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ORIGINAL ARTICLE

Development of a core outcome domain set for clinical research on capillary malformations (the COSCAM project)

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Abstract

Background Due to a large variety in treatment outcomes reported in therapeutic trials and lacking patient-relevant outcomes, it is hard to adequately compare and improve current therapies for patients with capillary malformations (CMs). The Core Outcome Set for Capillary Malformations (COSCAM) project aims to develop a core outcome set (COS) for use in future CM trials, in which we will first develop a core outcome (sub)domain set (CDS). Here, we describe the methods for the development of a CDS and present the results of the first development stage.

Methods The COSCAM project is carried out according to the recommendations of the Cochrane Skin Core OUtcomes Set INitiative (CS-COUSIN) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative. During the first stage, we identified all potentially relevant outcome subdomains based on a systematic review, two focus group sessions and input from patient representatives of Dutch patient organizations and the COSCAM-founding group. In stage two, we will present the subdomains in a three-round e-Delphi study and online consensus meeting, in which CM patients, parents/caregivers and CM experts worldwide rate the importance of the proposed subdomains, hereby finalizing the core outcome (sub)domains of the CDS.

Results A total of 67 potential outcome subdomains were included; sixteen were previously used in the literature, 20 were proposed by Dutch patients and their parents/caregivers (n = 13) in focus group sessions and 38 were suggested by the experts of the COSCAM-founding group. Seven were excluded because of overlap.

Conclusion The final CDS may serve as a minimum standard in future CM trials, thereby facilitating adequate comparison of treatment outcomes. After this CDS development, we will select appropriate outcome measurement instruments to measure the core outcome subdomains.

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Conflicts of interest

Dr. Haedersdal reports grants from Leo Pharma, grants from Procter and Gamble, non-financial support from Cherry Imaging, non-financial support from Cynosure-Hologic, grants and non-financial support from Lutronic, grants and non-financial support from Mirai Medical, grants and non-financial support from Novoxel, non-financial support from Perfaction Technologies, outside the submitted work. Dr. Kelly reports grants and other from Michaelson Diagnostics, personal fees and other from Sciton, personal fees from IQVIA, other from Candela, outside the submitted work; and Board member of the American Society for Lasers in Surgery and Medicine. Dr. Robertson reports personal fees from Candela, outside the submitted work. Prof. dr. Spuls has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received a departmental independent research grant for TREAT NL registry Pharma since December 2019 for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of, e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and one of the main investigator of the SECURE-AD registry. The other authors have nothing to declare.

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Introduction

Capillary malformations (CMs), also known as port-wine stains or birthmarks, are red-to-purple lesions affecting the dermis and are present at birth.[1] These congenital lesions have been associated with somatic mosaic mutations in the *GNA* (Q or 11) and *Pik3ca* gene.[2-4] They occur in 0.04–2.1% of newborns and frequently appear as flat, pink macules that may gradually evolve into more hypertrophic, red-to-purple lesions.[5,6] About two-thirds of the patients develop nodular or papular elements as a result of soft tissue overgrowth, possibly leading to asymmetry, dysmorphosis and sporadic spontaneous bleeding.[7-9] Furthermore, most CMs are located on the head and neck and have shown to seriously affect health-related quality of life (HRQoL), ranging from impaired emotional HRQoL to functional problems.[10] Over the last decades, the pulsed dye laser has been the treatment of choice. However, its effectiveness in terms of clearance rate has barely improved over the last decades, with post-treatment recurrences still possible leaving patients with a desire for improved treatment regimens.[11]

The existence of broad diverse treatment outcomes reported in CM research coupled with a lack of outcome measures relevant to patients poses challenges to improvement in the current treatment approach.[12] The development of a core outcome set (COS) may help reduce heterogeneity in outcome reporting and focus on more patient-relevant outcomes. A COS, containing a core outcome domain set (CDS) and a core outcome measurement set (COMS), comprises a minimum set of outcomes that should be measured and reported in clinical research when studying a specific health condition.[13,14] Thus, a COS comprises *what* (outcome domains and subdomains) should be measured and *how* to do so (outcome measurement instruments). A recent taxonomy, which classifies outcomes according to a hierarchy in core areas, domain and subdomain levels, was published to use as a starting point for dermatological COS developers.[15] Developing a COS has become a prerequisite to conduct meaningful research in the field of dermatology.[16-20] Delphi studies in particular have proven essential in the development of COSs, e.g. for atopic dermatitis and congenital melanocytic nevi.[17,20] Concerning vascular malformations, such a set of outcomes was recently developed for peripheral lymphatic, venous and arteriovenous malformations in the OVAMA-project.[16] Yet, no COS exists for CMs.

This Core Outcome Set for CApillary Malformations (COSCAM) project first aims to reach international consensus on a CDS as part of a COS, in order to unify outcome use and reporting for CMs worldwide. Here, we describe the methods to develop a CDS and present the results of the first development stage.

Methods/design

The research team

The research team consists of the COSCAM founding group and the international COSCAM steering group. The main responsibility of the founding group is the daily management of the study. It includes two methodological experts, one researcher, one plastic surgeon, one plastic surgeon in training and one dermatologist from the Amsterdam UMC. International CM experts form the steering group and contribute to crucial points in the study process (i.e. protocol development, stakeholder recruitment and the international consensus meeting).

Table 1 Outcome definitions according to the proposed hierarchy by Lange et al.[15]

Core Area	'An aspect of health or a health condition that needs to be measured to appropriately assess the effects of a health intervention. Core Areas are broad concepts consisting of a number of more specific concepts called outcome domains. Example: Life Impact'.
Outcome Domain	'Component of a Core Area: a concept to be measured, a further specification of an aspect of health, categorized within a core area. Example: Quality of Life'.
Outcome Subdomain level 1	'Component of an Outcome Domain: a concept to be measured, a further specification of an aspect of health, categorized within an Outcome Domain. Example: functioning'.
Outcome Subdomain level 2	'Component of an Outcome Domain: a concept to be measured, a further specification of an aspect of health, categorized within an Outcome Subdomain. Example: physical functioning'.

Definitions retrieved from Lange et al.[15]

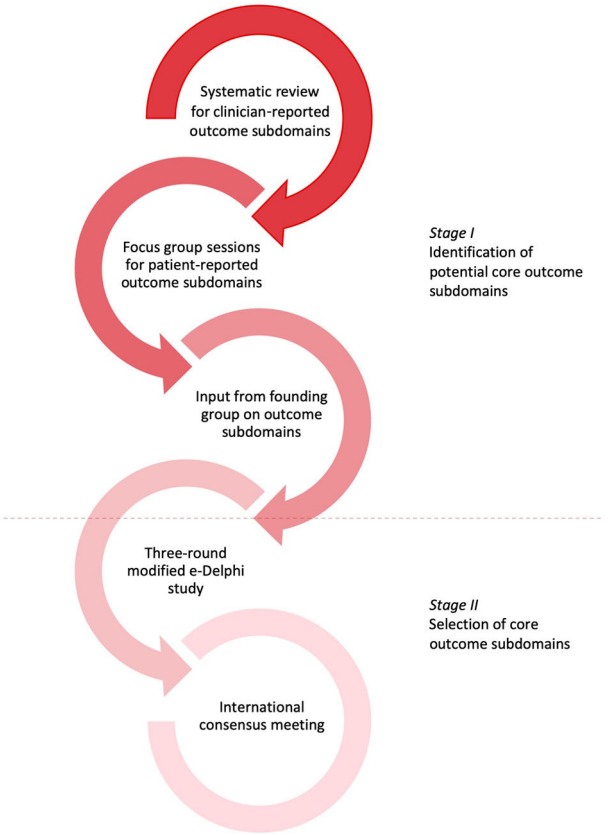

Figure 1 General developmental stages of the CDS.

Study design

The COSCAM project was registered at the Core Outcome Measures in Effectiveness Trials (COMET) website (http://www.comet-initiative.org/Studies/Details/1599; registration number: 1599) and the Cochrane Skin Core Outcome Set INitiative (CS-COUSIN) website (http://cs-cousin.org/coscam/). The steps of the HOME (Harmonizing Outcome Measures for Eczema) initiative roadmap and the COS-STAD (Core Outcome Set-STAndards for Development) guidelines will be followed to serve as a directory for the development of the CDS.[20,21] The recently proposed dermatological taxonomy by Lange *et al.*[15] will be used to categorize the outcomes into outcome domains and subdomains (see Table 1 for definitions). Additionally, the systematic review by Boulkedid *et al.*[22] provided guidance for the design of the Delphi study. The results of the Delphi study will be reported according to the Core Outcome Set- STAndards for Reporting (COS-STAR) checklist.[23]

Developmental stages of the CDS

The overall development stages of the CDS can be found in Fig. 1.

Stage I – Identification of potential outcome subdomains As the first step of stage I was already completed before the start of this project, predominantly clinician-reported outcome subdomains could be retrieved from a systematic review (literature search from 2005 to May 2020).[12] Next, two small online focus group sessions, including nine Dutch CM patients and/or their parents/caregivers, were organized to collect patient-reported outcome subdomains. The focus group sessions were conducted in May 2020. Patients visiting the outpatient clinic of the Amsterdam UMC between March and May 2020 were invited by telephone and joined following verbal consent. Two experienced researchers designed prespecified open questions and led the online meetings. The questions were discussed, ranging from the patients' experience with their CM to treatment outcomes. The sessions were audio-recorded, transcribed and analysed for content. In the analysis, topics were extracted, grouped and translated into English. Patient representatives of two Dutch patient organizations (n = 4) were asked to add potentially missing outcome subdomains. The list with retrieved clinician-reported and patient-reported subdomains was discussed with the founding group and complemented (Table 2) according to the taxonomy by *Lange et al.* Subsequently, a final list with potentially relevant outcome (sub)domains (1st and 2nd level; see Table 1 for outcome definitions) was generated. The study protocol and list with potential outcome subdomains was checked and approved by the CS-COUSIN methods working group and the COSCAM steering group prior to its application in the e-Delphi study.

Stage II – Selection of core outcome subdomains This stage entails an international modified e-Delphi study (i.e. an e-Delphi method with a set number of study rounds) followed by

Table 2 Proposed outcome domains and subdomains for capillary malformations in clinical research

Core area	Outcome domain	Subdomain 1st level	Subdomain 2nd level
(Skin) Pathophysiological manifestations	Clinical assessment	Appearance†	General appearance§
			Redness§
			Texture†
			Thickness§
			Size§
			Skin stiffness†
			Noticeability‡
		Signs and symptoms¶	Bleeding§
			Pain†
			Itching†
			Pyogenic granuloma¶
Life impact	Health-related Quality of Life	Overall HRQoL¶	Overall HRQoL¶
		Functioning¶	Emotional functioning‡
			Cognitive functioning¶
			Social functioning‡
			Occupational (role) functioning‡
			Physical functioning¶
		Family impact¶	Burden for parents/caregivers¶
			Parental HRQoL¶
		Perception of health¶	Perception of cosmetic results¶
			Perception of functional results¶
		Global perception of disease¶	Perception of symptoms related to CMs (e.g. sleeping problems)¶
			Perception of CM severity¶
		Coping¶	Specific skin (care) behavior‡
	Treatment	Adherence to treatment¶	Satisfaction with cosmetic and/or functional outcome‡
		No of required procedures‡	
		Tolerability of intervention¶	
		Patient satisfaction with treatment result§	
	Treatment adverse events	Pain‡	Presence and severity of pain¶
		Bruising‡	Presence and severity of bruising¶
		Wound‡	Presence and severity of wound¶
		Hypopigmentation†	Presence and severity of hypopigmentation¶
		Hyperpigmentation†	Presence and severity of hyperpigmentation¶
		Hypertrophic scarring†	Presence and severity of hypertrophic scarring¶
		Atrophic scarring†	Presence and severity of atrophic scarring¶
		Blistering‡	Presence and severity of blistering¶
		Crusting§	Presence and severity of crusting¶
		Swelling‡	Presence and severity of swelling¶
		Textural changes¶	Presence and severity of textural changes¶
		Bleeding¶	Presence and severity of bleeding¶
		Pyogenic granuloma¶	Presence and severity of pyogenic granuloma¶
		Adverse events of anesthetics‡	Presence and severity of adverse events of anesthetics¶
Practical issues	Economic	Treatment costs¶	
	Hospital	Number of hospital visits¶	

CM; capillary malformation, HRQoL; Health-related Quality of life.
†Outcome subdomains retrieved from a systematic review.
‡Patient-reported outcome subdomains collected from focus group sessions
§Overlapping outcome subdomains, as collected from a systematic review and focus group sessions.
¶Subdomains complemented by the COSCAM-founding group based on the taxonomy by Lange *et al* (2020).

a consensus meeting. The design and number of study rounds of this three-round e-Delphi study are based on common methods used in previously published COS studies.[16,17,24-26]

Stakeholders

Participants of the e-Delphi study comprise CM patients from various countries and an international group of CM experts. Selection criteria per stakeholder group are listed in Table 3. No official consensus exists on how many participants should be involved with an e-Delphi study.[27,28] We aim to include as many international CM experts and CM patients as possible, while striving for a representative group of people from various cultural and demographic backgrounds. Each member of the international COSCAM steering group will be responsible for

Table 3 Selection criteria per stakeholder group for the e-Delphi study

CM experts	CM patients and parents/caregivers
Inclusion criteria: • Physicians from different countries specialized in treating CMs • Prolific writers who published on CMs in the last 10 years, with sufficient expertise on measuring treatment outcome, such as researchers.	**Inclusion criteria:** • Patients from different countries or their parents/caregivers with a skin CM • All types of skin CMs, including CMs as part of a syndrome (e.g. Sturge-Weber syndrome) • CMs combined with another type of vascular malformation • CMs of all locations (head and neck, extremities and trunk) • Both sexes, all ages, all cultural and socioeconomic backgrounds • Patients with or without previous CM treatment
Exclusion criteria: • Physicians or prolific writers without any expertise in the field of CMs	**Exclusion criteria:** • Patients with mix of vascular malformations, in which no capillary malformation is present • Participants with solely 'central nervous system' CMs (leptomeningeal) or glaucoma • Participants who are unable to give consent or fill in questionnaires

CM, capillary malformation.

recruiting 5-10 CM patients and CM experts from their country. We aim to include at least 100 participants in total (CM patients, parents/caregivers and CM experts).[17] Since a 30% response rate among the invited participants is commonly expected, we aim to invite a total of approximately 300 participants.

CM experts CM expert selection criteria are presented in Table 3. Experts will be 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. Most of the COSCAM-founding group and steering group members are considered CM experts and therefore eligible for participation in the e-Delphi study.

CM Patients and parents/caregivers CM patient selection criteria are shown in Table 3. Patients aged 16 and over are invited to complete the survey themselves, if possible. For patients who are unable to complete the survey alone, and for patients below 16 years of age, the parent or caretaker will be asked to complete the survey. All participating patients will be approached and informed in person or via email by the COSCAM steering group, participating CM experts and through patient organizations from the Netherlands, Belgium, UK, Spain, Italy and USA. Patients may also register themselves via social media advertising on the social media channels (Facebook or Instagram) of the national and foreign patient organizations. At the start of the e-Delphi study, patients will be asked for their consent to use their data anonymously.

e-Delphi survey procedure

At the first round, general information will be given about the aim and content of the survey. The participants will be presented with the list of potentially relevant outcome subdomains via online Dutch and English surveys (by means of Google forms and Paperform) in lay language. In the first round, participants may also propose other relevant (missing) outcome subdomains concerning CMs. Data on baseline characteristics of the participants will be collected anonymously to allow for subgroup analyses. For the CM expert group, we will collect data on their specialty, years of experience, country of employment, type of hospital, member of multidisciplinary working group, and number of new patients seen and treated annually. For the CM patient and parent/caregiver group, we will collect data on educational level, age of the patient, country of residence, skin type, location of the CM, presence of hypertrophy, previous and current therapies and whether the CM is part of the Surge-Weber syndrome or other type of vascular anomaly.

Participants will have 4–6 weeks per round to fill out the survey. Reminders will be sent frequently. If the response rate is below 70%, an extra week is given to fill out the survey. Only participants who have completed all previous rounds will be invited for the next.

In the two subsequent rounds, participants will anonymously receive feedback on the scores of the previous round of both stakeholder groups. The outcome subdomains on which no consensus is reached are to be re-evaluated. Also, the proposed outcome subdomains suggested in the first round will be rated. Eventually, after three study rounds, the outcome subdomains will be labelled as '*excluded from the CDS*' (consensus on non-importance in both stakeholder groups), 'included in the CDS' (consensus on the importance in both stakeholder groups) or 'undecided' (no consensus on the importance reached yet, or consensus reached in only one stakeholder group).

Definition of consensus In each study round, participants can rate the importance of the proposed outcome subdomains on a seven-point Likert scale[1-7] (Table 4). Currently, there are no strict standards on the appropriate level of consensus for Delphi studies. This, however, depends on the importance of the issue for which consensus is required. As we aim to determine the fundamental outcome subdomains needed in clinical research for CMs, we therefore stipulate that an 80% level of consensus is fitting, which is in agreement with other e-Delphi studies.[16,29,30] If ≥80% of the CM expert group and ≥80% of the CM patient/parent/caregiver group both score an outcome subdomain a six or seven, it is deemed 'important' or 'crucial', respectively, and is included in the CDS. Outcome subdomains will be

Table 4 Scoring system for the importance of individual capillary malformation subdomains

Very unimportant	Unimportant	Slightly unimportant	Neutral	Slightly important	Important	Crucial
1	2	3	4	5	6	7
O	O	O	O	O	O	O

Scores of 6 ('important') or 7 ('crucial') and 1 ('very unimportant') or 2 ('unimportant') are counted towards in- or exclusion of a subdomain, respectively.
Red color means an outcome subdomain is 'unimportant'.
Orange color means an outcome subdomain is 'not important enough'.
Green color means an outcome subdomain is 'important/crucial'.

excluded from the CDS when there is ≥80% agreement on score one or two on the Likert scale in both stakeholder groups.

Consensus meeting

Following the third study round, the '*undecided*' outcome subdomains will be discussed in an international online consensus meeting. This meeting will be held with the COSCAM steering group and stakeholders who completed at least two e-Delphi rounds to reach a final IN or OUT decision for the remaining outcome subdomains. This vote will be held separately for the CM patient group and the CM expert group. When 80% or more of the participants in both stakeholder groups vote IN, the outcome subdomain will be included in the CDS. Otherwise, the outcome subdomain will be excluded. The final core outcome subdomains will be classified according to the prespecified outcome domains as proposed by Lange *et al.*[15]

Data analyses

Data will be analysed and presented in absolute numbers and percentages. The percentage agreement in each e-Delphi round will be calculated for all outcome subdomains. The results will be presented separately for the CM experts and the CM patient/parent/caregiver group. Furthermore, we will separately analyse results for patients with Sturge-Weber syndrome or a CM combined with another type of vascular malformation, to find any differences in relevant outcome subdomains between these subgroups.

Ethics approval and consent

The Medical Ethics Review Board of the Amsterdam University Medical Center location AMC confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) does not apply to this study (Committee reference number: W20_351 # 20.389). Hence, a full review of this study was not required. The Board waived the need for a written informed consent. Participants will, however, need to give online consent at the beginning of the first survey, for their data to be used anonymously.

Results

During the first stage of the CDS development, a total of 67 potential outcome subdomains (1st and 2nd level) were recognized (see Table 2). Sixteen, predominantly clinician-reported outcome subdomains, were retrieved from a previously published systematic review. These mostly focussed on CM appearance and treatment side-effects. In addition, 20 patient-reported outcome subdomains were collected from 13 Dutch CM patients and/or their parents/caregivers, of which seven overlapped with the outcome subdomains retrieved from the systematic review. The founding group complemented the list with 38 outcome subdomains. The results of the second stage will be published separately.

Discussion

This COSCAM study protocol describes the development process of a CDS for CMs as part of a COS for clinical research. The first development stage has been completed, which focussed on the identification of potential core outcome subdomains. Relatively few outcome subdomains were retrieved from the literature. Specifically, patient-reported clinical outcome subdomains were insufficiently reported, with no outcome subdomains on HRQoL or functioning.[12] This is remarkable since CM patients often experience a decreased HRQoL.[10] Furthermore, patient-reported outcome subdomains generally measured by Patient Reported Outcome Measures (PROMs) seem inevitable to ensure that treatment outcomes meet the patient's needs. Also, by integrating patient-reported outcomes, the principle of value-based health care, i.e. health care based on patient's individual needs and goals, is incorporated.[31] Even though a heightened importance has been put on the inclusion of patient-reported outcomes in dermatology, these relevant outcomes still seem to be lacking in CM trials.[12,18,19,32-34] Patient-reported outcome subdomains are therefore an important constituent in our CDS.

Once the CDS has been developed, we will focus on selecting appropriate outcome measurement instruments (OMI) measuring the core outcome subdomains according to the guidelines of the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative.[35] In a recent systematic review, the measurement properties of previously proposed and/or used OMIs for CMs were assessed using the COSMIN methodology.[36] However, the authors may have presented an incomplete overview of potential CM OMIs, as they did not follow the Harmonizing Outcome Measures for Eczema (HOME) roadmap recommending the establishment of a CDS prior to identifying adequate OMIs.[20] Only after the

development of the CDS, we will thus be able to determine whether the recommended OMIs cover all core outcome subdomains in the CDS, whether further OMI identification is needed or whether new OMIs need to be developed. The latter has been previously done for vitiligo and hidradenitis suppurativa outcome measurement.[37,38]

The development of the CDS will be the first step towards uniform CM outcome use and reporting worldwide, hereby facilitating adequate comparison of CM treatment outcomes. In addition, with the inclusion of patient-reported outcome subdomains in future CM trials, we aim to improve value-based health care. Lastly, the CDS may form the basis of internationally approved CM treatment guidelines, which are, until this date, still lacking.

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