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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. Characterized 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 (i.e., "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2) semi-structured patient interviews; 3) brochures, pamphlets, clinical trial registries, and other published and unpublished sources and documentation; and 4) interviews with non-patient, non-physician stakeholders, including federal regulators, industry scientists, and non-physician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 (IRB) (protocol ID: STU00201637). This study is registered with both the COMET and CS-COUSIN initiatives, and this protocol is in accordance with the guidelines for protocol development of both groups. All findings from the study described in this

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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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ARTICLE SUMMARY

Strengths and Limitations of This Study

- This protocol describes a planned process for the development of a minimum set of outcomes (i.e., "core outcome set") that should be measured in all clinical trials of melasma.
- A long list of potential outcomes will be extracted from a systematic literature review, semi-structured 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.
- A consensus meeting will be convened to review and process the results, and to vote on a final set of core outcomes.

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INTRODUCTION

Melasma is a chronic hyperpigmentation disorder primarily occurring in women.[1,2] The condition is characterized 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 to 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.[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 standardization 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

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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 standardized core outcome sets to be measured in health-related research.[10] A core outcome set (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 core outcome sets in dermatology.[11] CS-COUSIN provides methodological support, and much of its approach is based on the experience of the Harmonizing Outcome Measures for Eczema (HOME) initiative.[12–16]

To date, there has been no core outcome set published specifically for melasma. The data obtained from the investigation described in this protocol is expected to standardize the design of future clinical trials of melasma.

Objective

The aim of this study will be to develop an international core outcome set relevant to clinical trials of melasma. The objectives are to determine what outcomes should be measured at a minimum in all 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. The core outcome set to be developed is intended to apply to all individuals with melasma, regardless of age, gender, and ethnicity.

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METHODS AND ANALYSIS

This study was designed using guidance provided by the CS-COUSIN and COMET initiatives and has been registered with both organizations.[17–20] Additional guidance was provided by the Harmonising Outcome Measures for Eczema (HOME) roadmap.[16] The reporting of this protocol conforms to the COS-STAP (The Core Outcome Set-STAndardised Protocol Items) Statement checklist and the CS-COUSIN Core Domain Development Process guidance [supplementary file 1].[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 core outcome set development organization for dermatologic surgery-related conditions.[22]

Study Oversight

The international study steering committee developing this COS will include four physicians (MA, IAM, JFS, 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 core outcome sets 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.

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Study Design

Identification of Outcomes

A long list of outcomes will be generated from four sources. First, a systematic review of the literature will be performed to identify and extract outcomes measured in randomized controlled trials of melasma. Specifically, PubMed/Medline, and Embase will be searched for the period 2006-16 to detect English language human RCTs using the following terms: [(melasma [title/abstract]) AND (randomized controlled trial[publication type]) AND (treatment)]. Second, other printed and electronic sources, including clinical trial registries,[1] patient pamphlets,[2] medical society brochures, and relevant FDA/EMA 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 semi-structured interviews with patients diagnosed with melasma.[3] These interviews will be audio-recorded, transcribed, and analyzed by the methods of qualitative research to find outcomes considered relevant by patients. Fourth, semi-structured interviews will be performed to identify any remaining outcomes deemed relevant by representatives of key non-physician, non-patient stakeholder classes, including industry scientists,[4] pharmacologists and pharmacists, drug and device safety

[1] Clinicaltrials.gov searched for "melasma", 2017-2021, no exclusion criteria.

[2] American Academy of Dermatology website searched for "melasma", with inclusion criteria being "all patient education material", and no exclusion criteria.

[3] The Electronic Data Warehouse (EDW) of outpatient dermatology clinics at Northwestern University will be searched to identify patients who have received consultations or treatments for melasma. At least 20 patients will be contacted by telephone for interviews. Those who agree to respond will each be scheduled via email for a 30-minute interview.

[4] 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.

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regulators[5], nurses, and physician assistants. 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. The list of outcomes will then be placed into appropriate domains by two steering committee members using the COMET and CS-COUSIN taxonomies.[23,24]. 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 United States and from other countries on various continents, including a range of ethnicities.

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.

[5] 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).

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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 lecturer on the topic of melasma at national or international dermatology professional society meetings in any country; or a member of a national or international dermatologic society[6] 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.

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

[6] 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 Venerology; 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 Color Society; World Congress of Dermatology.

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recommended by the COMET and CS-COUSIN initiatives [17,18, 24]. Specifically, each Delphi participant will be asked to rate each outcome for its level of importance on a scale from 1-9. 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 using DelphiManager software available for this purpose from COMET.

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 (GRADE) working group, with "9" denoting "critically important "and "1," "not that important." [25] 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 analyzed by outcome and for each stakeholder group. After Round 1, a virtual meeting will be held with participants to discuss the results of the first round, and to allow participants to share their thoughts about items they found particularly salient or controversial. Then, Round 2 will commence. In Round 2, participants will be

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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, with any uncertainties addressed by the steering committee. Summarized scores from Round 2, analyzed by outcome and for each stakeholder group, will be presented at the consensus meeting.

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.[26] 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. Outcomes that have not reached consensus will also be retained for discussion during the consensus meeting.

Consensus Meeting

A consensus meeting will be held to discuss the results of Delphi, to review the provisional core outcome set as well as the outcomes for which consensus has not be reached, and to move towards selection of a final core outcome set. This meeting will be moderated by an independent facilitator, and invited participants will include all physicians and patients who participated in both rounds of the Delphi. If time constraints and other limitations preclude a single consensus meeting, multiple virtual consensus meetings will be held, with each having

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balanced representation across stakeholder groups and geographic regions to ensure the result is development of a global COS.

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 core outcome set 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 one year. Identification of an initial list of outcomes, including systematic review and qualitative interviews, will span approximately five months. An additional seven months will be dedicated to conducting the Delphi survey and convening the consensus meeting.

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

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patient representative will be included in the research team, as described earlier in this protocol. Additionally, patients will be recognized as key stakeholders during the identification and prioritization of outcomes, with fully one-half of the Delphi process reserved for patients. Patients will be encouraged to provide feedback before (semi-structured interviews), during, and after (at the consensus meeting) the Delphi process to ensure that patient-centered 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 core outcome set, 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 Institutional Review Board (IRB) (protocol ID: STU00201637). Informed consent will be obtained from all participants prior to their involvement in the study.

DISCUSSION

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Despite the numerous completed and ongoing clinical trials of treatments for melasma, there is currently no COS informing such investigations. The proposed core outcome set for melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus standardizing 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 core outcome set development, and the development of this protocol is in accordance with the guidelines for protocol development of both groups. The development of the core outcome set is currently in its initial phase of outcome extraction.

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DECLARATIONS:

Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials

COS: Core outcome set

CS-COUSIN: Cochrane Skin - Core Outcome Set Initiative

HOME: Harmonising Outcome Measures for Eczema

IMPROVED: Measurement of Priority Outcome Variables in Dermatologic Surgery Group

Consent for publication

All authors consent.

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Data availability statement

There are no data in this work.

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Competing Interests

None of the authors have personal or financial relationships with other people or organizations that may influence their interpretation of data or presentation of information. Several of the authors (JFS, TVC, IAN, JJK, KS, MA) have been involved also in the development of other core outcome sets, and several (JJK, JS, MA) are members of the CS-COUSIN Methods group.

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None

Author Contributions

Study concept and design: SAI, BYK, DIS, JT, JJK, JS, EP, IAM, JFS, TVC, and MA. *Drafting of the manuscript:* SAI, BYK, SCG, EP, TVC, and MA. *Critical revision of the manuscript for*

important intellectual content: SAI, BYK, DIS, JJK, EP, and MA. *Obtained funding:* MA. *Study supervision:* MA. All authors read and approved the final manuscript.

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Table 1. CS-COUSIN Core Domain Development Process Guidance Checklist

Requirement	Item No.	Explanation	Page
Title/Abstract			
Title	1	Identify in the title that the protocol is about the development of COS domains and specify disease / population of interest.	Pg 1
Abstract	2	Provide a structured summary.	Pg 3
Introduction			
Scientific background and relevance	3	Provide an overview of the need of the COS (more detailed than in the proposal form).	Pg 6
Objectives	4	State your objectives.	Pg 7
Define scope and applicability of the COS	5	Describe the setting(s) including geographical region, health condition(s), population(s), and intervention(s).	Pg 7
Methods			
Workplan and milestones	6	Describe work packages (e.g. protocol development, registration, literature search, databases). Specify the expected results of each work package. Provide the milestones (planned timelines for the work packages).	Beginning pg. 8
COS development group	7	Describe the COS project team consisting of at least patients, clinicians, and methodologists (and if applicable, Steering Committee and/or Advisory group members).	Pg 8
Method for involving Stakeholders	8	Describe who your stakeholders will be and how stakeholders will be contacted and involved. Describe the eligibility criteria for stakeholders for each group. Describe in detail how you will involve the patient perspective, healthcare professionals and provide (if possible at this stage) a list of potential representatives and stakeholders: names, affiliation, roles.	Pg 9-10
Method for the identification of	9	Provide a detailed plan for the identification of the core outcome domains (e.g. literature searches, focus groups, interviews).	Pg 9

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core outcome domains			
Consensus Process and Definition, Method for the definition of core outcome domains	10	Provide a detailed plan for conducting the consensus process (e.g. Delphi study, face to face group meetings). Describe the proposed consensus definition. Describe the analysis plan (i.e. how outcome domains will be scored and how scores will be summarized. Describe the consensus definition and criteria for including/dropping/adding domains.	Pg 10-12
Ethics and consent	11	Describe the ethics and consent issues. If this is not applicable please state this.	Pg 15
Results	12	Describe broadly how you will present your expected results.	Pg 15
Other Information			
Dissemination and Publication	13	Develop a dissemination and implementation plan.	Pg 15
Future research plan for developing a core set of outcome measurement instruments	14	Indicate if you intend to develop a core set of outcome measurement instruments for your identified core outcome domains and how you would do this.	N/A
Funding, Conflict of interest	15	State any sources of funding that you have received or plan to apply for and conflicts of interest (e.g. development or copyright for any instruments in this area, involvement in any other COS, involvement in any related groups).	Pg 17
Timeline	16	Please indicate the intended timeline from the study start until the Core Set of outcome domains will be completed	Pg 14

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Table 2. COS-STAP (The Core Outcome Set-STAndardised Protocol Items) Statement Checklist

REQUIREMENT			**Page**
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS	Pg 1
Abstract	1b	Provide a structured abstract	Pg 3
INTRODUCTION			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS and identify the reasons why a COS is needed and the potential barriers to its implementation.	Pg 6
	2b	Describe the specific objectives with reference to developing a COS	Pg 7
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS	Pg 7
	3b	Describe the intervention(s) that will be covered by the COS	Pg 7
	3c	Describe the context of use for which the COS is to be applied	Pg 7
METHODS			
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study	Pg 9-10
Information sources	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers	Pg 9
	5b	Describe how outcomes may be dropped/combined, with reasons	Pg 10
Consensus process	6	Describe the plans for how the consensus process will be undertaken	Pg 10-12
Consensus definition	7a	Describe the consensus definition	Pg 13

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	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	Pg 13
ANALYSIS			
Outcome scoring/feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	Pg 10
Missing data	9	Describe how missing data will be handled during the consensus process	Pg 13
ETHICS and DISSEMINATION			
Ethics approval/informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant)	Pg 15
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination	Pg 15
ADMINISTRATIVE INFORMATION			
Funders	12	Describe sources of funding, role of funders	Pg 17
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed	Pg 17 -18

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Protocol for Development of a Core Outcome Set for Clinical Trials in Melasma

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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. Characterized 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 (i.e., "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) semi-structured 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 (IRB) (protocol ID: STU00201637). This study is registered with both the COMET and CS-COUSIN initiatives, and this protocol is in accordance with the guidelines for protocol development of both groups. All findings from the study described in this

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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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ARTICLE SUMMARY

Strengths and Limitations of This Study

- This protocol describes a planned process for the development of a minimum set of outcomes (i.e., "core outcome set") that should be measured in all clinical trials of melasma.
- A long list of potential outcomes will be extracted from a systematic literature review, semi-structured 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.

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INTRODUCTION

Melasma is a chronic hyperpigmentation disorder primarily occurring in women.[1,2] The condition is characterized 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 to 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.[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 standardization 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

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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 standardized core outcome sets to be measured in health-related research.[10] A core outcome set (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 core outcome sets in dermatology.[11] CS-COUSIN provides methodological support, and much of its approach is based on the experience of the Harmonizing Outcome Measures for Eczema (HOME) initiative.[12–16]

To date, there has been no core outcome set 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.

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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 organizations.[17–20] Additional guidance was provided by the Harmonising Outcome Measures for Eczema (HOME) roadmap.[16] The reporting of this protocol conforms to the COS-STAP (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 core outcome set development organization for dermatologic surgery-related conditions.[22]

Study Oversight

The international study steering committee developing this COS will include four physicians (MA, IAM, JFS, 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 core outcome sets 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

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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 randomized controlled trials of melasma. Specifically, with the help of a medical librarian, PubMed/Medline and Embase will be searched for the period 2006-16 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 randomized 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; (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, quality of life (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.

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Second, other printed and electronic sources, including clinical trial registries,[1] patient pamphlets,[2] medical society brochures, and relevant FDA/EMA 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 semi-structured interviews with patients diagnosed with melasma.[3] These interviews will be audio-recorded, transcribed, and analyzed by the methods of qualitative research to find outcomes considered relevant by patients. Fourth, semi-structured interviews will be performed to identify any remaining outcomes deemed relevant by representatives of key non-physician, non-patient stakeholder classes, including industry scientists,[4] pharmacologists and pharmacists, drug and device safety regulators[5], nurses, and physician assistants. Semi-structured 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 semi-structured interview, stakeholders will be asked to

[1] Clinicaltrials.gov searched for "melasma", 2017-2021, no exclusion criteria.

[2] American Academy of Dermatology website searched for "melasma", with inclusion criteria being "all patient education material", and no exclusion criteria.

[3] The Electronic Data Warehouse (EDW) of outpatient dermatology clinics at Northwestern University will be searched to identify patients who have received consultations or treatments for melasma. At least 20 patients will be contacted by telephone for interviews. Those who agree to respond will each be scheduled via email for a 30-minute interview.

[4] 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.

[5] 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).

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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 semi-structured 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 (i.e., outcomes with "original meaning and context") will be preserved, and other outcomes (i.e., 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

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the United States 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 lecturer on the topic of melasma at national or international dermatology professional society meetings in any country; or a member of a national or international dermatologic society[6] 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

[6] 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 Venerology; 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 Color Society; World Congress of Dermatology.

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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 1-9. 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 using DelphiManager software available for this purpose from COMET.

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 (GRADE) working group, with "9" denoting "critically important "and "1," "not that important."[32] In each round,

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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 analyzed by outcome and for each stakeholder group. After Round 1, a virtual meeting will be held with participants to discuss the results of the first round, and to allow participants to share their thoughts about items they found particularly salient or controversial. 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]

Summarized scores from Round 2, analyzed by outcome and for each stakeholder group, will be presented at the consensus meeting. Attrition is possible between Delphi rounds, and although numeric data (e.g., mean, median, and range of scores) from Round 2 alone will be analyzed 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.

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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 virtual consensus meeting will be held to discuss the results of Delphi, to review the provisional core outcome set as well as the outcomes for which consensus has not be reached, and to move towards selection of a final core outcome set. This 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. If time constraints and other limitations preclude a single consensus meeting, multiple virtual consensus meetings will be held, with each having balanced representation across stakeholder groups and geographic regions to ensure the result is development of a global COS. In total, the meeting(s) will aim to include 30 to 60 physicians and at least 5 patients. 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 core outcome set that reflects the priorities and concerns of all stakeholders.

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Timeline

The expected timeline from the start of the study to full development of the core set of outcome domains will be 18 to 24 months. Identification of an initial list of outcomes, via systematic review followed by qualitative interviews, will span approximately seven to eight months. An additional seven to ten months will be dedicated to conducting the Delphi survey and convening the consensus meeting, followed by approximately four to six months for analyzing feedback and drafting, circulating, and finalizing 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 recognized as key stakeholders during the identification and prioritization of outcomes, with fully one-half of the Delphi process reserved for patients. Patients will be encouraged to provide feedback before (semi-structured interviews), during, and after (at the consensus meeting) the Delphi process to ensure that patient-centered 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

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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 core outcome set, 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 core outcome set for melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus standardizing 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.

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Trial Registration and Status

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

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DECLARATIONS:

Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials

COS: Core outcome set

CS-COUSIN: Cochrane Skin - Core Outcome Set Initiative

HOME: Harmonising Outcome Measures for Eczema

IMPROVED: Measurement of Priority Outcome Variables in Dermatologic Surgery Group

Consent for publication

All authors consent.

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Data availability statement

There are no data in this work.

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Competing Interests

None of the authors have personal or financial relationships with other people or organizations that may influence their interpretation of data or presentation of information. Several of the authors (JFS, TVC, IAN, JJK, KS, MA) have been involved also in the development of other core outcome sets, and several (JJK, JS, MA) are members of the CS-COUSIN Methods group.

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None

Author Contributions

Study concept and design: SAI, BYK, DIS, JT, JJK, JS, EP, IAM, JFS, TVC, and MA. *Drafting of the manuscript:* SAI, BYK, SCG, EP, TVC, and MA. *Critical revision of the manuscript for*

important intellectual content: SAI, BYK, DIS, JJK, EP, and MA. *Obtained funding:* MA. *Study supervision:* MA. All authors read and approved the final manuscript.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 16
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Page 17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

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	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 8
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	N/A
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	N/A
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	N/A
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	N/A
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A

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	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	N/A
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	N/A
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			

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Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	N/A
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

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Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 15

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	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 15
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 15
Appendices			

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Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Table 1. CS-COUSIN Core Domain Development Process Guidance Checklist

Requirement	Item No.	Explanation	Page
Title/Abstract			
Title	1	Identify in the title that the protocol is about the development of COS domains and specify disease / population of interest.	Pg 1
Abstract	2	Provide a structured summary.	Pg 3
Introduction			
Scientific background and relevance	3	Provide an overview of the need of the COS (more detailed than in the proposal form).	Pg 6
Objectives	4	State your objectives.	Pg 7
Define scope and applicability of the COS	5	Describe the setting(s) including geographical region, health condition(s), population(s), and intervention(s).	Pg 7
Methods			
Workplan and milestones	6	Describe work packages (e.g. protocol development, registration, literature search, databases). Specify the expected results of each work package. Provide the milestones (planned timelines for the work packages).	Beginning pg. 8
COS development group	7	Describe the COS project team consisting of at least patients, clinicians, and methodologists (and if applicable, Steering Committee and/or Advisory group members).	Pg 8
Method for involving Stakeholders	8	Describe who your stakeholders will be and how stakeholders will be contacted and involved. Describe the eligibility criteria for stakeholders for each group. Describe in detail how you will involve the patient perspective, healthcare professionals and provide (if possible at this stage) a list of potential representatives and stakeholders: names, affiliation, roles.	Pg 9-10
Method for the identification of core outcome domains	9	Provide a detailed plan for the identification of the core outcome domains (e.g. literature searches, focus groups, interviews).	Pg 9

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Consensus Process and Definition, Method for the definition of core outcome domains	10	Provide a detailed plan for conducting the consensus process (e.g. Delphi study, face to face group meetings). Describe the proposed consensus definition. Describe the analysis plan (i.e. how outcome domains will be scored and how scores will be summarized. Describe the consensus definition and criteria for including/dropping/adding domains.	Pg 10-12
Ethics and consent	11	Describe the ethics and consent issues. If this is not applicable please state this.	Pg 15
Results	12	Describe broadly how you will present your expected results.	Pg 15
Other Information			
Dissemination and Publication	13	Develop a dissemination and implementation plan.	Pg 15
Future research plan for developing a core set of outcome measurement instruments	14	Indicate if you intend to develop a core set of outcome measurement instruments for your identified core outcome domains and how you would do this.	N/A
Funding, Conflict of interest	15	State any sources of funding that you have received or plan to apply for and conflicts of interest (e.g. development or copyright for any instruments in this area, involvement in any other COS, involvement in any related groups).	Pg 17
Timeline	16	Please indicate the intended timeline from the study start until the Core Set of outcome domains will be completed	Pg 14

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Table 2. COS-STAP (The Core Outcome Set-STAndardised Protocol Items) Statement Checklist

REQUIREMENT			**Page**
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS	Pg 1
Abstract	1b	Provide a structured abstract	Pg 3
INTRODUCTION			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS and identify the reasons why a COS is needed and the potential barriers to its implementation.	Pg 6
	2b	Describe the specific objectives with reference to developing a COS	Pg 7
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS	Pg 7
	3b	Describe the intervention(s) that will be covered by the COS	Pg 7
	3c	Describe the context of use for which the COS is to be applied	Pg 7
METHODS			
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study	Pg 9-10
Information sources	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers	Pg 9
	5b	Describe how outcomes may be dropped/combined, with reasons	Pg 10
Consensus process	6	Describe the plans for how the consensus process will be undertaken	Pg 10-12
Consensus definition	7a	Describe the consensus definition	Pg 13

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	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	Pg 13
ANALYSIS			
Outcome scoring/feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	Pg 10
Missing data	9	Describe how missing data will be handled during the consensus process	Pg 13
ETHICS and DISSEMINATION			
Ethics approval/informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant)	Pg 15
Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination	Pg 15
ADMINISTRATIVE INFORMATION			
Funders	12	Describe sources of funding, role of funders	Pg 17
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed	Pg 17 -18

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Protocol for Development of a Core Outcome Set for Clinical Trials in Melasma

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Protocol for Development of a Core Outcome Set for Clinical Trials in Melasma

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Keywords: core outcome set, protocol, development, clinical trials, melasma

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ABSTRACT

Introduction: Melasma is a pigmentation disorder of the skin. Characterized 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 (i.e., "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) semi-structured 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 (IRB) (protocol ID: STU00201637). This study is registered with both the COMET and CS-COUSIN initiatives, and this protocol is in accordance with the guidelines for protocol development of both groups. All findings from the study described in this

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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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ARTICLE SUMMARY

Strengths and Limitations of This Study

- This protocol describes a planned process for the development of a minimum set of outcomes (i.e., "core outcome set") that should be measured in all clinical trials of melasma.
- A long list of potential outcomes will be extracted from a systematic literature review, semi-structured 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.

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INTRODUCTION

Melasma is a chronic hyperpigmentation disorder primarily occurring in women.[1,2] The condition is characterized 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 to 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.[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 standardization 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

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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 standardized core outcome sets to be measured in health-related research.[10] A core outcome set (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 core outcome sets in dermatology.[11] CS-COUSIN provides methodological support, and much of its approach is based on the experience of the Harmonizing Outcome Measures for Eczema (HOME) initiative.[12–16]

To date, there has been no core outcome set 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.

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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 organizations.[17–20] Additional guidance was provided by the Harmonising Outcome Measures for Eczema (HOME) roadmap.[16] The reporting of this protocol conforms to the COS-STAP (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 core outcome set development organization for dermatologic surgery-related conditions.[22]

Study Oversight

The international study steering committee developing this COS will include four physicians (MA, IAM, JFS, 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 core outcome sets 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

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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 randomized controlled trials of melasma. Specifically, with the help of a medical librarian, PubMed/Medline and Embase will be searched for the period 2006-16 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 randomized 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; (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, quality of life (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.

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Second, other printed and electronic sources, including clinical trial registries,[1] patient pamphlets,[2] medical society brochures, and relevant FDA/EMA 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 semi-structured interviews with patients diagnosed with melasma.[3] These interviews will be audio-recorded, transcribed, and analyzed by the methods of qualitative research to find outcomes considered relevant by patients. Fourth, semi-structured interviews will be performed to identify any remaining outcomes deemed relevant by representatives of key non-physician, non-patient stakeholder classes, including industry scientists,[4] pharmacologists and pharmacists, drug and device safety regulators[5], nurses, and physician assistants. Semi-structured 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 semi-structured interview, stakeholders will be asked to

[1] Clinicaltrials.gov searched for "melasma", 2017-2021, no exclusion criteria.

[2] American Academy of Dermatology website searched for "melasma", with inclusion criteria being "all patient education material", and no exclusion criteria.

[3] The Electronic Data Warehouse (EDW) of outpatient dermatology clinics at Northwestern University will be searched to identify patients who have received consultations or treatments for melasma. At least 20 patients will be contacted by telephone for interviews. Those who agree to respond will each be scheduled via email for a 30-minute interview.

[4] 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.

[5] 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).

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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 semi-structured 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 (i.e., outcomes with "original meaning and context") will be preserved, and other outcomes (i.e., 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

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the United States 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 lecturer on the topic of melasma at national or international dermatology professional society meetings in any country; or a member of a national or international dermatologic society[6] 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

[6] 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 Venerology; 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 Color Society; World Congress of Dermatology.

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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 1-9. 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 using DelphiManager software available for this purpose from COMET.

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 (GRADE) working group, with "9" denoting "critically important "and "1," "not that important."[32] In each round,

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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 analyzed by outcome and for each stakeholder group. After Round 1, a virtual meeting will be held with participants to discuss the results of the first round, and to allow participants to share their thoughts about items they found particularly salient or controversial. 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]

Summarized scores from Round 2, analyzed by outcome and for each stakeholder group, will be presented at the consensus meeting. Attrition is possible between Delphi rounds, and although numeric data (e.g., mean, median, and range of scores) from Round 2 alone will be analyzed 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.

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To avoid having a core outcome set 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 core outcome set as well as the outcomes for which consensus has not been reached, and to move towards selection of a final core outcome set. 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 multiplate 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 geographic regions to ensure the result is development of a global COS. Other non-physician, non-patient stakeholders will be invited, as well.

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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 core outcome set 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 to 24 months. Identification of an initial list of outcomes, via systematic review followed by qualitative interviews, will span approximately seven to eight months. An additional seven to ten months will be dedicated to conducting the Delphi survey and convening the consensus meeting, followed by approximately four to six months for analyzing feedback and drafting, circulating, and finalizing 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 recognized as key stakeholders during the identification and prioritization of outcomes, with fully one-half of the Delphi process reserved for patients.

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Patients will be encouraged to provide feedback before (semi-structured interviews), during, and after (at the consensus meeting) the Delphi process to ensure that patient-centered 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 core outcome set, 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

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Despite the numerous completed and ongoing clinical trials of treatments for melasma, there is currently no COS informing such investigations. The proposed core outcome set for melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus standardizing 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 core outcome set development, and the development of this protocol is in accordance with the guidelines for protocol development of both groups. The development of the core outcome set is currently in its initial phase of outcome extraction.

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DECLARATIONS:

Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials

COS: Core outcome set

CS-COUSIN: Cochrane Skin - Core Outcome Set Initiative

HOME: Harmonising Outcome Measures for Eczema

IMPROVED: Measurement of Priority Outcome Variables in Dermatologic Surgery Group

Consent for publication

All authors consent.

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Data availability statement

There are no data in this work.

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Competing Interests

None of the authors have personal or financial relationships with other people or organizations that may influence their interpretation of data or presentation of information. Several of the authors (JFS, TVC, IAN, JJK, KS, MA) have been involved also in the development of other core outcome sets, and several (JJK, JS, MA) are members of the CS-COUSIN Methods group.

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None

Author Contributions

Study concept and design: SAI, BYK, DIS, JT, JJK, JS, EP, IAM, JFS, TVC, and MA. *Drafting of the manuscript:* SAI, BYK, SCG, EP, TVC, and MA. *Critical revision of the manuscript for*

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