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ORIGINAL ARTICLE

Protocol for the development of core set of domains of the core outcome set for patients with congenital melanocytic naevi (OCOMEN project)

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Abstract

Background Having large congenital melanocytic naevi (CMN) is associated with a psychosocial burden on patients and their parents because of its remarkable appearance and the extra care it may require. Large CMN also pose an increased risk of malignant melanoma or neurocutaneous melanosis. There is a lack of international consensus on what important outcome domains to measure in relation to treatment. This makes it difficult to compare options, to properly inform patients and their parents, and to set up treatment policy for CMN. Therefore, we aim to develop a core outcome set (COS), i.e. the minimum set of outcomes that are recommended to be measured and reported in all clinical trials of a specific health condition. This COS can be used in the follow-up of CMN patients with or without treatment, in clinical research and practice.

Methods In the Outcomes for Congenital Melanocytic Nevi (OCOMEN) projects, we follow the recommendations from the Core Outcome Measures in Effectiveness Trials (COMET) initiative and the Cochrane Skin Core Outcomes Set Initiative (CS-COUSIN). This project entails the following: (i) a systematic review to identify the previous reported outcomes in literature; (ii) focus groups with national and international patients and parents to identify patient-important outcomes; (iii) classification of outcomes into outcome domains; (iv) e-Delphi surveys in which stakeholders (patients/parents and professionals) can rate the importance of domains and outcomes; and (v) an online consensus meeting to finalize the core outcome domains of the COS.

Results The results will be disseminated by means of publication in a leading journal and presentations in international meetings or conferences. We engage international experts in CMN, both patients and professionals, to ensure the international utility and applicability of the COS.

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Conflicts of interest

We declare that we have no conflict of interest.

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Introduction

Scientific background and relevance

Congenital melanocytic naevi (CMN) are birthmarks that sometimes cover large areas of the body.[1–4] They are present at birth or appear within 3 months after birth. An estimated 1% of infants worldwide are born with CMN. However, large [>20 cm projected adult size (PAS)] and giant (>40 cm PAS) are rare, with an estimated incident of 1 : 20.000 and 1 : 50.000 infants, respectively.[5] CMN may be associated with a psychosocial burden on patients and their families due to

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their remarkable appearances and the extra care.[6] Large CMN also pose an increased risk of malignant melanoma, soft-tissue tumours or neurocutaneous melanosis.[7] Adequate treatment and monitoring the impact of CMN on patients' lives are therefore crucial. Different interventions for CMN such as laser, curettage and excision are available,[7] but conservative management such as watchful waiting is also possible. Patients with large CMN may undergo several surgeries, which do not always yield satisfactory cosmetic and functional results. It is also not clear whether these surgeries reduce the risk of melanoma.[7] Moreover, guidance on how to perform and the frequency of watchful waiting is not available. Scientific evidence on the best treatment policy in CMN is unfortunately still lacking.

To date, multiple articles describe the impact of having CMN or the effects of treatment on the lives of patients. However, a wide heterogeneity in outcomes used in these articles makes it difficult to combine, compare or contrast the results. Development of a 'core outcome set' (COS), i.e. the minimum set of outcomes that should be measured and reported in all clinical trials for a specific health condition, is an effective method to reduce heterogeneity and reporting bias in future CMN research.[8] In a strict sense, a COS consists of 'what' (outcome domains) and 'how' (outcome measurement instruments) to measure.[9] This project, the Outcomes for Congenital Melanocytic Nevi (OCOMEN), focuses first on the development of the core outcome domains, and what specific outcomes these domains need to cover. We define a domain as an aspect of disease that should be measured such as cognitive functioning,[10] whereas an outcome describes a subgranular concept/construct of a domain such as learning difficulties or memory lapse.[11] We aim to reach consensus on the core domains of the COS and initiate the selection of the outcomes of the domains that can be used in the follow-up of the CMN patients without, during and after treatment. We focus on patients with medium and larger sizes of CMN.[12]

Key objectives

The key objectives of the Outcomes for Congenital Melanocytic Nevi (OCOMEN) projects are as follows:

- To identify a list of outcomes as previously reported in the literature and proposed by patients/parents in the focus groups;
- To try to reach consensus on the domains and outcomes from the perspective of professionals and patients/parents;
- To compare those domains and outcomes from the perspectives of the professionals with those of the patients/parents; and
- To integrate the domains and outcomes important to professionals and patients/parents into a combined set of core outcome domains for clinical research and for practice

Scope definition and applicability of the COS

- Population: patients with medium size or larger CMN (Fig. 1).[12] This includes those patients with M1 (1.5–10 cm PAS) on the face or M2 (>10–20 cm PAS) elsewhere, either single or multiple. We chose this subgroup of patients with CMN because we expect that having medium size of CMN or larger may have a 'considerable' impact on patients' lives.
- Intervention: surgical (laser/curettage/excision) and conservative (watchful waiting).
- Setting: clinical research and practice.
- Geographical: International.

Methods

The research team

The research team consists of the 'Study Management Group' (SMG) and the 'Study Advisory Group' (SAG). The SMG is responsible for the day-to-day management of the study. It consists of two CMN experts, three methodological experts, four researchers, two plastic surgeons and three dermatologists, and one patient representative. The SAG consists of international CMN experts who provide their input at critical points of the study such as protocol development, stakeholder recruitment and the consensus meeting. The SMG and SAG both participated in the consensus process.

Study design

The OCOMEN project is registered at the Core Outcome Measures in Effectiveness Trials (COMET) website (http://www.comet-initiative.org/studies/details/1124) and the Cochrane Skin

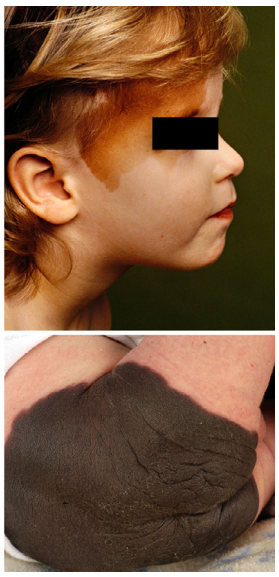

Figure 1 Congenital melanocytic naevi of a patient with medium size naevi on the face (upper) and of a patient with giant naevi on the lower back trunk (lower).

Core Outcomes Set Initiative (CS-COUSIN) website (http://cs-cousin.org/cos-project-groups). We used the guidelines of the COMET initiative and the CS-COUSIN.[9,13,14]

The study is done in two phases:

Phase 1: Identification of potential outcomes and domains important in clinical research and practice by means of:

1 A systematic review and review of clinical guidelines.
2 Focus group with patients and parents to include patient-important outcomes.
3 Classification of outcomes into domains.

Phase 2: A consensus process where relevant stakeholders (patients/parents and professionals) can rate the importance of the identified list of outcomes and domains to reach consensus on the domains of the COS. This is done by means of

1 Three rounds of e-Delphi survey.
2 Consensus meeting.

Phase 1: Identification of potential outcomes and domains

Phase 1.1: Systematic review The systematic review was registered in PROSPERO number CRD42018095235. We included all research that focuses on patients with CMN, regardless of age or sizes and locations of CMN. We looked at all types of CMN treatment: interventional (laser, curettage and excision) and conservative (watchful waiting). We did not perform quality assessment of methodological quality of the studies because we aim to include all outcomes regardless of the methodological quality of the studies.

We searched in PubMed, EMBASE (Ovid) and the Cochrane Library for relevant studies published between 2006 and 2018. We chose the year 2006 because Krengel *et al.*[12] published an article that year about the risk of melanoma being lower than previously thought. From then on, the focus of CMN treatment may have shifted to favour cosmetic results rather than prevention of melanoma. We engaged a clinical librarian to help with the search terms. Key words, MeSH terms and synonyms of 'Nevi', 'Congenital' or 'Giant' were used.

All English, Dutch, Italian or French human studies with 10 or more CMN patients that completed the investigated intervention were included. Original articles and systematic reviews are included, whereas letters to the editor, case reports, conference reports, books and descriptive reviews are excluded. Evidence of CMN diagnosis by means of histology or dermatoscopy is lacking. Therefore, we excluded studies that diagnosed CMN solely by histology or dermatoscopy.

Two reviewers selected articles and extracted the data independently. Disagreement was resolved by discussion and by consulting a third review author if necessary. The following data were extracted from the articles: authors, year of publication, study design, intervention, objectives, number of patients, age and gender of patients, location of CMN, size CMN, size classification system used and outcomes reported in the methods or results, including patient-reported outcomes and outcome measurement instruments. Information about outcome measurement instruments can later be used in a follow-up study on defining the core set of outcome measurement instruments for the domains identified in the current study.

We assessed the following: what outcomes and outcome measurement instrument are used, consistency in outcomes, number of times an outcome was used, number of patient-reported outcomes, consistency in size classification used, correlation between reported outcomes and size of CMN (when there is consistency in classification tools of the size of CMN) and correlation between outcomes and visibility of CMN (when descriptions of visible CMN are available).

To exhaust all potentially relevant outcomes for CMN, we also looked at existing guidelines. We found one guideline developed for clinical care of CMN patients.[7]

Phase 1.2: Focus groups The SMG worked together in recruiting patients and parents for the national focus groups. We also involved patients and parents from Europe and the United States through collaboration with the SAG and the international

Table 1 Summary of the focus group discussions

No	Date	Location	Parents/family	Patients
1	5 July 2018	Erasmus MC, the Netherlands	4 Dutch parents of giant CMN patients. All patients were treated	–
2	6 July 2018	Erasmus MC	5 Dutch parents	3 Dutch patients (2 teenagers and 1 child). All patients were treated
3	31 July 2018	Erasmus MC	3 Dutch parents. All patients were treated	–
4	12 September 2018	Paris, France	7 multinational parents	3 patients from European countries, all were treated
5	19 September 2018	Amsterdam UMC, the Netherlands	2 Dutch parents	4 Dutch patients (1 not treated)
6	20 September 2018	Online	–	4 patients in the United States and Canada (3 not treated)
7	24 September 2018	Amsterdam UMC	1 Dutch family member	4 Dutch patients. All were treated

patient support groups. A topic list, which contains open questions in lay language, was prepared. Questions ranged from the impact of having CMN on patients' lives to experiences with treatment. Experienced researchers in the focus group discussions facilitated the sessions. Participants signed an informed consent prior to each session. Participation is treated confidentially and semi-anonymously. Participants in a focus group knew who were participating in the same group, but they did not know other participants in the other focus groups.

We conducted three focus groups at the Erasmus MC, two at the Amsterdam UMC, the Netherlands, one in Paris, France, and one online by means of GoToMeeting application. The focus groups in the Netherlands were conducted in Dutch. Table 1 summarizes the stakeholders' background of the focus groups.

The process was audio-recorded, transcribed and analysed for content. Full data analysis was not done in this study as the purpose of these qualitative data was to identify the outcome. In the analysis, themes were picked up and grouped (Box 1). The themes from the Dutch focus groups were translated into English by two of our researchers.

Phase 1.3: Classification of outcomes into domains Outcomes identified in the review and focus groups were classified into domains by following the taxonomies published by the COMET initiative website.[10,15] Since CMN is a specific skin condition, we also consulted the WHO website for a more detailed classification of the skin anatomy and functions (http://apps.who.int/classifications/icfbrowser/).

Two researchers did this grouping independently. Differences were discussed and solved by the SMG. The preliminary list of outcome domains is included in the consensus process (Fig. 2).

Phase 2: Consensus process

Phase 2.1: Delphi study Relevant stakeholders were presented with the identified list of domains and outcomes. They were asked to rate the importance of these domains and outcomes in three rounds of e-Delphi surveys. Stakeholders consist of two groups: patient/parents and professionals. We approached the stakeholders by the aid of international patient support organizations, among other patient networks from the UK, Germany, Belgium and the Netherlands. A detailed description of stakeholders' recruitment and methods used to approach them is presented in Table 2. Patients/parents who showed interest in participating were formally invited through email. There is no guideline to optimal sample size for the Delphi method.[16,17] In general, having more participants will increase the reliability of groups' judgement.[18] Nevertheless, a small sample size of experts in the field of interest can provide reliable knowledge.[17] We aimed at having 100 participants in total (patients/parents and professionals). Variable response rates in Delphi studies have been reported.[17,19] We anticipated a response rate around 30% to the invitation for participation. Therefore, we invited around 300 stakeholders in equal proportion to participate in the study.

We prepared the list of domains and outcomes in lay language. A patient/parent representative and a native English speaker reviewed the test version of the survey to ensure clarity and ease of use. We informed participants that agreeing to

Box 1 Themes abstracted from the transcripts of the focus groups

1. Lack of information on the condition
2. Frightening when first time see the CMN
3. Try to cover the naevi vs. not bothered by visibility of naevi
4. Very self-conscious about the naevi
5. Try to find others with the same condition
6. Satisfied with treatment choice
7. Scare of bullying
8. Understanding/knowing about the condition helps with coping
9. Acceptance of having the CMN
10. Support from a therapist or psychologist is well-appreciated
11. Negative body image
12. Dark) colour of the naevi
13. Hairiness of the naevi
14. Satisfied with life
15. Scars
16. Comfortable with having scars
17. Skin graft
18. Support from patient network
19. The risk of having cancer
20. Work on the body image
21. Would not recommend to have surgeries
22. Having CMN has made a patient tough (affects the personality)
23. Rejection (hard making friends) because of CMN
24. Missed (3 years of) school due to surgeries
25. Support from school
26. Parents' behaviour influences the way a patient sees the CMN
27. Itch
28. Asymmetrical size of body parts due to the naevi
29. Accept CMN as a natural tattoo (in a cool way)
30. Very emotional period around the first-time diagnosis and surgeries
31. Addiction to morphine
32. Neurological complications
33. Feeling guilty because of having a CMN child

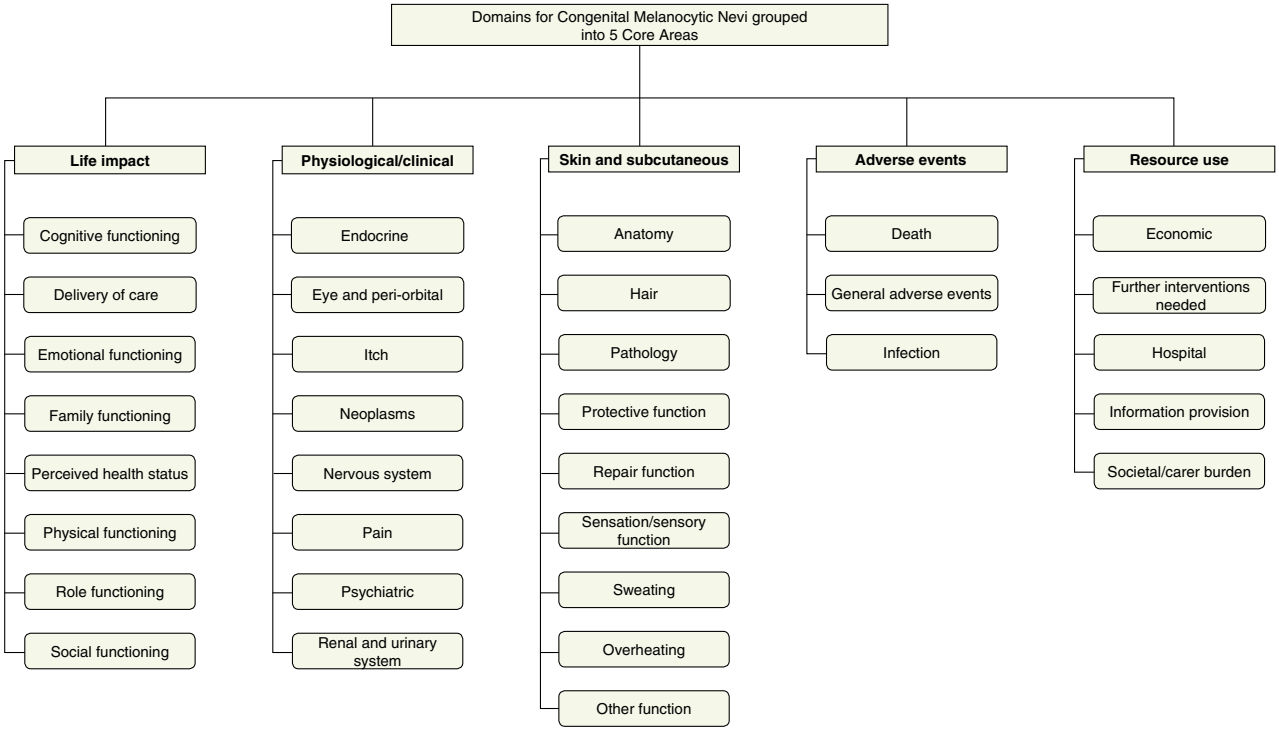

Figure 2 Preliminary list of outcome domains presented in five core areas for the e-Delphi rounds.

Table 2 Stakeholders groups and methods of approaching potential participants

Stakeholder groups	Details	Methods of approach
Patients and parents	Patients Parents/caregivers* Family members	• Identification via the Erasmus MC and Amsterdam UMC database. Invitation to participate is done via email • Call for participation, in collaboration with patient advocates, on the websites and social media of international patient support organizations such as Naevus Network Netherlands, Naevus Global, Nävus-Netzwerk Deutschland, Nevus Outreach, Caring Matters Now and Naevus International
Professionals**	Dermatologists Plastic surgeons Paediatricians Pathologists Neurologists Psychologists Researchers	• Identification of names from the literature, attendance of meetings/conferences in paediatric dermatology/plastic surgery and trough personal network of the SMG. Invitation to participate is done by email • Snowball-sampling method: Ask professionals to suggest names of other professionals who may be interested to participate. We approached those names by email and invited them to participate • Call for participants on the Naevus International website and their first meeting in Paris, France (12 September 2018)

* Parents can fill out the survey based on their own personal perspective or on behalf of their young child. In the latter case, they need to do the rating based on the child's perspective.
**Patients/parents who also happen to be one of the professionals can choose in which role (as a professional or patient/parent) they would like to fill out the survey.

participation implies that participants give consent to retaining their background information and their rating anonymously. Participants were given 1–2 weeks to fill out the survey, and reminders were sent frequently. If the response rate is <70%, an extra week is given to accomplish the task. Only participants who completed a round will be invited for the subsequent round.

Table 3 presents the geographical distribution of the stakeholders who completed the first round of the Delphi study.

Definition of consensus. For the domains, we used the 9-point Likert scoring system, where 1–3 signifies a domain of limited importance, 4–6 somehow important but not critical and 7–9 critical. Domains will be defined as 'important' when scored 7–9

Table 3 Country of residence of participants of the e-Delphi study

No	Countries	Number of participants (%)
1	Argentina	2 (1)
2	Armenia	1 (1)
3	Australia	1 (1)
4	Belgium	4 (3)
5	Brazil	1 (1)
6	Canada	4 (3)
7	Czech Republic	3 (2)
8	Denmark	2 (1)
9	Finland	1 (1)
10	France	8 (6)
11	Germany	5 (3)
12	Greece	1 (1)
13	India	1 (1)
14	Ireland	1 (1)
15	Israel	1 (1)
16	Italy	5 (5)
17	South Korea	2 (1)
18	Netherlands	43 (30)
19	Norway	3 (2)
20	Poland	1 (1)
21	Romania	1 (1)
22	Slovakia	1 (1)
23	South Africa	1 (1)
24	Spain	4 (3)
25	Switzerland	4 (3)
26	UK	17 (12)
27	USA	26 (18)

by at least 70% of participants in each stakeholder groups in the previous round, 'unimportant' when scored 1–3 by 70% of participants and 'undecided' when not in any of those two groups.

For the outcomes, we define consensus to have been reached if the outcomes are suggested to be included in a particular domain by at least 70% of participants from each stakeholder group. Outcomes are only scored during the third Delphi round.

First round. In the first round, a list of domains was presented to the participants together with information on the aim and structure of the survey. For each domain, a list of outcomes was presented for illustration purposes. Participants needed to indicate how important they find a domain is for the clinical research setting and how important they find it is for the practice. They could also provide comments to elaborate why they deemed a certain domain important. Participants could suggest additional domains, which will be included in the next round if only they are suggested by at least two participants from either stakeholder groups.

Second round. In the second round, we aimed to reach convergence on the domains. We asked the participants to rate the domains in a similar fashion, but based on the first round, the domains are highlighted in the following categories: 'important', 'unimportant' and 'undecided'. They had the opportunity to change their ratings. Additional domains suggested in the previous round were also rated.

Third round. In the third round, participants are asked to only rate the domains that are in the 'undecided' category. Domains in the 'important' category will be highlighted but cannot be re-rated. Domains that were scored as 'unimportant' in the second round will not be retained in the third round. 'Important' and 'unimportant' domains can only be re-scored in this round if at least two participants from either stakeholder groups propose to do so. Stakeholders will also be asked to rate the importance of the outcomes for each domain in the 'important' or 'undecided' category.

Feedback. Between rounds, the rating of domains in the previous round is aggregated across stakeholder groups and summary statistics are presented. We looked at the rating for the clinical research and for practice separately. Domains are summarized in the 'important', 'unimportant' and 'undecided' categories. Domains that are considered to be 'important' after the second round will be directly included in the COS, while domains in the 'unimportant' category will be excluded and not be retained in the third round.

The abovementioned rules to reach consensus are often used, but there are also other rules being used in other COS development studies.[20]

Phase 2.2: Determination of the core set of domains of the COS during the consensus meeting To reach consensus and finalize the core set of domains of the COS, we will organize an online consensus meeting. We will involve the SAG and representatives of stakeholders who completed the 3-round surveys. We will include equal proportion of patients/parents and professionals in this consensus meeting. The stakeholder representatives will be randomly selected from those Delphi completers who noted that they are interested in participating. Participants will be sent a reminder of their personal Delphi scoring prior to the meeting. We have the following criteria for inclusion of domains and outcomes into the COS:

Selection of domains. Domains for which consensus definition has been reached during the Delphi will be included in the core set of domains of the COS.

Domains that are still considered 'undecided' after the third Delphi round will be evaluated during the consensus meeting. During this meeting, we will discuss and vote whether or not a domain should be included in the final COS. A domain that reaches at least 70% positive vote from the meeting participants will be included, otherwise not.

Selection of outcomes in the selected domains. Once the domains for the core set of domains of the COS have been selected, we

will select the outcomes to be included in those domains. Outcomes that are selected by at least 70% of participants in the third Delphi round will be automatically included in the COS. Outcomes for which consensus definition during the Delphi has not been reached will be voted here. An outcome for which at least 70% positive votes have been reached during the meeting will be included in the COS.

Ethics and consent

We have applied for ethical approval prior to the implementation of this project from the METC board at the Erasmus Medical Center and Amsterdam University Medical Center. In this project, we collected information from patients on their health status and experiences with treatments. Informed consent for each of the participating patients is sought prior to participation. We will treat all information confidentially and partially anonymously. The data will be treated anonymously in the analysis, but the email addresses of each participant are encoded in the data as an identifier. However, participants cannot know who the other participants are and what information they provide.

Results

We will report the results separately for the systematic review and the focus groups with the consensus process. We will present the selected core set of domains of the COS separately for clinical research and practice.

Dissemination and publication

The protocol and the actual development process will be reported transparently using the COS-STAR guidance.[21] The results will also be disseminated by means of publication in leading journals and presentation in international meetings/conferences. We will engage international experts in CMN, patients and professionals to ensure an international dissemination, utility and applicability of the research outcomes.

Future research plan

The scope of this research is limited to the core outcome domains. Future research would be to define the core set of outcome measurement instruments of the COS.

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