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A core outcome domain set for clinical research on capillary malformations (the COSCAM project): an e-Delphi process and consensus meeting

Running head: core outcome domain set for capillary malformations

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement: The Medical Ethics Review Committee of the Academic Medical Center, the Netherlands, has confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and an official approval of this study by the committee was not required. (Reference number W20_351 # 20.389)

What is already known about this topic?

- Besides physical and functional sequelae, capillary malformations (CMs) often cause emotional and social burden.
- The lack of uniform outcome measures obstructs proper evaluation and comparison of treatment strategies. As a result, there is limited evidence on the best available treatment options.
- The development of a core outcome set (COS) may improve standardized reporting of trial outcomes.

What does this study add?

- A core outcome domain set (CDS), as part of a COS, was developed for clinical research on CMs.
- International consensus was reached on the recommended core outcome subdomains to be measured in CM trials: colour/redness, thickness, noticeability, distortion of anatomical structures, glaucoma, overall HR-QoL, emotional functioning, social functioning, tolerability of treatment, patient satisfaction with treatment results and recurrence.
- This CDS enables the next step in the development of a COS, i.e. to reach consensus on the core outcome measurement instruments to score the core outcome subdomains.

What are the clinical implications of this work?

- The obtained CDS will facilitate standardized reporting of treatment outcomes, hereby enabling proper comparison of treatment results.
- This comparison is likely to provide more reliable information for patients about the best available treatment options.

Abstract

Background:

There is limited evidence on the best available treatment options for capillary malformations (CMs), mainly due to the absence of uniform outcome measures in trials on therapies. A Core Outcome Set (COS) enables standard reporting of trial outcomes, which facilitates comparison of treatment results.

Objectives:

To develop a core outcome domain set (CDS), as part of a core outcome set (COS), for clinical research on CMs.

Methods:

Sixty-seven potentially relevant outcome subdomains were recognized based on the literature, focus group sessions, and input from the COSCAM working group. These outcome subdomains were presented in an online Delphi study to CM experts (medical specialists and authors of relevant literature) and (parents of) CM patients (international patient associations). During three e-Delphi study rounds, the participants repeatedly scored the importance of these outcome subdomains on a 7-point Likert scale. Participants could also propose other relevant outcome subdomains. Consensus was defined as ≥80% agreement as to the importance of an outcome subdomain amongst both stakeholder groups. The CDS was finalized during an online consensus meeting.

Results:

A total of 269 participants from 45 countries participated in the first e-Delphi study round. Of these, 106 were CM experts from 32 countries, counting predominantly dermatologists (59%)

and plastic surgeons (18%). Moreover, 163 (parents of) CM patients from 28 countries participated, of whom 58 percent had Sturge-Weber syndrome (SWS). During the two subsequent e-Delphi study rounds, 189 and 148 participants participated, respectively. After the entire consensus process, consensus was reached on 11 outcome subdomains: colour/redness, thickness, noticeability, distortion of anatomical structures, glaucoma, overall health-related quality of life, emotional functioning, social functioning, tolerability of treatment, patient satisfaction with treatment results and recurrence.

Conclusion:

We recommend the CDS to be used as a minimum reporting standard in all future CM therapy trials. Our next step will be to select suitable outcome measurement instruments to score the core outcome subdomains.

Introduction

Capillary malformations (CMs) are caused by a hyperdilation of capillaries and post-capillary venules in the dermis or subcutaneous tissue[1, 2]. They are commonly known as port-wine stains or birthmarks and have been associated with somatic mosaic mutations in the *GNAQ*, *GNA11* and *PIK3CA* genes[3-6]. Besides physical and functional effects, CMs often lead to decreased emotional and social overall health-related quality of life (HR-QoL) as most are visibly located in the head and neck region[7-12].

Multiple therapeutic strategies are available, including cosmetic camouflage, medical tattooing, surgical excision, and laser and light therapies[13]. Even though the pulsed dye laser is still the treatment of choice, its effectiveness in terms of clearance rate has barely improved over the last three decades[14]. Due to this and frequent post-treatment lesion recurrences, CM patients are left with a desire for improved treatment regimens[15]. Novel therapies might be promising, but have no permanent place in the CM treatment palette yet[16-19].

Currently, there is no consensus on which outcomes should be measured when evaluating treatment results[20]. This hampers the evaluation and comparison of treatment modalities and, as a result, there is limited evidence available on the best treatment options[13]. A core outcome set (COS) facilitates standard reporting of trial outcomes and, by including patients in the development process, incorporates patient-relevant outcomes. A COS, containing a core outcome domain set (CDS) and a core outcome measurement set (COMS), includes a minimum set of outcomes that should be measured and reported in clinical research when studying a specific health condition[21, 22]. So, a COS involves *what* to measure (outcome domains and subdomains) and *how* to measure (outcome measurement instruments). COS development has

become an essential part in conducting meaningful research in the field of dermatology[23]. Over the last years, a rise in dermatological COS has become evident, for example in peripheral vascular malformations, congenital melanocytic naevi, and vitiligo[24-26]. Moreover, a dermatology-specific framework was recently developed to support COS developers in this field[27].

The Core Outcome Set for CApillary Malformations (COSCAM) project was initiated, as currently no COS exists for CMs. We have previously reported on the methods to develop the CDS for CMs, including the results of the first development stage[28]. The objective of this study was to finalize the second development stage, i.e. to reach international consensus on the core outcome domain set (CDS) for clinical research on CMs.

Patients and methods

Scope and methodological guidelines

Our previously published protocol describes our methods in detail[28]. The CDS is focused on patients of any age with any form of CM. It is intended for use in clinical research on CMs with any type of intervention, including watchful waiting. This study was registered on the CS-COUSIN website (http://cs-cousin.org/coscam/) and the COMET website (http://www.comet-initiative.org/Studies/Details/1599). The guidelines of the COMET initiative, CS-COUSIN, COS-STAD, and HOME initiative roadmap were followed[23, 29-31]. Study results are reported according to the COS-STAR checklist[32].

Stakeholders and recruitment

Two main stakeholder groups were included: CM patients (and their caregivers/parents) and CM experts. Both groups were considered the most essential stakeholders in CM clinical research and therefore included. CM patients were invited to participate via the COSCAM steering group, participating CM experts, national and international patient organizations, and the social media channels (Facebook or Instagram) of the various patient organizations. CM experts were sought among authors of published CM literature, through personal networks of the COSCAM steering group, contact lists of the International Society of the Study for Vascular Anomalies (ISSVA), and through the OVAMA (Outcome measures for VAscular MAlformations) project participant list. See the protocol for details on stakeholder eligibility and recruitment[28].

Identification of potential core outcome subdomains

The protocol describes the first CDS development stage in detail. In brief, potential core outcome subdomains were retrieved from a systematic review (*n*=16), focus group sessions (*n*=20) and discussions with the COSCAM founding group (*n*=38)[20]. Seven outcome subdomains overlapped (Figure 1). As suggested by Lange *et al*, the relatively broad outcome domains (such as clinical assessment) were specified by more precise sub-domains (such as redness) (see Table S1 for definitions)[27]. Subsequently, a final list with 67 potentially relevant outcome subdomains was generated (Table S2).

Selection of core outcome subdomains: e-Delphi study

An international modified e-Delphi study was conducted to evaluate the importance of the potential core outcome subdomains. The potential core outcome subdomains, written in lay language, formed the material for online surveys in Dutch and English (Google forms and Paperform Pty. Ltd., Sydney, Australia). To prevent overlap, these outcome subdomains were presented on either a 1st or 2nd level in the e-Delphi study together with their corresponding definitions. This resulted in 43 outcome subdomains that were presented in the first e-Delphi round (Figure 1). Before the first round, one Dutch patient and one American patient checked the surveys for readability and comprehensibility.

A total of 3 to 4 weeks was anticipated to complete each survey per study round. This deviated from our previously published protocol, in which 4 to 6 weeks were foreseen. In each round, a maximum of 3 reminders were sent. A response rate of at least 70% compared to the previous study round was maintained.

During the first round, we collected baseline characteristics of both stakeholder groups, as described in our study protocol[28]. Both stakeholder groups were asked to rate the importance of the potential core outcome subdomains. Only during this round, participants were able to suggest other potentially relevant outcome subdomains. Before being introduced in the second study round for evaluation, the suggested outcome subdomains were checked by the COSCAM founding group if they could measure treatment effect and if they were truly new outcome subdomains. In the subsequent rounds, participants received feedback on the scores of the

previous study round for each stakeholder group. The outcome subdomains on which no consensus was reached were then reevaluated.

The consensus definitions are specified in detail in our protocol[28]. Briefly, the importance of the proposed outcome subdomains was rated on a seven-point Likert scale (1-7). If at least 80% of both stakeholder groups scored the outcome subdomain a six or seven, the outcome subdomain was deemed 'important' or 'crucial', respectively. These were included in the CDS. Outcome subdomains were excluded from the CDS if at least 80% of both stakeholder groups scored a one or two on the Likert scale. After the third round, outcome subdomains were categorized as: '*included in the CDS*' (consensus on the importance in both stakeholder groups), '*excluded from the CDS*' (consensus on non-importance in both stakeholder groups), and '*undecided*' (no consensus on the importance reached yet, or consensus reached in only one stakeholder group).

Selection of core outcome subdomains: Consensus meeting

Following the third e-Delphi round, an online consensus meeting (Zoom Video Communications, Inc., V.5.0.1) was organized to reach consensus on the final CDS. The consensus rules were identical to those in the e-Delphi study. Stakeholders who completed the second e-Delphi round were invited to participate in this meeting. An online date planner was sent to pick a date based on availability of the stakeholders.

Two members of the COSCAM steering group (AW and GBL) chaired the meeting and one expert (PS) provided methodological support. During the meeting, stakeholders discussed and voted on the '*included*' outcome subdomains as well as the '*undecided*' outcome subdomains on which only one stakeholder group reached consensus. Stakeholders also had the opportunity to discuss and, if necessary, vote on the '*undecided*' outcome subdomains on which no consensus had been reached yet in both stakeholder groups and make suggestions on the outcome subdomain definitions. Re-voting on any of the latter outcome subdomains would be initiated only when there were strong advocates during the meeting to do so. The final IN or OUT vote was held separately per stakeholder group via an online poll to select the definitive core outcome subdomains of the CDS. The CDS was categorized according to the framework by Lange *et al*[27].

Statistical analyses

Microsoft Excel (V16.16.27, Microsoft Corporation, Redmond, WA, USA) was used for data analyses. Categorical data were presented as absolute numbers and percentages. The percentage agreement in each e-Delphi round was calculated for all outcome subdomains and rounded to the next whole percentage. Sub-analyses for '*included*' outcome subdomains of Sturge-Weber syndrome (SWS) patients were presented descriptively. Absolute numbers of IN and OUT votes were presented for the consensus meeting. All results were calculated separately per stakeholder group.

Ethics and consent

The Medical Ethics Review Board of the Amsterdam University Medical Center, location AMC, approved this study (W20_351#20.389). Stakeholders gave online consent for their data to be used anonymously at the first online survey.

Results

Participant characteristics

A total of 269 participants from 45 countries participated in the first study round. Of these, 163 were (parents of) CM patients from 28 countries. Of all participating patients, 95 (58%) had SWS. Some patients had a CM in combination with a venous malformation (*n*=18), an arteriovenous malformation (*n*=4), a lymphatic malformation (*n*=1), or combinations of these (*n*=24). In addition, 106 CM experts from 32 countries participated, of which the majority were dermatologists (59%) or plastic surgeons (18%). Most physicians had 10-15 years (39%) or more than 20 years (39%) experience in the field of CMs. Table 1 presents the participant characteristics of the first e-Delphi round and Table 2 shows the number of participants and response rates per e-Delphi round. Overall, the response rate was 70% or more in each round. Participant characteristics of round 3 can be found in Supplementary Table S3.

e-Delphi study

Table 3 shows the results of each stakeholder group per e-Delphi round. Of the list with comments and suggested outcome subdomains during the first round, 13 outcome subdomains were eventually added to the second round (see Table 3 and Appendix S2 for full list with

comments and suggested outcome subdomains). After the third round, consensus was reached for '*thickness'*, '*noticeability'*, '*facial deformity'*, '*overgrowth of underlying structures*', '*glaucoma'*, '*overall HR-QoL*', '*emotional functioning*', '*social functioning*', '*tolerability of the intervention*', '*patient satisfaction with treatment results*', and '*recurrence*'.

Sub-analysis showed that in the SWS group consensus was also reached for: '*physical functioning'*, '*occupational functioning'*, '*cognitive functioning*', '*coping*' and '*pain'*.

Eventually, none of the outcome subdomains reached consensus on 'non-importance'. Both the 11 '*included'* and the 45 '*undecided'* outcome subdomains were discussed in the consensus meeting (Figure 1).

Consensus meeting

During the consensus meeting, a total of 61 participants with various geographical backgrounds joined, including 6 patients, 8 parents/caregivers and 47 experts (Appendix S1). Throughout the meeting and polls, the number of participants varied. It was decided during the meeting that a minimum of 8 patients (or parents/caregivers) would need to participate during the voting, otherwise the meeting would be closed. This was not defined in the study protocol. Table 4 presents the results of the votes and comments raised during the meeting.

Of the '*included'* outcome subdomains during the e-Delphi study, '*glaucoma'*, '*facial deformity*', *'overgrowth of underlying structures*' and '*recurrence'* were re-voted on during the meeting.

Glaucoma was re-voted on as only a minority of the patients have (an increased risk for) glaucoma: i.e. patients with a CM in which any part of the forehead is involved, including the upper eyelids[33]. Furthermore, current therapies for CMs do not have any effect on glaucoma. Despite elaborate discussions on the pros and cons, '*Glaucoma'* remained in the CDS after re-voting. Furthermore, due to overlap it was suggested to combine both '*facial deformity*' and *'overgrowth of underlying structures*' into '*distortion of anatomical structures'.* After voting, this newly combined outcome subdomain was included in the CDS. It was also discussed if '*recurrence'* is a separate outcome subdomain or if it is defined as repeated measurements of other core outcome subdomains and should therefore be removed from the CDS. A re-vote was held and it was kept in the CDS.

Of the '*undecided'* outcome subdomains, only the outcome subdomains with consensus in 1 stakeholder group (*n*=7) were voted on. Eventually, only '*colour/redness*' was included in the CDS. The '*undecided'* outcome subdomains with no consensus in both stakeholder groups (*n*=38) were discussed but not voted on, as there were no strong advocates during the meeting to re-vote.

Additional vote on glaucoma

Because there were still strong advocates after the consensus meeting that *'glaucoma'* might not be an outcome measure for CMs and that it is not applicable to all CM patients, the COSCAM steering group and the CS-COUSIN Methods advisory group were consulted. Based on these deliberations different conditions were proposed in which glaucoma should be considered

as an outcome measure and when it should be assessed in clinical research (Figure 2). These conditions were approved by an online vote, in which a total of 94 participants responded, including 61 experts, 20 patients, and 13 parents/caregivers (Appendix S1).

Final CDS

Following the consensus process, the final CDS consisted of three outcome domains containing 11 outcome subdomains (Table 5).

Discussion

Through this international e-Delphi study, involving a large group of patients (and parents/caregivers) and experts, we identified the core outcome subdomains for CMs by applying transparent pre-defined methods. The final inclusion of eleven core outcome subdomains belonging to only a limited number of outcome domains makes the CDS feasible to be used in future CM research.

Expectedly, '*overall HR-QoL'*, '*emotional functioning'* and '*social functioning'* were included in the CDS. CMs are well known to affect QoL due to their disfiguring appearance, specifically when located in the head and neck region[7, 34]. Wanitphakdeedecha *et al* (2021) found a statistically significant difference between QoL scores of patients with a facial CM and patients without a facial CM or with no CM[35]. They concluded that patients with facial CMs face discrimination more likely than patients with non-facial CMs. In addition, '*recurrence'* was

ranked as a crucial outcome subdomain. This was foreseen, as CMs often recur and re-darken post laser therapy[36, 37].

Notably, *'Colour/redness'* was only voted in the CDS during the consensus meeting. It was anticipated that its importance would already become clear at the start of the e-Delphi study, since for years treatment effects have been evaluated by colour measurements and degrees of colour improvement. Its inclusion in the CDS is therefore justifiable and preferable, as colour can be more easily (and objectively) measured, compared to, for example, the more subjective '*patient satisfaction with treatment results'*. The latter patient-reported outcome subdomain, however, is an essential constituent of our CDS, as it supports future treatment outcomes to better match the patient's needs and goals.

We have recommended practical conditions in which '*glaucoma'* should be measured in future CM clinical trials. Previous research concluded that outcomes should be feasible to measure and responsive to interventions[38]. As glaucoma is only present in a minority of CM patients and current CM therapies do not affect glaucoma, we believe this might decrease the uptake of our CDS. Our proposed conditions will make our CDS more suitable and will promote its implementation. The OCOMEN project has provided a similar practical solution to such a problem[39].

Overall, our CDS is similar to those of other cosmetically burdensome dermatological conditions, such as vitiligo, in which '*repigmentation'* and '*tolerability of treatment*' are also included[24].

However, in our CDS no adverse events (AEs) are included. This may be due to the fact that AEs are not that common post (laser) therapy and were possibly not found important enough to be measured in all future clinical trials on CMs[13]. Yet, our core outcome subdomains are the minimum set that should be measured in clinical trials on therapies. Researchers are free to measure additional outcomes, such as AEs, that may be important depending on the study objective and type of treatment.

The methods used in this study are in harmony with internationally agreed standards for COS development, i.e. the guidelines of the COMET initiative and CS-COUSIN[23, 31]. Moreover, our project is one of the first to use the recently developed framework for dermatological COS, which facilitated the categorization of outcomes into core areas, outcome domains and subdomains[27]. Compared to other previously conducted dermatological COS development projects, our study included a relatively large group of participants from 45 countries and 6 continents, albeit mostly limited to small numbers of participants per country[24, 40]. Especially during the first e-Delphi round a large number of patients participated. In contrast, during the second and third rounds, a drop in the number of stakeholders became evident despite frequent survey reminders.

Despite preceding efforts to identify potentially relevant outcome subdomains during stage 1, as many as 13 new ones were suggested during round 1 and were partly eventually included in the CDS. These outcome subdomains might have been missed due to the relatively small number of participants during the focus groups and discussions with the founding group. Also, some

outcome subdomains were first seen as subitems of an outcome subdomain, whereas later on they were considered as separate outcome subdomains. This shows the subjective character of classifying outcomes.

A known limitation in COS studies is the problem of possibly having a different set of participants in the Delphi study than in the consensus meeting, which might affect the final CDS. During our consensus meeting, a relatively low and inconsistent number of patients participated compared to the number of participating experts. The discussions during the meeting might therefore have been more expert-led. Yet, the number of patients during our consensus meeting is similar to that of other COS development projects[25, 39]. We believe that, as long as no decision to include or exclude an outcome subdomain was overturned by the small patient cohort, it is inconsequential. Furthermore, a clear predominance of SWS patients was evident during both the e-Delphi rounds and the consensus meeting, which could have biased the results. The inclusion of '*glaucoma*' in our CDS is likely to be a consequence of this. The CDS was developed to be applicable to all patients with all types of CMs. Hopefully, the small number of participants per country, the inclusion of few patients with skin type V and VI, and the relatively large number of patients from the USA and the Netherlands will not impact the applicability of the CDS.

Especially in times of the COVID-19 pandemic, the use of an online consensus meeting allowed us to meet with CM patients (or parents/guardians) and CM experts from all over the world. Yet, international time differences might have discouraged participants to join. Moreover, participants may have been less engaged than in a face-to-face meeting. Still, we believe online

consensus meetings are an effective way to discuss and directly vote on the outcome subdomains, provided that it is executed with a predefined meeting agenda.

In conclusion, we recommend to use our core outcome domain set as a minimum reporting standard for clinical research on all types of CMs. The next step in the COSCAM project is to define the core outcome measurement set. Previous research sought to identify the most appropriate outcome measurement instruments for CMs, but the authors concluded that further evaluation of the measurement properties is needed[41]. The developed CDS will now provide a better guide for this process. Future research is thus needed to further define the core outcome subdomains and determine the *how* and *when* to measure them.

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Figure legends

Figure 1. Overview of CDS development stages.

Figure 2. Conditions for glaucoma.

Tables

Table 1 Complete overview of participant characteristics e-Delphi round 1.

Characteristics CM Patients*		**N (%)**	***Characteristics CM Experts***		**N (%)**
Total group		163 (100%)	**Total group**		106 (100%)
Age ranges			**Specialty**		
0-<5 years		11 (6.7%)	Dermatology		64 (60.4%)
5-<10 years		15 (9.2%)	Plastic surgery		19 (17.9%)
10-<18 years		32 (19.6%)	Other		5 (4.7%)
18-<35 years		34 (20.9%)	Otolaryngology		4 (3.8%)
35-<50 years		35 (21.5%)	Paediatrics		4 (3.8%)
>50 years		36 (22.1%)	Paediatric surgery		3 (2.8%)
Educational level**			No specialty		3 (2.8%)
Primary school		52 (31.9%)	Vascular surgery		2 (1.9%)
High school		26 (16.0%)	Intervention radiology		1 (0.9%)
Associate degree		25 (15.3%)	Ophthalmology		1 (0.9%)
University		60 (36.8%)	Oral and Maxillofacial surgery		1 (0.9%)
Continent	**Country of residence**		**Continent**	**Country of residence**	
Africa	Ethiopia	1 (0.6%)	*Africa*	Egypt	2 (1.9%)
	South Africa	2 (1.2%)	*Asia*	China	3 (2.8%)
Asia	India	1 (0.6%)		India	1 (0.9%)
	Japan	3 (1.8%)		Iran	1 (0.9%)
	Malaysia	1 (0.6%)		Iraq	2 (1.9%)
	Philippines	2 (1.2%)		Japan	6 (5.7%)
	Russia	1 (0.6%)		Saudi Arabia	1 (0.9%)
	Saudi Arabia	1 (0.6%)		South Korea	1 (0.9%)
	Singapore	1 (0.6%)		Thailand	1 (0.9%)
	Thailand	3 (1.8%)	*Australia*	Australia	12 (11.3%)
Australia	Australia	10 (6.1%)		New Zealand	1 (0.9%)
Europe	Spain	8 (4.9%)	*Europe*	Belgium	2 (1.9%)
	Austria	1 (0.6%)		Finland	1 (0.9%)
	Belgium	4 (2.5%)		France	3 (2.8%)
	Denmark	1 (0.6%)		Germany	2 (1.9%)
	Finland	1 (0.6%)		Greece	1 (0.9%)
	France	3 (1.8%)		Ireland	2 (1.9%)
	Germany	2 (1.2%)		Italy	4 (3.8%)
	Italy	5 (3.1%)		Lithuania	1 (0.9%)
	Netherlands	25 (15.3%)		Poland	1 (0.9%)
	Norway	1 (0.6%)		Scotland	1 (0.9%)
	Romania	1 (0.6%)		Spain	12 (11.3%)
	United Kingdom	10 (6.1%)		Sweden	1 (0.9%)
North America	Canada	3 (1.8%)		Switzerland	1 (0.9%)
	Mexico	2 (1.2%)		The Netherlands	10 (9.4%)
	Puerto Rico	1 (0.6%)		United Kingdom	7 (6.6%)
	United States of America	68 (41.7%)	*North America*	Canada	3 (2.8%)
South America	Argentina	1 (0.6%)		United States of America	16 (15.1%)
Skin type			*South America*	Aruba	1 (0.9%)
Type I		26 (16.0%)		Brazil	1 (0.9%)
Type II		63 (38.7%)		Chile	4 (3.8%)
Type III		52 (31.9%)		Peru	1 (0.9%)
Type IV		15 (9.2%)	**Years of experience in the field of CMs**		
Type V		6 (3.7%)	0-<5 years		9 (8.5%)
Type VI		1 (0.6%)	5-<10 years		15 (14.2%)

Location of CM		10-<15 years	41 (38.7%)
Head and neck	106 (65.0%)	15-<20 years	22 (20.8%)
Mixed locations	46 (28.2%)	>20 years	41 (38.7%)
Lower extremities	7 (4.3%)	**Type of hospital**	
Trunk	2 (1.2%)	University hospital	80 (75.5%)
Upper extremities	2 (1.2%)	Urban hospital	5 (4.7%)
Presence of skin/soft tissue hypertrophy		Private clinic	9 (8.5%)
Yes	33 (20.2%)	Mixed	12 (11.3%)
No	130 (79.8%)	**Member of multidisciplinary working group**	
Sturge-Weber Syndrome (SWS)		Yes	77 (72.6%)
Yes	95 (58.3%)	No	22 (20.8%)
No	56 (34.4%)	Maybe	7 (6.6%)
I don't know	12 (7.4%)	**Number of new patients visiting the hospital annually**	
CM combined with another type of vascular malformation		0-20	12 (11.3%)
No	76 (46.6%)	20-100	53 (50.0%)
I don't know	40 (24.5%)	100-200	21 (19.8%)
Combination	24 (14.7%)	200-400	14 (13.2%)
Venous malformation	18 (11.0%)	>400	6 (5.7%)
Arteriovenous malformation	4 (2.5%)	**Number of new CM patients treated annually**	
Lymphatic malformation	1 (0.6%)	0-20	25 (23.6%)
Previous therapies		20-100	58 (54.7%)
Laser therapy	86 (52.8%)	100-200	13 (12.3%)
Camouflage	6 (3.7%)	200-400	7 (6.6%)
Surgery	3 (1.8%)	>400	3 (2.8%)
Combination of therapies	25 (15.3%)	**Types of vascular malformations treated**	
Other	4 (2.5%)	Only CMs	12 (11.3%)
No	39 (23.9%)	Combinations	94 (88.7%)
Currently undergoing therapy			
Yes	55 (33.7%)		
No	108 (66.3%)		

CM; capillary malformation, SWS; Sturge-Weber Syndrome, '*'; Data refer to the patients with the CM, not to their parents/caregivers, '**'; Educational levels were similar for all countries, except for Dutch patients. The Dutch 'MBO' and 'HBO' educational levels were categorized in the 'associate degree' group.

Table 2. Number of participants and response rates per e-Delphi study round.

Round 1	
Patients	163
Experts	106
Total (RR)	**269 (unknown)˜**
Round 2	
Patients	99
Experts	90
Total (RR)	**189 (70)**
Round 3	
Patients	65
Experts	83
Total (RR*)(RR)**	**148 (78) (55)**

Data is presented as *n;* RR= Response rate; '˜'= RR of first round could not be determined, as participants were invited via various ways, including open invitations via social media accounts of patient organizations and personal contacts of CM experts; '*'= percentage relative to previous round; '**'= percentage relative to first round.

Table 3. Overview of the outcome subdomains that were rated as 'important' or 'crucial' by each stakeholder group per e-Delphi study round.

Outcome Domain	Outcome subdomains rated as important/crucial by a stakeholder group	First Round		Second Round		Third Round	
		Patients	*Experts*	*Patients*	*Experts*	*Patients*	*Experts*
Clinical assessment	General appearance	58%	92%	74%	96%	78%	92%
	Colour	58%	92%	74%	89%	69%	90%
	Texture	65%	73%	75%	69%	77%	58%
	Thickness	62%	80%	80%	83%	IN	IN
	Size	61%	70%	69%	59%	71%	49%
	Skin stiffness	54%	25%	58%	18%	57%	11%
	Noticeability	60%	87%	74%	90%	80%	90%
	Facial deformity*	n/a	n/a	85%	92%	IN	IN
	Overgrowth of underlying structures*	n/a	n/a	87%	88%	IN	IN
Signs & symptoms	Bleeding	60%	64%	72%	47%	66%	33%
	Pain	62%	58%	74%	46%	75%	36%
	Itching	44%	31%	44%	13%	46%	10%
	Pyogenic granuloma	61%	57%	69%	38%	65%	24%
	Glaucoma*	n/a	n/a	80%	81%	IN	IN
	Infections*	n/a	n/a	61%	31%	65%	10%
	Eczema in the birthmark*	n/a	n/a	48%	17%	48%	2%
	Headache*	n/a	n/a	68%	30%	57%	19%
	Sensibility problems*	n/a	n/a	64%	30%	55%	14%
Health-related quality of life	Overall health-related quality of life	80%	88%	IN	IN	IN	IN
	Emotion functioning	85%	86%	IN	IN	IN	IN
	Cognitive functioning	67%	44%	72%	41%	85%	31%
	Social functioning	77%	88%	83%	91%	IN	IN
	Occupational (role) functioning	72%	66%	79%	68%	86%	67%
	Physical functioning	74%	66%	82%	77%	89%	77%
	Family impact	57%	51%	61%	42%	55%	30%
	Perception of cosmetic results	53%	76%	64%	81%	69%	82%
	Perception of functional results	62%	69%	72%	61%	77%	52%
	Perception of symptoms related to CMs	59%	59%	73%	38%	60%	46%
	Perception of CM severity	63%	71%	75%	67%	75%	59%
	Coping	63%	66%	71%	58%	82%	45%
Treatment	Adherence to treatment	60%	69%	70%	72%	75%	76%
	Number of required treatment procedures	56%	75%	68%	77%	75%	76%
	Total duration of treatment process*	n/a	n/a	59%	53%	55%	30%
	Tolerability of the intervention	67%	77%	73%	88%	80%	88%
	Patient satisfaction with treatment results	74%	91%	85%	94%	IN	IN
	Recurrence*	n/a	n/a	77%	88%	82%	80%
Adverse events	Pain	72%	79%	78%	77%	78%	72%
	Bruising	58%	39%	46%	23%	51%	13%
	Wound	62%	74%	67%	63%	60%	43%
	Hypopigmentation	42%	67%	44%	54%	40%	35%
	Hyperpigmentation	50%	59%	54%	49%	54%	40%
	Hypertrophic scarring	61%	86%	65%	84%	69%	77%
	Atrophic scarring	52%	75%	57%	67%	60%	43%
	Blistering	61%	55%	58%	32%	57%	16%
	Crusting	53%	47%	58%	24%	58%	6%

	Swelling	56%	35%	56%	10%	60%	4%
	Textural changes	62%	57%	66%	34%	68%	19%
	Bleeding	66%	56%	69%	27%	60%	20%
	Pyogenic granuloma	64%	45%	68%	26%	68%	13%
	Adverse events of anesthetics	57%	54%	58%	42%	62%	28%
	Burning of skin*	n/a	n/a	62%	34%	65%	17%
	Itching*	n/a	n/a	47%	13%	42%	4%
	Infection*	n/a	n/a	65%	37%	66%	17%
	Eczema in birthmark*	n/a	n/a	55%	21%	46%	7%
PRACTICAL ISSUES	Treatment costs	63%	59%	61%	56%	72%	52%
	Number of hospital visits	55%	60%	58%	49%	62%	34%

CM; capillary malformation, '*'; Outcome subdomains proposed by stakeholders during the first e-Delphi round. Green = Consensus reached on the importance of an outcome subdomain.

Table 4 Results and comments online consensus meeting

Outcome domains	Outcome subdomains	Results after last e-Delphi round	Votes	Final results	Comments from consensus meeting
CLINICAL ASSESSMENT	General appearance	?	Vote IN: Patients 6/10 (60%), Experts 22/41 (54%)	OUT	This outcome subdomain is covered by noticeability
	Colour	?	Vote IN: Patients 10/10 (100%), Experts 36/38 (95%)	IN	
	Texture	-	~	OUT	
	Thickness	+	n/a	IN	
	Size	-	~	OUT	
	Skin stiffness	-	~	OUT	
	Noticeability	+	n/a	IN	
	Facial deformity*	+	Vote for combining into 'Distortion of anatomical contours': Patients 9/11 (82%), Experts 36/41 (88%)	IN ('Distortion of anatomical contours')	Overlap with overgrowth of underlying structures, new vote was suggested to combine both
	Overgrowth of underlying structures*	+	Vote for combining into 'Distortion of anatomical contours': Patients 9/11 (82%), Experts 36/41 (88%)	IN ('Distortion of anatomical contours')	Overlap with facial deformity, new vote was suggested to combine both
SIGNS & SYMPTOMS	Bleeding	-	~	OUT	
	Pain	-	~	OUT	
	Itching	-	~	OUT	
	Pyogenic granuloma	-	~	OUT	
	Glaucoma*	+	Vote to remove glaucoma from the CDS: Patients 8/11 (73%), Experts 35/41 (84%)	IN	Glaucoma only occurs in a minority of the patients with CMs and it is debatable if it really is an outcome subdomain
	Infections*	-	~	OUT	
	Eczema in the birthmark*	-	~	OUT	
	Headache*	-	~	OUT	
	Sensibility problems*	-	~	OUT	
HEALTH-RELATED QUALITY OF LIFE	Overall health-related quality of life	+	n/a	IN	
	Emotional functioning	+	n/a	IN	
	Cognitive functioning	?	Votes IN: Patients 5/9 (56%), Experts 2/36 (6%)	OUT	It is rarely affected by CMs
	Social functioning	+	n/a	IN	
	Occupational (role) functioning	?	Votes IN: Patients 11/11 (100%), Experts 13/35 (37%)	OUT	
	Physical functioning	?	Votes IN: Patients 6/8 (75%), Experts 10/37 (27%)	OUT	It is only relevant in a selected group of patients with CMs
	Family impact	-	~	OUT	
	Perception of cosmetic results	?	Votes IN: Patients 9/10 (90%), Experts 25/37 (68%)	OUT	
	Perception of functional results	-	~	OUT	
	Perception of symptoms related to CMs	-	~	OUT	
	Perception of CM severity	-	~	OUT	
	Coping	?	Votes IN: Patients 10/10 (100%), Experts 7/37 (19%)	OUT	
TREATMENT	Adherence to treatment	-	~	OUT	
	Number of required treatment procedures	-	~	OUT	
	Total duration of treatment process*	-	~	OUT	

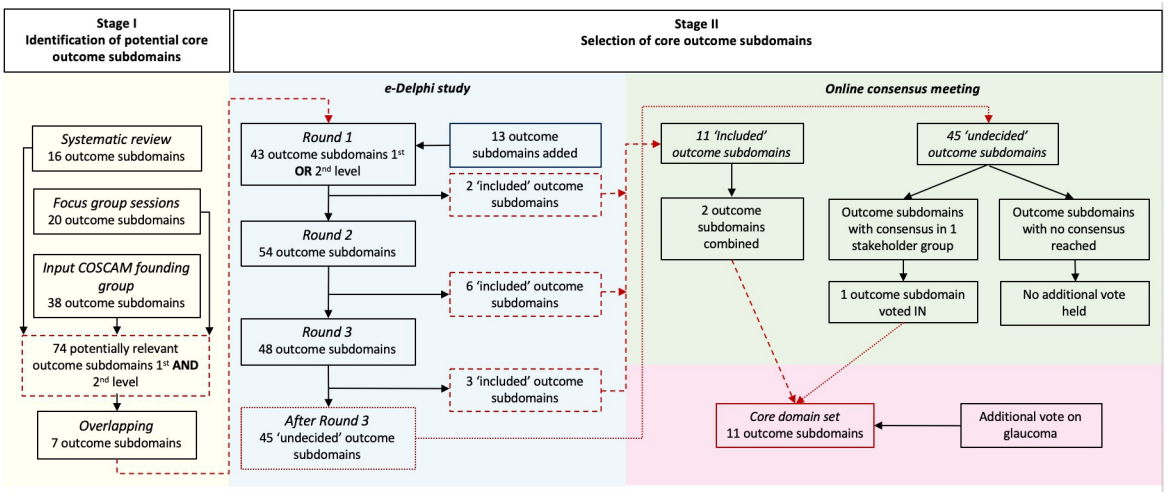
	Tolerability of intervention	+	n/a	IN	
	Patient satisfaction with treatment results	+	n/a	IN	
	Recurrence*	+	Vote to remove 'Recurrence' from the CDS: Patients 2/10 (20%), Experts 12/38 (32%)	IN	Some see recurrence as a separate outcome subdomain that should be covered by a measurement instrument, yet others see it as a repeated measurement of other core outcome subdomains.
ADVERSE EVENTS	Pain	-	~	OUT	
	Bruising	-	~	OUT	
	Wound	-	~	OUT	
	Hypopigmentation	-	~	OUT	
	Hyperpigmentation	-	~	OUT	
	Hypertrophic scarring	-	~	OUT	
	Atrophic scarring	-	~	OUT	
	Blistering	-	~	OUT	
	Crusting	-	~	OUT	
	Swelling	-	~	OUT	
	Textural changes	-	~	OUT	
	Bleeding	-	~	OUT	
	Pyogenic granuloma	-	~	OUT	
	Adverse events of anesthetics	-	~	OUT	
	Burning of skin*	-	~	OUT	
	Itching*	-	~	OUT	
	Infection*	-	~	OUT	
	Eczema in birthmark*	-	~	OUT	
PRACTICAL ISSUES	Treatment costs	-	~	OUT	
	Number of hospital visits	-	~	OUT	

'*' = outcome subdomains suggested in the first e-Delphi round, '+' = included in the CDS, '?' = undecided outcome subdomains with consensus in only 1 stakeholder group, '-' = undecided outcome subdomains with no consensus reached in both stakeholder groups, 'x' = excluded from the CDS, '~' = no vote was held during the consensus meeting, as this outcome subdomain was not found important enough by both stakeholder groups during the e-Delphi study and there were no strong advocates during the consensus meeting to open a vote, 'n/a' = not applicable, CMs = capillary malformations

Table 5 Final CDS for capillary malformations in clinical research

CORE AREA	OUTCOME DOMAIN	SUB-DOMAIN 1ST LEVEL	SUB-DOMAIN 2ND LEVEL
(Skin) Pathophysiological manifestations	*Clinical assessment*	Appearance	Colour/redness Thickness Noticeability Distortion of anatomical structures
		Signs and symptoms	*Glaucoma**
Life impact	*Quality of Life*	Overall QoL	Overall health-related QoL
		Functioning	Emotional functioning Social functioning
	Treatment	Tolerability of intervention	
		Patient satisfaction with treatment results	Satisfaction with cosmetic and/or functional outcome
		Recurrence	

CDS; Core outcome domain set, QoL; Quality of life. '*'; should only be measured based on the proposed conditions.



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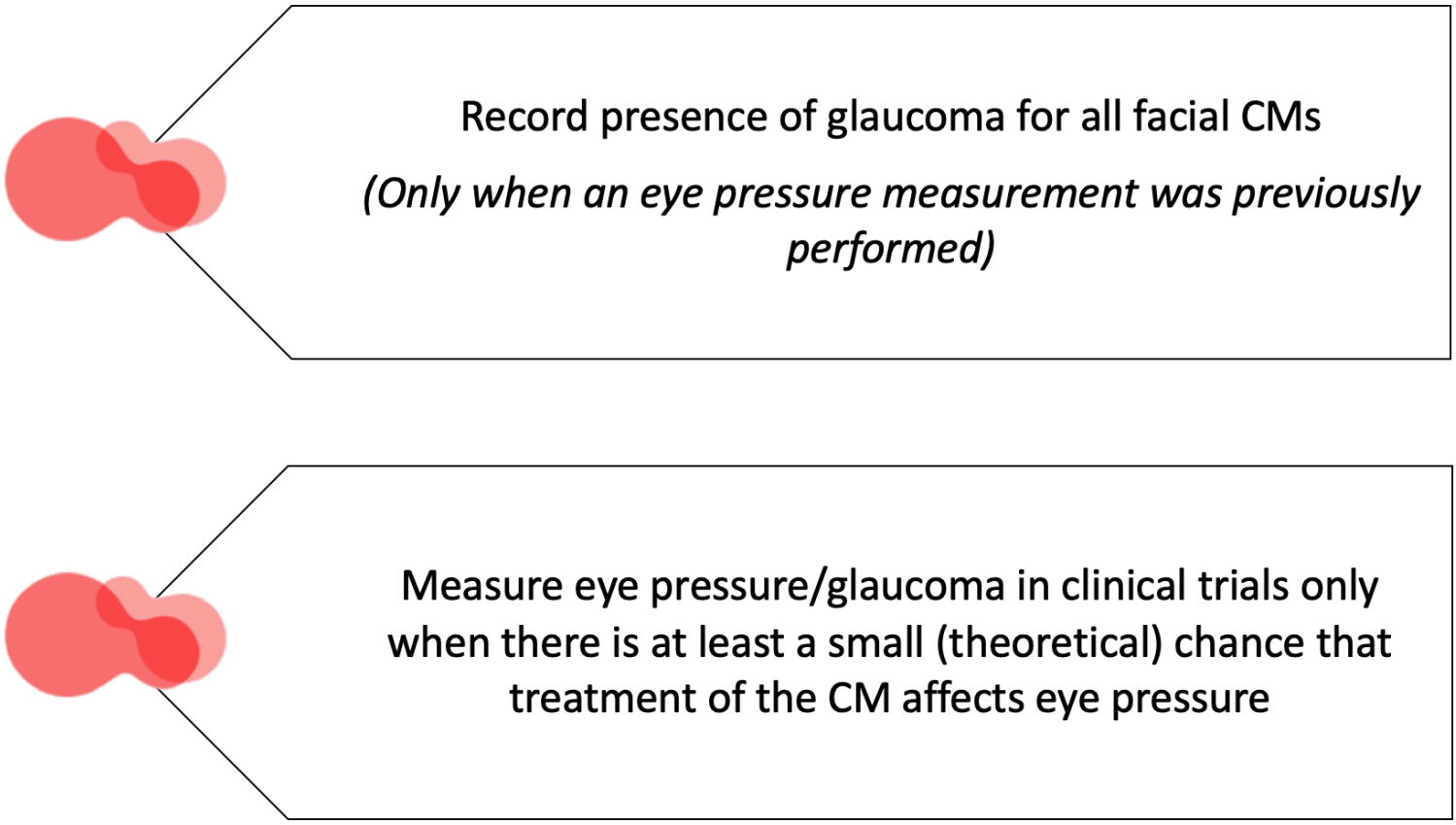

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