

BMJ Open Protocol for development of a core outcome set for clinical trials in melasma

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ABSTRACT

Introduction Melasma is a pigmentation disorder of the skin. Characterised by brown to gray-brown patches on the face and neck, the condition predominantly affects women and has been associated with pregnancy, hormonal variation and sun exposure. Melasma can be disfiguring and anxiety-provoking, and quality of life is often adversely impacted. Management includes sun protection, laser and energy device therapy, topical and oral skin-bleaching agents and chemical peels. While clinical trials of melasma exist, there is a lack of consistency in reported outcomes, which has been a barrier to the aggregation of data in systematic reviews and meta-analyses. This protocol describes a planned process for development of a minimum set of outcomes (ie, 'core outcome set') that should be measured in all clinical trials of melasma.

Methods and analysis An exhaustive list of potential outcomes will be extracted from four sources: (1) systematic literature review of outcomes in clinical trials; (2) semistructured patient interviews; (3) brochures, pamphlets, clinical trial registries, and other published and unpublished sources and documentation; and (4) interviews with non-patient, non-physician stakeholders, including federal regulators, industry scientists and non-physician providers. An international two-round Delphi process will then be performed to identify the outcomes deemed most important to patients and physicians.

Subsequently, a consensus meeting will be convened to review and process the results, and to vote on a final set of core outcomes.

Ethics and dissemination Ethics approval was provided by the Northwestern University Institutional Review Board (protocol ID: STU00201637). This study is registered with both the Core Outcome Measures in Effectiveness Trials and Cochrane Skin-Core Outcome Set Initiative initiatives, and this protocol is in accordance with the guidelines for protocol development of both groups. All findings from the study described in this protocol will be disseminated to all stakeholders involved in the development process and will be submitted for publication in peer-reviewed journals.

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INTRODUCTION

Melasma is a chronic hyperpigmentation disorder primarily occurring in women.^{1,2} The

Strengths and limitations of this study

- This protocol describes a planned process for the development of a minimum set of outcomes (ie, 'core outcome set (COS)') that should be measured in all clinical trials of melasma.
- A long list of potential outcomes will be extracted from a systematic literature review, semistructured interviews, brochures and pamphlets, clinical trial registries and other published and unpublished sources and documentation.
- An international group of stakeholders, including patients, physicians, federal regulators, industry scientists, pharmacologists and pharmacists, nurses and non-physician providers will be included in the process.
- At least two rounds of Delphi process will then be performed to identify a provisional list of outcomes meeting a 70% consensus level for patient and physicians, followed by the convening of a consensus meeting to review and process the results, and to vote on a final set of core outcomes.
- This COS will establish 'what' should be measured, but not 'how' or 'when,' which will be defined in later development of core outcome measure set for melasma.

condition is characterised by brown, irregularly shaped macules and patches, commonly of the bilateral upper cheeks, mid forehead and upper lip. Predisposing risk factors for the development of melasma include darker skin types III and IV, genetic predisposition, ultraviolet radiation and hormonal changes due to pregnancy, menopause or medications.^{3–5} However, melasma remains a poorly understood condition that also arises in the absence of traditional risk factors, with a significant minority of cases occurring in men.⁶ Histologically, there is an increase of melanocytes and solar elastosis in the epidermis of melasma lesions compared with normal skin.^{2,4,7} Due to its sometimes striking impact on cosmetic appearance, melasma can

cause psychological distress, thereby negatively affecting quality of life (QoL).³

Melasma is typically divided into three subtypes (epidermal, dermal or mixed) and can be classified via Wood's Lamp examination. Severity of lesions and area of involvement can be assessed using validated or more ad hoc measurement tools. Melasma has been treated with various modalities, including lasers and lights, chemical peels, skin-bleaching agents, such as hydroquinone, or oral agents, like tranexamic acid.^{1 8} However, current treatments are of limited efficacy and recurrence is the norm. Additionally, extant studies seldom assess patient-reported outcomes, which are particularly relevant given the disfiguring nature of melasma.

Systematic reviews of treatments for melasma are limited in utility by the lack of standardisation in outcomes across trials.⁸ The selective inclusion of outcomes in publications, so-called selective outcome reporting bias, remains a problem in the reporting of clinical trials. In particular, the heterogeneity of outcomes reported across trials may affect the recommendations and conclusions of systematic reviews.⁹ In order to address the heterogeneity of outcomes in clinical trials of the same disease or condition, The Core Outcome Measures in Effectiveness Trials (COMET) initiative was created, with the goal of providing methodological support to facilitate development of standardised core outcome sets (COS) to be measured in health-related research.¹⁰ A COS is defined as a consensus-derived set of outcomes that are measured at minimum in all clinical studies of a given condition or disease. Similarly, another group, the Cochrane Skin-Core Outcome Set Initiative (CS-COUSIN), was developed specifically to address COSs in dermatology.¹¹ CS-COUSIN provides methodological support, and much of its approach is based on the experience of the Harmonising Outcome Measures for Eczema (HOME) initiative.¹²⁻¹⁶

To date, there has been no COS published specifically for melasma. The data obtained from the investigation described in this protocol will define the minimum set of outcomes that should be reported in future clinical trials of melasma interventions.

Objective

The aim of this study will be to develop a COS through an international consensus process, for use in future clinical trials of melasma. The objective is to determine what outcomes should be reported as a minimum in future clinical trials of melasma.

Scope of this COS

This COS is envisioned as the global standard for all clinical trials examining the efficacy and safety of all melasma interventions, including both early and late phase trials. The COS to be developed is intended to apply to all individuals with melasma, regardless of age, gender and ethnicity.

This COS will establish 'what' should be measured, but not 'how' or 'when,' which will be defined in a later consensus study specific to outcome measures.

METHODS AND ANALYSIS

This study was designed using guidance provided by the CS-COUSIN and COMET initiatives and has been registered with both organisations.¹⁷⁻²⁰ Additional guidance was provided by the HOME roadmap.¹⁶ The reporting of this protocol conforms to the The Core Outcome Set-STANDARDISED Protocol Items Statement checklist and the CS-COUSIN Core Domain Development Process guidance.^{18 21} This protocol is also based on prior work in protocol development by the Measurement of Priority Outcome Variables in Dermatologic Surgery (IMPROVED) Group, a COS development organisation for dermatological surgery-related conditions.²²

Study oversight

The international study steering committee developing this COS will include four physicians (MA, IAM, JFS and TVC) as well as a patient representative. The latter, who will also have melasma, will represent others with this condition by providing input at key points to ensure that the patient perspective is incorporated. The four physicians have prior experience in developing COSs in dermatology, and therefore, also act as researchers in COS development. The steering committee will lead each stage of COS development and ensure methodological quality throughout the study. In addition, an independent member of the CS-COUSIN Methods Group (JJK) will provide guidance on the most current methodological recommendations for COS development.

Study design

Identification of outcomes

A long list of outcomes will be generated from four sources. First, a systematic review of the literature, which has been registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020214189), will be performed to identify and extract outcomes measured in randomised controlled trials of melasma. Specifically, with the help of a medical librarian, PubMed/Medline and Embase will be searched for the period 2006–2016 to detect English language human RCTs including, but not limited to, the following terms: [(melasma [title/abstract]) AND (randomized controlled trial [publication type]) AND (treatment OR therapy OR therapeutics)]. RCTs will be used to identify outcomes of interest, since it is usual and customary in COS methodology to focus on RCTs when they are available in sufficient variety and quantity.²³⁻²⁶ Inclusion criteria will be studies that: (1) are randomised and controlled; (2) assess the efficacy and/or safety of one or more interventions for treatment of melasma; (3) are available in the English language and (4) and involve human subjects. Articles will be excluded if they:

(1) were published as a poster or conference abstract; or (2) the full text of the article is unavailable. Articles will be independently screened for eligibility by two investigators, and disagreements will be resolved by a third investigator. Two independent reviewers will then extract outcomes from individual studies. During extraction, QoL outcomes will be separated into distinct categories to ensure all of the various components of QoL that have been measured in previous investigations are included as possible core outcomes. Outcome measures will also be extracted during this step, and this data will be recorded for the future development of a core outcome measure set for melasma.²⁷ The results of the systematic review will be published separately from the COS.

Second, other printed and electronic sources, including clinical trial registries (ClinicalTrials.gov searched for 'melasma', 2017–2021, no exclusion criteria), patient pamphlets (American Academy of Dermatology website searched for 'melasma', with inclusion criteria being 'all patient education material', and no exclusion criteria.) medical society brochures and relevant US Food and Drug Administration/European Medicines Agency guidance documents, will be reviewed to identify any additional outcomes not detected in the systematic review. Third, outcomes valued by patients will be identified by conducting semistructured interviews with patients diagnosed with melasma. These interviews will be audio recorded, transcribed and analysed by the methods of qualitative research to find outcomes considered relevant by patients. Fourth, semistructured interviews will be performed to identify any remaining outcomes deemed relevant by representatives of key non-physician, non-patient stakeholder classes, including industry scientists, (Leaders at a purposive sample of large, medium-sized and small US drug, device, and cosmetic companies involved in research on products for melasma will be contacted to ask for identification of qualified industry scientists in their employ who can help identify additional outcomes. In total, up to 20 industry scientists will be contacted. Drug and device safety regulators from the countries most represented in the systematic review will be contacted for interviews. When their names are publicly available, officials from dermatology or cosmetic-related offices within these regulatory agencies will be contacted first). pharmacologists and pharmacists, drug and device safety regulators, (US Food and Drug Administration, European Medicines Agency, Ministry of Food and Drug Safety (Korean), Pharmaceuticals and Medical Devices Agency (Japan), Health Canada, Brazilian Health Regulatory Agency (ANVISA)), nurses and physician assistants. Semistructured interviews with patients and other stakeholders will be conducted by investigators who have been trained in this qualitative research technique. Specifically, such interviews will be comprised of a series of open-ended questions, followed by pre-established prompts, in the event that respondents are unclear as to the primary question. At the end of the semistructured interview, stakeholders will be asked

to volunteer any additional information about the topic that they may wish to share. Interviewers will be strictly prohibited from using off-script leading questions that may bias data collection. After the semistructured interviews are completed, they will be transcribed, and the iterative methods of qualitative methods will be used to extract common themes. These themes, if not already present in the list of outcomes, will then be used to create new outcomes that will be appended to the long list. Non-physician, non-patient stakeholders will not be invited to participate in the subsequent Delphi process but will be invited to the final consensus meeting.

Final review of long list of outcomes

The outcomes obtained from the sources above will be collated into a long list of provisional outcomes. Members of the steering committee will review and condense this list, eliminating duplicate items and combining items when possible, without loss of content. In accordance with the proposed definition of a unique outcome by Young *et al*, unique outcomes (ie, outcomes with 'original meaning and context') will be preserved, and other outcomes (ie, those 'with different words, phrasing or spelling addressing the same concept and context') will be lumped together.²⁸ The list of outcomes will then be placed into appropriate domains by two steering committee members using the COMET and CS-COUSIN taxonomies.^{29 30} Lay definitions will be appended to all outcomes and reviewed by the melasma steering group patient representative to assure that patient stakeholders can actively participate in the forthcoming Delphi consensus process.

Delphi participants

Two separate groups, consisting of physicians and patients, respectively, will be invited to take part in the Delphi process. A global context will be provided by inviting physicians from the USA and from other countries on various continents, including a range of ethnicities. To include the perspective of researchers, the senior authors of all clinical trials extracted in our literature review will be included in the physician group. Eligible physician stakeholders will include dermatologists, clinical researchers, primary care providers and other medical specialists who have experience treating melasma. Demographic information, including participants' ethnicity, gender and specialty will be recorded. To account for potential dropouts, at least 100 physicians meeting any of the following criteria will be invited: corresponding author of a clinical trial of melasma included in our systematic review; among the most frequently published authors on melasma treatment, as identified through electronic databases; recent lecturers on the topic of melasma at national or international dermatology professional society meetings in any country; or members of a national or international dermatological society (Representative board members of the following societies will be invited to participate as individuals in the

Delphi to ensure inclusion of the perspectives of expert clinicians and researchers who may not have recently published in the literature: American Academy of Dermatology Association; American Society for Laser Medicine and Surgery; African Society of Dermatology and Venereology; Asian Academy of Dermatology and Venereology; Arab Academy of Dermatology and Aesthetics; Argentine Society of Dermatology; Brazilian Society of Dermatology; British Association of Dermatologists; Canadian Dermatology Association; European Academy of Dermatology and Venereology; French Society of Dermatology; Mexican Society of Dermatology; Skin of Colour Society; World Congress of Dermatology). with clinical expertise in melasma treatment, as demonstrated by committee or other affiliations.

Physicians who agree to participate will be asked to identify one or more melasma patients who may be invited to join the patient Delphi group, with a goal of 15 patient stakeholders participating in the Delphi. All recruitment will be done by our study team and will be approved by our ethics committee. However, this will not entail limiting patient recruitment from our site only, since we will be asking physician Delphi participants located elsewhere to volunteer patients who may choose to participate in the study. Such patient volunteers will contact the research staff at our site, who will consent and enroll them, if appropriate. Additional methods will be taken to ensure patient involvement throughout the study, including: (1) specifying patient involvement in the Institutional Review Board (IRB) protocol; (2) seeking relevant input from patients; (3) maintenance of investigator open-mindedness to the patient perspective; (4) careful reviewing of all outcomes with patient representatives; (5) thorough note taking; (6) taking time to reflect on patient feedback and (7) identifying and engaging a diverse group of patient participants.³¹

Modified Delphi process

From the long list of potential outcomes vetted by the steering committee, a core set of outcomes will be provisionally selected by stakeholders through a Delphi process, as recommended by the COMET and CS-COUSIN initiatives.^{17 18 30} Specifically, each Delphi participant will be asked to rate each outcome for its level of importance on a scale from 1 to 9. Average ratings for each outcome, and relevant participant comments, will then be redistributed to each survey participant, who will have the option of changing his or her earlier ratings based on the additional information surfaced in this process. Prior to a consensus meeting, at least two Delphi rounds will be conducted.

Delphi rounds

During each Delphi round, the provisional outcomes in the long list will be presented to each participant for rating. Participants will rate each outcome on a 9-point scale developed by the Grading of Recommendations Assessment, Development and Evaluation working group, with '9' denoting 'critically important' and '1,' 'not that

important.'³² In each round, each participant will have the option to select '10' if they are uncertain about an outcome's need for inclusion. Also in each round, each participant will have the option to identify new outcomes that they feel should be added in the subsequent round. All previously included outcomes will be carried to the next round. Participants will have 3 weeks to complete each Delphi round, and will receive weekly reminders until they do, or time expires.

Results from round 1 will be analysed by outcome and for each stakeholder group. Then, round 2 will commence. In round 2, participants will be graphically shown the distribution of scores for each item for each stakeholder group from round 1, and also their own individual ratings for each outcome from the previous round, and asked to score each item again. New outcomes will be added to round 2 if suggested by two or more participants in round 1, if the steering committee determines the suggested outcome(s) to be unique from existing outcomes.²⁸

Summarised scores from round 2, analysed by outcome and for each stakeholder group, will be presented at the consensus meeting. Attrition is possible between Delphi rounds, and although numeric data (eg, mean, median and range of scores) from round 2 alone will be analysed and presented at the consensus meeting, written feedback from both rounds will be collated and discussed at the consensus meeting, as well.

Definition of provisional consensus

Outcomes will be retained in the provisional consensus pool if 70% of the participants score 7, 8 or 9 with less than 15% scoring 1–3.³³ Outcomes will be removed from the provisional consensus pool if 70% or more of the participants score 1, 2 or 3 and less than 15% score 7–9. To avoid having a COS that entails too many items, if the provisional list of included outcomes is longer than expected, participants at the consensus meeting will be urged to further refine and abbreviate this list. The definition of consensus is based on previous, published COS consensus methodology and guidance of the COMET Methodology Group.^{17 34–36} Outcomes that have not reached consensus will also be retained for discussion during the consensus meeting.

Consensus meeting

A series of virtual consensus meetings will be held to discuss the results of the Delphi, to review the provisional COS as well as the outcomes for which consensus has not been reached, and to move towards selection of a final COS. The reason to have more than one consensus meeting is to avoid the scenario in which the loudest voices dominate, and patients in particular are not heard as clearly and to the extent that they should be. Since we anticipate 30–60 healthcare professionals, and approximately five patients to participate in the process, we anticipate three virtual consensus meetings of 15–20 participants each, with each meeting also including patient participants. An additional benefit of having multiple consensus

meetings is that different schedules and time zones can be accommodated. Finally, if the outcomes of the different consensus meetings are not fully consistent, an email ballot will be sent to all participants individually to resolve any remaining issues. Each meeting will be moderated by an independent facilitator, and invited participants will include all physicians and patients who participated in at least the first round of the Delphi. Each meeting will have balanced representation across stakeholder groups and geographical regions to ensure the result is development of a global COS. Other non-physician, non-patient stakeholders will be invited, as well.

Informed by the Delphi results, feedback regarding the consensus-derived set of provisional outcomes and outcomes for which consensus has not been reached will be elicited from the consensus meeting participants with the assistance of the facilitator. Using live polling software, participants will vote to include or not include outcomes into the final core set of outcomes. If multiple consensus meetings are held, and if there is any inconsistency between the outcomes selected in these, a final email ballot will be circulated to all consensus meeting participants to confirm the final COS. The result will be a COS that reflects the priorities and concerns of all stakeholders.

Timeline

The expected timeline from the start of the study to full development of the core set of outcome domains will be 18–24 months. Identification of an initial list of outcomes, via systematic review followed by qualitative interviews, will span approximately 7–8 months. An additional seven to ten months will be dedicated to conducting the Delphi survey and convening the consensus meeting, followed by approximately 4–6 months for analysing feedback and drafting, circulating and finalising the manuscript.

Patient and public involvement

The patient and public perspective will be sought at multiple points in this study. Patient stakeholders will review plain language summaries of outcome definitions. A minimum of one patient representative will be included in the research team, as described earlier in this protocol. Additionally, patients will be recognised as key stakeholders during the identification and prioritisation of outcomes, with fully one-half of the Delphi process reserved for patients. Patients will be encouraged to provide feedback before (semistructured interviews), during and after (at the consensus meeting) the Delphi process to ensure that patient-centred outcomes are incorporated. Lastly, with their consent, patient representatives will be named as contributors in any published work that arises from the study.

ETHICS AND DISSEMINATION

Dissemination and implementation of results

The full development of this COS and the results of the study will be reported in peer-reviewed journals. The

main results of the study, including the COS, will be disseminated to all participants through email at the time of study publication. Researchers will be encouraged to use the COS when performing future trials.

Ethical approval and consent to participate

Ethical approval and consent to participate for the study has been granted from the Northwestern University IRB (protocol ID: STU00201637). Informed consent will be presented before registering for the Delphi. The Northwestern University IRB has waived written informed consent and has approved verbal consent for interviews, and online consent for the Delphi process.

DISCUSSION

Despite the numerous completed and ongoing clinical trials of treatments for melasma, there is currently no COS informing such investigations. The proposed COS for melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus standardising future outcomes reporting. Investigators would be free to consider and include additional outcomes beyond the core set, but their use of at least the core set would allow aggregation and comparison of data across melasma trials. Cross-trial comparisons of treatments and large-scale meta-analyses would, in turn, enable more definitive conclusions on the merits of available treatments.

Trial registration and status

This study has been registered with both the COMET and CS-COUSIN initiatives for COS development, and the development of this protocol is in accordance with the guidelines for protocol development of both groups. The development of the COS is currently in its initial phase of outcome extraction.

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