Identify the outcomes describing the domains of the core outcome set of congenital melanocytic naevi: a protocol

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ABSTRACT

Background: Congenital melanocytic naevi (CMN) can have great impact on patients' life due to perceived stigmatization and the risk of melanoma development and neurological complications. Development of a core outcome set for care and research of CMN will enable standard reporting of outcomes. This will benefit comparison of outcomes allowing professionals to advise about best management options. In previous research, stakeholders (patients, parents, and professionals) reached consensus on the core domains of the core outcome set. To select the appropriate measurement instruments, the domains should be specified by outcomes.

Objectives: To reach consensus on the specific outcomes describing the core domains of care and research.

Methods: A list of provisional outcomes, obtained in previous research, will be critically reviewed by our OCOMEN research team and by the relevant stakeholders through an online questionnaire, in order to improve this list and provide clear definitions for every outcome. During an online consensus meeting, stakeholders will discuss the inclusion of potential outcomes. After the meeting, participants will vote for inclusion of outcomes.

INTRODUCTION

Scientific background and relevance

Medium, large and giant congenital melanocytic naevi (CMN) can have great impact on patients' life especially due to remarkable appearance and a risk for developing melanoma and neurological complications (1-3). Comparison of management strategies is currently hindered by the lack of standard and uniform outcome reporting(1, 4). This impedes guidance on optimal management policy based on high-evidence research(1).

To address this problem, a core outcome set (COS) can be developed, i.e. a consensus-derived minimum set of outcomes that should be measured and reported in all clinical trials and care of a certain health condition. A COS should describe *what* should be measured (domains and outcomes) and *how* this should be measured (measurement instruments)(5). We aim to develop the core domain set (CDS) of a COS for medium, large and giant CMN for both research and care.

Recently, we reached consensus, together with all relevant stakeholders (professionals, patient and parents), on what domains should be included in the CDS. Table 1 shows the domains considered to be core for care and research setting.

Table 1- Top five domains, for care and research setting, voted for during an online consensus meeting in January 2019. These domains are included in the CDS for CMN.

No	Domains for the care setting	No	Domains for the research setting
1	Quality of life (including the sub-domains social, family, emotional and physical function)	1	Pathology
2	Neoplasms	2	Neoplasms
3	Nervous system	3	Nervous system
4	Anatomy of skin	4	Quality of life (including the sub domain: emotional function)
5	General adverse events	5	Anatomy of skin

In this study we have defined a domain as an aspect of disease that could be measured, such as 'Quality of Life', whereas an outcome as a sub granular concept/construct of a domains and sub-domain, for instants: 'Emotional distress' is a outcome of the domain 'Quality of life'. To be able to select the right measurement instrument per domain and to avoid heterogeneity in the interpretation of domains, domains should be described more precisely. Therefore, we try to reach consensus on the outcomes i.e. that should describe the domains included into the CDS.

In previous research, relevant stakeholders had the opportunity for an initial vote what outcomes should describe the included domains. The aim of this study is to discuss this

initial list of outcomes with relevant stakeholders and try to reach consensus on the final outcomes that should describe the domains.

Objective

Try to reach consensus on what outcomes should describe the domains included into the CDS.

Scope and applicability of the COS

Patients: patient with medium to giant CMN; patients with CMN size 1.5 cm projected adult size (PAS) or larger on the face and CMN larger than 10 cm PAS elsewhere on the body(6).
Intervention: all types of management of CMN: interventional (excision, laser, curettage and dermabrasion) and conservative (watchful waiting).
Setting: clinical care and research.

Geographical region: international

COS development group

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METHODS

The OCOMEN project was registered at COMET database, including a systematic review, focus groups, Delphi study and two consensus meetings. To reach consensus about the outcomes that should describe the domains and sub-domains we aim to organize a consensus meeting. We used the protocols of research groups who organized such a consensus meeting to identify the outcomes of the included domains (7,8).

Method for involving Stakeholders

Table 4 shows the methods of involving stakeholders for the consensus meeting in 2020.

Table 4 Stakeholders groups and methods of approaching potential participants

Stakeholder groups	Details	Methods of approach
Patients and parents	Patients Parents/caregivers* Family members	➢ Identify patients who participated into the online Delphi study ➢ Call for participation on social media of the patient support organizations ➢ Collaboration with national and international patient advocates who will use their network to invite patients ➢ Call for participants on the Naevus International conference (12 September 2019)
Professionals**	Dermatologists Plastic surgeons Pediatricians Pathologists Neurologists Psychologists Researchers	➢ Identy professionals who participated into the online Delphi study ➢ Identification of names from the literature, attendance of meetings/conferences in pediatric dermatology/plastic surgery and trough personal network of the SMG. ➢ Invitation of professionals and ask them to suggest names of other professionals who may be interested to participate. ➢ Call for participants on the Naevus International conference (12 September 2019)

* Parents can fill out the survey based on their own personal perspective or on behalf of their young child, in that 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.

Identification of outcomes that describe the domains included in the CDS

Descriptions of previously conducted consensus for COS meetings will be used to organize this consensus meeting (7, 8).

The consensus will take place in four different phases:

1) Feedback before the consensus meetings
2) Consensus meeting
3) Voting

<u>Before the consensus meetings:</u>

Participants will receive the following information before the consensus meeting:

- What is a COS and CDS and why is it necessary
- Explanations about core outcomes; when an outcome is core, it should be measured in all clinical trials and care
- Information about the previously conducted research of the CDS development
- The list of domains included in the CDS for care and research
- The list of proposed outcomes

- The list of outcomes excluded during the Delphi round and consensus meeting for the CDS in 2019
- A definition list of outcomes in lay language
- A list of aspects that we would like to discuss with the participants
- Explanation on what should be expected of the meeting

List of provisional outcomes:

Previous conducted research:

A list of outcomes was identified from a systematic review and seven focus groups(9, 10). These outcomes were classified into domains according to the COMET taxonomy. The World Health Organization International Classification of Functioning, Disability and Health was used for a more detailed classification of the skin anatomy and functions. During the last round of the online Delphi of the CDS development, participants could vote what outcomes should describe the provisional included domains. Outcomes that were selected by at least 70% of participants of this last round are describe 'initial outcomes'. During the online consensus meeting, participant could vote on these outcomes again. The outcomes voted for during the consensus meeting are included in the CDS (outcomes selected by at least 70% of participants). The list of 'provisional starting list of outcomes' voted for during the online consensus meeting in January 2019 are presented in Table 2.

Table 2: List 1: list of provisional outcomes

Core domains	Provisional outcomes (not yet core outcomes)
1. Quality of life*	1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Coping mechanisms 4. Aesthetic issues 5. Perceived stigmatization 6. Social relations* 7. Acceptance by parents/family members of having CMN*
2.Neoplasms/malignancy	8. Incidence of melanoma 9. Incidence of other malignancy 10. Frequency of monitoring for malignancy 11. Biopsy findings/ histological characteristics
3. Nervous system	12. Epilepsy 13. MRI findings 14. Hydrocephalus 15. Motor development 16. Brain complications due to melanocytosis, melanoma, or metastasis
4. Anatomical characteristics of skin	17. Color of the CMN (hypo-, hyperpigmentation, vitiligo) 18. Hairiness 19. Lumpiness 20. Spontaneous regression of nevi

	21. New satellite nevi 22. Change of nevus over time 23. Rugosity
5. General adverse events[$]	24. Growth-related problem in the area of operated nevus 25. Skin graft issues (flap, graft failure) 26. Change in scar (keloid, hypertrophic, atrophic, widening, contracture) 27. Cranial or facial deformation by treatment
6. Pathology[&]	28. Histo-pathological characteristics

Consensus was reached on the following aspects in previous research.

* Quality of life entails emotional, physical, family, and social functioning for the care setting whereas for the research setting it entails only emotional functioning.

[$] General adverse events was voted for care setting only.

[&] Pathology was voted for research setting only.

The list of provisional outcomes for the consensus meeting:

To be able to find the right measurement instruments that measure the domains and outcomes, the OCOMEN research team will critically review the list of outcomes voted for after the consensus meeting in January 2019 (Table 2, List 1: provisional list of outcomes). The 'quality of life' outcomes will be reviewed by a psychologist with experience in COS development (Lotte Haverman). We will review if some outcomes could be renamed to make them clear for all participants and if some outcomes measuring the same aspect can be lumped together. This altered list is described as ‘List 2: reviewed provisional list of outcomes’. Definitions will be provided in order to make the outcomes clear for all participants. For the domain ‘quality of life’ we will use the definitions of 'Patient Reported Outcomes Measurement Information System' (PROMIS). A patient/parent will be consulted to ensure that all outcomes are written in lay language.

1) Feedback before the meetings

Before the online meetings in 2020, participants will receive the reviewed list of provisional outcomes (list 2) including explanations on why alterations were made and aspects to discuss with participants. A list of outcomes excluded in previous research is added as well. Participants will have the opportunity to send feedback on list 2 before the meeting. This feedback could then be discussed during the consensus meeting.

2) Consensus meeting

The aim of this meeting is to

1. Discuss the feedback of participants on list 2 ‘reviewed list of provisional outcomes’.

2. Discuss which provisional outcomes should be included or excluded into the CDS for care and for research.

3) Voting

The whole-group will vote anonymously enduring the whole-group consensus meeting. Voting will be done through e-mail.

- Participants could vote in or exclusion of the proposed outcomes that should describe a domain included into the CDS for care setting and into the CDS for research setting.

Methods for the consensus Process and Definition

Consensus rules on voting for the online consensus meeting:

Participants could vote an outcome in or out the CDS. When at least 70% of participants consider an outcome to be 'in', it will be included into the CDS.

Ethics and consent

We will apply for an ethical approval prior to the implementation of this project from the METC board at the Amsterdam University Medical Center. In this project we collect information from patients on their health status and experiences with treatments. Informed consent for each participating patient will be prepared prior to participation. We will treat all information confidentially and anonymously.

Results

We will provide a list of core outcomes that described the domains of the CDS.

Dissemination and publication

The results will be reported transparently using the COS-STAR guidance (7, 11). The results will be disseminated by means of publication in leading journals and presentation in international meetings/conferences for patients and professionals. 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

This project defines the domains and outcomes included into the CDS. The next step is to define the core set of outcome measurement instruments of the COS for this specific subgroup of CMNs. Participants should try to reach consensus on what outcome measurement instruments should be used to measure the domains and outcomes included into the CDS.

Reverences

1. Pasmans S, Eggen C.A.M., van der Horst CMAM, Bergman W, Kukutsch N, Wolkerstorfer A, et al. Multidisiplinaire Richtlijn Congenitale Melanocytaire Naevi 2017.
2. Koot HM, de Waard-van der Spek F, Peer CD, Mulder PG, Oranje AP. Psychosocial sequelae in 29 children with giant congenital melanocytic naevi. Clin Exp Dermatol. 2000;25(8):589-93.
3. Krengel S, Hauschild A, Schafer T. Melanoma risk in congenital melanocytic naevi: a systematic review. Br J Dermatol. 2006;155(1):1-8.

4. Eggen CAM, Lommerts JE, van Zuuren EJ, Limpens J, Pasmans S, Wolkerstorfer A. Laser treatment of congenital melanocytic naevi: a systematic review. The British journal of dermatology. 2018;178(2):369-83.
5. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. The British journal of dermatology. 2017;18(Suppl 3):280.
6. Krengel S, Scope A, Dusza SW, Vonthein R, Marghoob AA. New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. J Am Acad Dermatol. 2013;68(3):441-51.
7. Chalmers JR, Thomas KS, Apfelbacher C, Williams HC, Prinsen CA, Spuls PI, et al. Report from the fifth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). The British journal of dermatology. 2018;178(5):e332-e41.
8. Schmitt J, Spuls P, Boers M, Thomas K, Chalmers J, Roekevisch E, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. Allergy. 2012;67(9):1111-7.
9. Fledderus AC, Franke CJJ, Eggen CAM, van Etten-Jamaludin FS, van der Horst C, Brinkmann SJH, et al. Outcomes and measurement instruments used in congenital melanocytic naevi research: A systematic review. J Cosmet Dermatol. 2020;73(4):703-15.
10. Oei W. Protocol for the development of core set of domains of the core outcome set for patients with congenital melanocytic naevi (OCOMEN project). Br J Dermatol. 2020;34(2):267-73.
11. Kirkham JJ, Davis K, Altman DG, Blazeby JM, Clarke M, Tunis S, et al. Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLoS Med. 2017;14(11):e1002447.