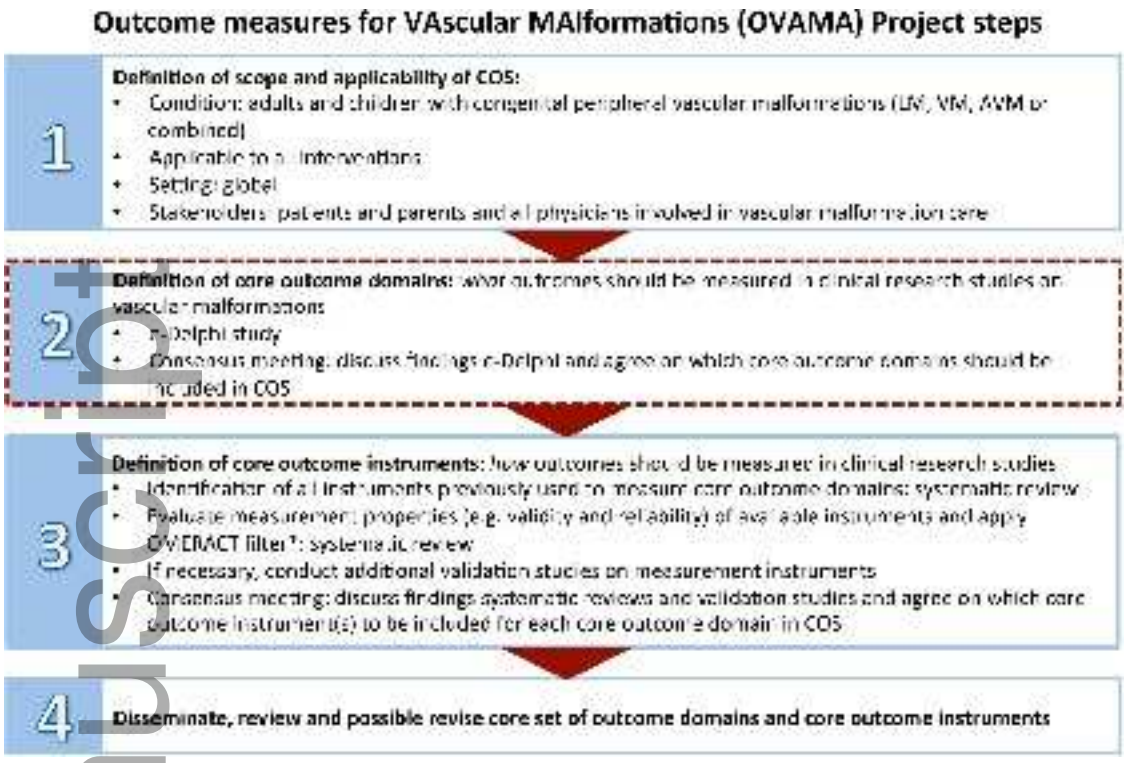
| Domain category | Outcome domain | LM | | | VM | | | AVM | | | Remarks from consensus meeting |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | e-Delphi | Vote IN/OUT | Meet-ing | e-Delphi | Vote IN/OUT | Meet-ing | e-Delphi | Vote IN/OUT | Meet-ing | |
| **Anatomy** | Radiological assessment | ● | | **IN** | ● | | **IN** | ● | | **IN** | |
| **Appearance** | Appearance as assessed by physician | - | Pat 7/1 Phys 25/3 | **IN*** | - | Pat 5/2 Phys27/2 | **IN*** | ● | | **IN** | *Recommended by majority despite e-Delphi results. Needs further discussion. Voted IN for LM, no consensus for VM & AVM* |
| | Appearance as assessed by patient/parent | ? | Pat 6/2 Phys 22/7 | **IN** | - | Pat3/5 Phys 18/10 | **OUT*** | - | Pat 2/5 Phys 21/9 | **OUT*** | |
| **Signs *assessedby physician*** | Bleeding | - | | **OUT** | - | | **OUT** | ● | | **IN** | |
| | Cardiac function (high output failure) | - | | **OUT** | - | | **OUT** | ● | Pati5/2 Phys 23/6 | **IN*** | *Measuring high output failure in AVM is crucial because of its severity, despite rarity* |
| | 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** | |
| **Symptoms *reported by patient*** | Overall severity of symptoms | ● | | **IN** | ● | | **IN** | ● | | **IN** | |
| | 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** | *All subdomains of health-related QoL should fall under domain QoL* |
| ***QoL* Physical well-being** | Activities of Daily Living | ● | | **IN** | ● | | **IN** | ● | | **IN** | |
| | Mobility | ● | | **IN** | ● | | **IN** | ● | | **IN** | |
| | Work/study | - | Pat 7/0 Phys 23/5 | **IN*** | ● | | **IN** | ● | | **IN** | *Included for uniformity* |
| | Sports | - | | **OUT** | - | | **OUT** | - | | **OUT** | |
| | Leisure/playing | - | | **OUT** | - | | **OUT** | - | | **OUT** | |
| ***QoL* Psycho-logical well-being** | Confidence/self-esteem | ? | Pat 5/1 Phys 29/2 | **IN** | ● | | **IN** | ● | | **IN** | |
| | 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*** | *Included for uniformity* |
| | 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** | *All types of adverse events should be included in COS and fall under domain adverse events.* |
| | Bleeding-related complications | - | *(No vote)* | **OUT** | ? | Pat 7/0 Phys 20/9 | **IN** | ? | Pat 6/0 Phys 27/0 | **IN** | |
| | Wound-related complications | ● | | **IN** | ● | | **IN** | ? | Pat 7/0 Phys 29/0 | **IN** | |
| | Nerve-related complications | ● | | **IN** | ● | | **IN** | ● | | **IN** | |
| | 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** | |
| | Number of procedures required | - | **OUT** | - | | **OUT** | - | **OUT** | |
| | Economic issues | - | **OUT** | - | | **OUT** | - | **OUT** | |
| | Financial issues | - | **OUT** | - | | **OUT** | - | **OUT** | |
| **Proposed by participants** | Recurrence | ● | **IN** | ● | | **IN** | ● | **IN** | *Recommended but needs further specification* |
| | 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<br>• Lymphatic fluid leakage | • Localized thrombosis | • Bleeding<br>• Cardio-vascular health issues |
| **Patient or parent-reported symptoms** | • Pain<br>• Overall severity of symptoms | | | • Bleeding |
| **Quality of Life** | • Overall health-related QoL, including (sub)domains:<br>- Work<br>- Activities of Daily Living<br>- Mobility<br>- Emotional well-being<br>- Confidence | | | |
| **Satisfaction** | • Patient satisfaction with treatment<br>• Patient satisfaction with outcome | | | |
| **Adverse events** | • All | | • Venous thrombo-embolism | • Mortality<br>• 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<br>• 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.

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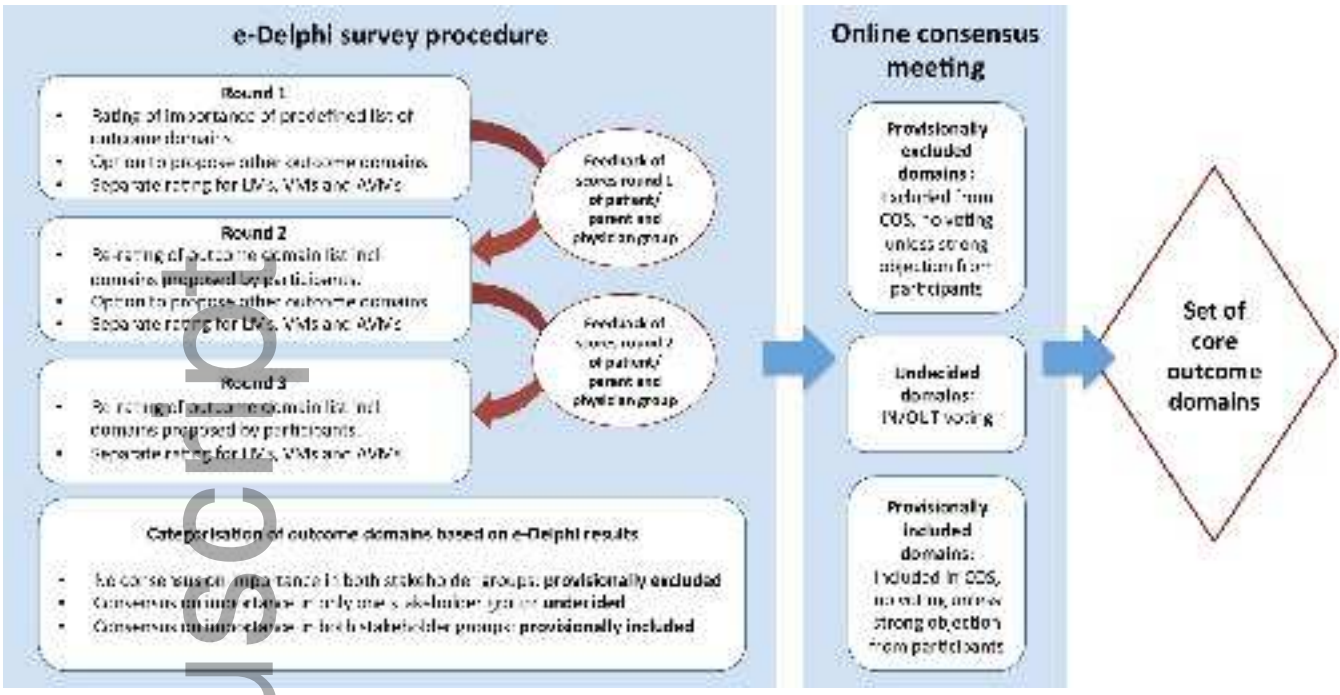


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Title:
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Date:
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