PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for Development of a Core Outcome Set for Clinical Trials in Melasma
AUTHORS	Ibrahim, Sarah; Kang, Bianca; Schlessinger, Daniel; Chiren, Sarah; Tang, Jennifer; Kirkham, Jamie J.; Schmitt, Jochen; Poon, Emily; Maher, Ian; Sobanko, Joseph; Cartee, Todd; Alam, Murad

VERSION 1 – REVIEW

REVIEWER	Millward, C University of Liverpool, Institute of Systems, Molecular, & Integrative Biology
REVIEW RETURNED	16-Dec-2020

GENERAL COMMENTS	Dear Author Generally, this is a well-written protocol for the development of a COS for melasma. However, detail is lacking in a number of areas which I feel are necessary to ensure that this protocol serves its purpose as an "a priori" statement of study methodology. This will avoid ambiguity during the conduct of the study, and provide confidence to the future users of your COS. Introduction: The final sentence is poorly written. The COS is not expected to standardise the design of future clinical trials of melasma, but to define the minimum outcomes that should be reported in future clinical trials of melasma. Aim and objectives: Could be re-worded. Is the aim... To develop a COS through an international consensus process, for use in future melasma clinical trials. Is the objective - to determine what outcomes should be reported as a minimum in future melasma clinical trials. Scope: You say that the intended use of the COS is for trials examining efficacy and safety. Are you suggesting the COS is not just for effectiveness trials, but for earlier phase studies too? In addition, the systematic review will identify RCTs. Is there a particular reason for this? Why not phase 1 or 2 trials if the COS is for safety and efficacy as described in the scope.

	This needs to be made very clear. What is the purpose of this COS. Systematic review: Overall, there is very little detail on how the systematic review will be performed or the search of grey literature. Is the systematic review protocol being published separately or is it on a systematic review database? If not, the detail should be included in the protocol, and if not in the text, as a supplement. This systematic review would not be eligible for registration on PROSPERO; however, the template provided gives an indication of the level of detail that should be provided. In addition, do you intend to use a librarian/expert in literature searching? MESH terms for RCT may not be exhaustive and the word "treatment" may not identify studies of interest either. Finally, how will QoL outcomes be handled/extracted? Semi-structured interviews: There is insufficient detail describing this aspect of the study. There is no description of how the interviews will be conducted and how this would inform the long list. Final review of the long list: This section is rather brief and lacks detail on exactly how this will be achieved. For instance; what constitutes a duplicate and what constitutes loss of content. I would recommend reviewing Young et al, 2019 - A systematic review of core outcome set development studies demonstrates difficulties in defining unique outcomes. It may also be of benefit to specifically incorporate patient opinion not just in lay interpretation, but other design issues. See Smith et al, 2018 - Defining and evaluating novel procedures for involving patients in Core Outcome Set research: creating a meaningful long list of candidate outcome domains. Delphi participants: Does your ethical approval extend to multiple sites allowing for healthcare professionals to recruit patients at sites other than your own? In addition, is there a particular reason why patient participant recruitment is being performed in this manner? Does this not incorporate a selection bias? How will participants register for the study? Will pre-registration take place before the Delphi starts? Are international stakeholders covered by your ethical approval? Delphi process: What you describe is a modified Delphi process, as the outcomes to rate by participants are given at the start. You state that new outcomes will be added if suggested by 2 or more participants. How will you decide if the outcome gets added? It has to be a new unique outcome I presume. Do participants have to complete both rounds of the Delphi? How will incomplete data be managed? Definition of consensus:

	What is the rational for the consensus definitions? Is 70% too low to achieve consensus in? Is 70% too high to achieve consensus out? Consensus meeting: Will this be face-to-face or online? How many participants will be recruited? Do the participants have to have completed the Delphi. Limitations: This COS will establish 'what' should be measured but not 'how' or 'when'. This should be made clear. Will you extract this information at the time of the systematic review to be used in the future? Ethics: How is fully informed consent being obtained (as stated at the end of your protocol)? Are you planning on taking consent for each participant individually? Timeline: I struggle to see how the systematic review, interviews, Delphi and consensus meeting could be performed in 1 year. Have the interview participants already been identified? Are interviews taking place concurrently while the review is being performed?

REVIEWER	Gagnier, Joel University of Michigan
REVIEW RETURNED	21-Dec-2020

GENERAL COMMENTS	Nothing major to add here. This is a very nice protocol.

REVIEWER	Baddeley, Elin Cardiff University, Department of Population Medicine
REVIEW RETURNED	26-Feb-2021

GENERAL COMMENTS	This protocol is a well described and clearly well researched process for the development of a COS for Melasma. This study has been registered with appropriate bodies, and it is clear the experience of the authors is appropriate and the rationale behind undertaking this study is evidently well founded. I am happy to accept this protocol for publication as it is.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1:
Comment 1: Introduction: The final sentence is poorly written. The COS is not expected to standardise the design of future clinical trials of melasma, but to define the minimum outcomes that should be reported in future clinical trials of melasma.
Response 1: Thank you so much for this comment. The final sentence has been changed to, “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.”

Comment 2: Aim and objectives: Could be re-worded. Is the aim... To develop a COS through an international consensus process, for use in future melasma clinical trials. Is the objective is to determine what outcomes should be reported as a minimum in future melasma clinical trials.
Response 2: Thank you for the suggestion. We have changed this section to read, “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.”

Comment 3: Scope: You say that the intended use of the COS is for trials examining efficacy and safety. Are you suggesting the COS is not just for effectiveness trials, but for earlier phase studies too?
Response 3: Thank you very much for noting this. We have changed the scope to state, “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.” We are suggesting that the intended use of this COS is for trials examining both efficacy and safety in late phase studies and pilot investigator-initiated studies.

Comment 4: Scope: In addition, the systematic review will identify RCTs. Is there a particular reason for this? Why not phase 1 or 2 trials if the COS is for safety and efficacy as described in the scope.
Response 4: Thank you so much for noting this. We have clarified this with the following statement: “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.” In addition, references 23-26 have been added to support this statement.

Comment 5: Scope: This needs to be made very clear. What is the purpose of this COS.
Response 5: Thank you for this comment. We have further clarified the scope: “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 core outcome set to be developed is intended to apply to all individuals with melasma, regardless of age, gender, and ethnicity. This COS will establish “what” should be measured, but not “how” or “when,” which will be defined in a later consensus study specific to outcome measures.”

Comment 6: Systematic review: Overall, there is very little detail on how the systematic review will be performed or the search of grey literature. Is the systematic review protocol being published separately or is it on a systematic review database? If not, the detail should be included in the protocol, and if not in the text, as a supplement. This systematic review would not be eligible for registration on PROSPERO; however, the template provided gives an indication of the level of detail that should be provided.
Response 6: Thank you for this comment. The systematic review has been registered with PROSPERO, which we now specify in the text, along with further clarifications regarding methodology for the systematic review: “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 using 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. 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. The results of the systematic review will be published separately from the COS."

Comment 7: Systematic review: In addition, do you intend to use a librarian/expert in literature searching? MESH terms for RCT may not be exhaustive and the word "treatment" may not identify studies of interest either.
Response 7: Yes, we will consult a medical librarian in the literature search, and we now clarify this in the manuscript text: "…with the help of a medical librarian, PubMed/Medline and Embase will be searched for the period 2006-16…"

Comment 8: Systematic review: Finally, how will QoL outcomes be handled/extracted?
Response 8: Thank you for this important comment. We have added the following to the Study Design: "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."

Comment 9: Semi-structured interviews: There is insufficient detail describing this aspect of the study. There is no description of how the interviews will be conducted and how this would inform the long list.
Response 9: Thank you for this feedback. We have further clarified the semi-structured interviews: "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 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.

Comment 10: Final review of the long list: This section is rather brief and lacks detail on exactly how this will be achieved. For instance; what constitutes a duplicate and what constitutes loss of content. I

would recommend reviewing Young et al, 2019 - A systematic review of core outcome set development studies demonstrates difficulties in defining unique outcomes. It may also be of benefit to specifically incorporate patient opinion not just in lay interpretation, but other design issues. See Smith et al, 2018 - Defining and evaluating novel procedures for involving patients in Core Outcome Set research: creating a meaningful long list of candidate outcome domains.
Response 10: Thank you so much for this important comment. To address the Young et al. 2019 study, we have added the following statement, and also the supporting reference: "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." Regarding Smith et al. 2018, we have added the following statement, and the reference, as well: "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."

Comment 11: Delphi participants: Does your ethical approval extend to multiple sites allowing for healthcare professionals to recruit patients at sites other than your own? In addition, is there a particular reason why patient participant recruitment is being performed in this manner? Does this not incorporate a selection bias? How will participants register for the study? Will pre-registration take place before the Delphi starts? Are international stakeholders covered by your ethical approval?
Response 11: Thank you for pointing this out. We have clarified this further: "All recruitment will be done by our study team and will be approved by our ethics committee. However, this will not entail limiting patient recruitment from our site only, since we will be asking physician Delphi participants located elsewhere to volunteer patients who may choose to participate in the study. Such patient volunteers will contact the research staff at our site, who will consent and enroll them, if appropriate."

Comment 12: Delphi process: What you describe is a modified Delphi process, as the outcomes to rate by participants are given at the start. You state that new outcomes will be added if suggested by 2 or more participants. How will you decide if the outcome gets added? It has to be a new unique outcome I presume. Do participants have to complete both rounds of the Delphi? How will incomplete data be managed?
Response 12: Thank you for this suggested revision. We have changed the header from "Delphi Process" to "Modified Delphi Process," and also added the following: "All recruitment will be done by our study team and will be approved by our ethics committee. However, this will not entail limiting patient recruitment from our site only, since we will be asking physician Delphi participants located elsewhere to volunteer patients who may choose to participate in the study. Such patient volunteers will contact the research staff at our site, who will consent and enroll them, if appropriate."

Comment 13: Definition of consensus: What is the rational for the consensus definitions? Is 70% too low to achieve consensus in? Is 70% too high to achieve consensus out?
Response 13: Thank you for this comment. We have added supporting references (17, 33-35, which include the COMET Handbook) and the following clarifying statement: "The definition of consensus is based on previous, published COS consensus methodology, and guidance of the COMET Methodology Group."

Comment 14: Consensus meeting: Will this be face-to-face or online? How many participants will be recruited? Do the participants have to have completed the Delphi.
Response 14: Thank you so much again. We have clarified that this will be a virtual consensus meeting, and that "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."

Comment 15: Limitations: This COS will establish 'what' should be measured but not 'how' or 'when'. This should be made clear. Will you extract this information at the time of the systematic review to be used in the future?
Response 15: Thank you so much for this comment. We have added the following to the Scope and Limitations, as well as to the text, under Scope of this COS: "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." Additionally, we have added the following to Study Design: "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."

Comment 16: Ethics: How is fully informed consent being obtained (as stated at the end of your protocol)? Are you planning on taking consent for each participant individually?
Response 16: Thank you for this comment. We have clarified this further: "Informed consent will be presented before registering for the Delphi. Our IRB has waived written informed consent and has approved verbal consent for interviews, and online consent for the Delphi process."

Comment 17: Timeline: I struggle to see how the systematic review, interviews, Delphi and consensus meeting could be performed in 1 year. Have the interview participants already been identified? Are interviews taking place concurrently while the review is being performed?
Response 17: Thank you so much for this comment. We have changed the timeline to 18 to 24 months.

REVIEWER 2:

Comment 1: Nothing major to add here. This is a very nice protocol.
Response 1: Thank you very much.

REVIEWER 3:

Comment 2: This protocol is a well described and clearly well researched process for the development of a COS for Melasma. This study has been registered with appropriate bodies, and it is clear the experience of the authors is appropriate and the rationale behind undertaking this study is evidently well founded. I am happy to accept this protocol for publication as it is.
Response 2: Thank you very much.

Thank you for the opportunity to revise our submission, which we hope is now ready for publication.

Sincerely,
Murad Alam

VERSION 2 – REVIEW

REVIEWER	Millward, C University of Liverpool, Institute of Systems, Molecular, & Integrative Biology
REVIEW RETURNED	16-May-2021

GENERAL COMMENTS	Dear Authors

	Thank you for your response to my first review. This is a well-written manuscript. I am satisfied that the previous review comments have been addressed and I wish you luck with the study. I have only three further comments that you may wish to consider but do not feel that this would justify me not accepting the paper in its current form. 1) Level of consensus - this is not set at 70%, and you do not want the COS to be too big. A higher percentage is an option to mitigate against this. COS methodology is evolving and you should choose an approach appropriate to your disease/study. 2) In your response letter you say that your research team will consent patients from other sites if appropriate, and your IRB has approved online consent, so why do you need patient participants to contact your research team, if they can consent online at the time of registration? 3) Finally, 30-60 online healthcare professionals is surely not sensible in one meeting. How will discussion take place? The loudest voices are likely to dominate, and the 5 patients (which is a small number) may not be heard either. Why not 15-20 of each, with 50/50 split? Again, this is up to yourselves to decide. Best of luck with the study.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Comment 1: 1) Level of consensus - this is not set at 70%, and you do not want the COS to be too big. A higher percentage is an option to mitigate against this. COS methodology is evolving and you should choose an approach appropriate to your disease/study.

Response 1: Thank you very much for this insightful comment. To address this, the following sentence was added under the section heading, Definition of Provisional Consensus: “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.”

Comment 2: In your response letter you say that your research team will consent patients from other sites if appropriate, and your IRB has approved online consent, so why do you need patient participants to contact your research team, if they can consent online at the time of registration?

Response 2: Thank you so much for your comment. While we do have IRB approval to consent patients from multiple sites, as you note, there are two reasons why we would like patients to contact our research team. First, in some cases, our physician collaborators may not have patients' contact information or may not prefer to discuss the study in detail, and would rather we discuss the study and enroll them, and as we may not be familiar with the participants, we would need them to contact us to initiate the process. A second reason we would like patient participants to contact us directly before we proceed to enroll them is that in some cases, they may be members of vulnerable populations, as defined by our IRB, and as such may require special management.

Comment 3: 3)Finally, 30-60 online healthcare professionals is surely not sensible in one meeting. How will discussion take place? The loudest voices are likely to dominate, and the 5 patients (which is a small number) may not be heard either. Why not 15-20 of each, with 50/50 split? Again, this is up to yourselves to decide.

Response 3: Thank you so much for the thoughtful comment that raises an important potential barrier to effectively developing a COS. To address this, the following has been edited in the section titled, 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."

Thank you for the opportunity to revise our submission, which we hope is now ready for resubmission.