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

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Manuscripts

1 **Protocol for Development of a Core Outcome Set for Clinical Trials in** 2 **Melasma**

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For peer review only

1
2
3 50 **ABSTRACT**
4

5 51 **Introduction:** Melasma is a pigmentation disorder of the skin. Characterized by brown to gray-
6 brown patches on the face and neck, the condition predominantly affects women and has been
7
8 52 brown patches on the face and neck, the condition predominantly affects women and has been
9
10 53 associated with pregnancy, hormonal variation, and sun exposure. Melasma can be disfiguring
11
12 54 and anxiety-provoking, and quality of life is often adversely impacted. Management includes sun
13
14 55 protection, laser and energy device therapy, topical and oral skin-bleaching agents, and chemical
15
16 56 peels. While clinical trials of melasma exist, there is a lack of consistency in reported outcomes,
17
18 57 which has been a barrier to the aggregation of data in systematic reviews and meta-analyses. This
19
20 58 protocol describes a planned process for development of a minimum set of outcomes (i.e., “core
21
22 59 outcome set”) that should be measured in all clinical trials of melasma.
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25

26 60 **Methods and Analysis:** An exhaustive list of potential outcomes will be extracted from four
27
28 61 sources: 1) systematic literature review of outcomes in clinical trials; 2) semi-structured patient
29
30 62 interviews; 3) brochures, pamphlets, clinical trial registries, and other published and unpublished
31
32 63 sources and documentation; and 4) interviews with non-patient, non-physician stakeholders,
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34 64 including federal regulators, industry scientists, and non-physician providers. An international
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36 65 two-round Delphi process will then be performed to identify the outcomes deemed most
37
38 66 important to patients and physicians. Subsequently, a consensus meeting will be convened to
39
40 67 review and process the results, and to vote on a final set of core outcomes.
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44 68 **Ethics and Dissemination:** Ethics approval was provided by the Northwestern University
45
46 69 Institutional Review Board (IRB) (protocol ID: STU00201637). This study is registered with
47
48 70 both the COMET and CS-COUSIN initiatives, and this protocol is in accordance with the
49
50 71 guidelines for protocol development of both groups. All findings from the study described in this
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3 72 protocol will be disseminated to all stakeholders involved in the development process and will be
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5 73 submitted for publication in peer-reviewed journals.
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74 ARTICLE SUMMARY

75 Strengths and Limitations of This Study

- 76 • This protocol describes a planned process for the development of a minimum set of
77 outcomes (i.e., “core outcome set”) that should be measured in all clinical trials of
78 melasma.
- 79 • A long list of potential outcomes will be extracted from a systematic literature review,
80 semi-structured interviews, brochures and pamphlets, clinical trial registries, and other
81 published and unpublished sources and documentation.
- 82 • An international group of stakeholders, including patients, physicians, federal regulators,
83 industry scientists, pharmacologists and pharmacists, nurses, and non-physician providers
84 will be included in the process.
- 85 • At least two rounds of Delphi process will then be performed to identify a provisional list
86 of outcomes meeting a 70% consensus level for patient and physicians.
- 87 • A consensus meeting will be convened to review and process the results, and to vote on a
88 final set of core outcomes.

97 INTRODUCTION

98 Melasma is a chronic hyperpigmentation disorder primarily occurring in women.[1,2]
99 The condition is characterized by brown, irregularly shaped macules and patches, commonly of
100 the bilateral upper cheeks, mid forehead, and upper lip. Predisposing risk factors for the
101 development of melasma include darker skin types III and IV, genetic predisposition, ultraviolet
102 radiation, and hormonal changes due to pregnancy, menopause, or medications.[3–5] However,
103 melasma remains a poorly understood condition that also arises in the absence of traditional risk
104 factors, with a significant minority of cases occurring in men.[6] Histologically, there is an
105 increase of melanocytes and solar elastosis in the epidermis of melasma lesions compared to
106 normal skin.[2,4,7] Due to its sometimes striking impact on cosmetic appearance, melasma can
107 cause psychological distress, thereby negatively affecting quality of life.[3]

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

115 Systematic reviews of treatments for melasma are limited in utility by the lack of
116 standardization in outcomes across trials.[8] The selective inclusion of outcomes in publications,
117 so-called selective outcome reporting bias, remains a problem in the reporting of clinical trials.
118 In particular, the heterogeneity of outcomes reported across trials may affect the
119 recommendations and conclusions of systematic reviews.[9] In order to address the

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3 120 heterogeneity of outcomes in clinical trials of the same disease or condition, The Core Outcome
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5 121 Measures in Effectiveness Trials (COMET) initiative was created, with the goal of providing
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8 122 methodological support to facilitate development of standardized core outcome sets to be
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10 123 measured in health-related research.[10] A core outcome set (COS) is defined as a consensus-
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12 124 derived set of outcomes that are measured at minimum in all clinical studies of a given condition
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15 125 or disease. Similarly, another group, the Cochrane Skin - Core Outcome Set Initiative (CS-
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17 126 COUSIN), was developed specifically to address core outcome sets in dermatology.[11] CS-
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19 127 COUSIN provides methodological support, and much of its approach is based on the experience
20
21 128 of the Harmonizing Outcome Measures for Eczema (HOME) initiative.[12–16]

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24 129 To date, there has been no core outcome set published specifically for melasma. The data
25
26 130 obtained from the investigation described in this protocol is expected to standardize the design of
27
28 131 future clinical trials of melasma.
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31 132 32 33 34 133 **Objective**

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37 134 The aim of this study will be to develop an international core outcome set relevant to
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39 135 clinical trials of melasma. The objectives are to determine what outcomes should be measured at
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41 136 a minimum in all clinical trials of melasma.
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45 137 46 47 48 138 **Scope of this COS**

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51 139 This COS is envisioned as the global standard for all clinical trials examining the efficacy
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53 140 and safety of all melasma interventions. The core outcome set to be developed is intended to
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55 141 apply to all individuals with melasma, regardless of age, gender, and ethnicity.
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142 **METHODS AND ANALYSIS**

143 This study was designed using guidance provided by the CS-COUSIN and COMET
144 initiatives and has been registered with both organizations.[17–20] Additional guidance was
145 provided by the Harmonising Outcome Measures for Eczema (HOME) roadmap.[16] The
146 reporting of this protocol conforms to the COS-STAP (The Core Outcome Set-STANDARDISED
147 Protocol Items) Statement checklist and the CS-COUSIN Core Domain Development Process
148 guidance [supplementary file 1].[18,21] This protocol is also based on prior work in protocol
149 development by the Measurement of Priority Outcome Variables in Dermatologic Surgery
150 (IMPROVED) Group, a core outcome set development organization for dermatologic surgery-
151 related conditions.[22]

153 **Study Oversight**

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

163

164 Study Design

165 Identification of Outcomes

166 A long list of outcomes will be generated from four sources. First, a systematic review of
167 the literature will be performed to identify and extract outcomes measured in randomized
168 controlled trials of melasma. Specifically, PubMed/Medline, and Embase will be searched for
169 the period 2006-16 to detect English language human RCTs using the following terms:
170 [(melasma [title/abstract]) AND (randomized controlled trial[publication type]) AND
171 (treatment)]. Second, other printed and electronic sources, including clinical trial registries,¹
172 patient pamphlets,² medical society brochures, and relevant FDA/EMA guidance documents, will
173 be reviewed to identify any additional outcomes not detected in the systematic review. Third,
174 outcomes valued by patients will be identified by conducting semi-structured interviews with
175 patients diagnosed with melasma.³ These interviews will be audio-recorded, transcribed, and
176 analyzed by the methods of qualitative research to find outcomes considered relevant by patients.
177 Fourth, semi-structured interviews will be performed to identify any remaining outcomes
178 deemed relevant by representatives of key non-physician, non-patient stakeholder classes,
179 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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3 180 regulators⁵, nurses, and physician assistants. Non-physician, non-patient stakeholders will not be
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5 181 invited to participate in the subsequent Delphi process but will be invited to the final consensus
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8 182 meeting.

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184 Final Review of Long List of Outcomes

185 The outcomes obtained from the sources above will be collated into a long list of
186 provisional outcomes. Members of the steering committee will review and condense this list,
187 eliminating duplicate items and combining items when possible without loss of content. The
188 list of outcomes will then be placed into appropriate domains by two steering committee
189 members using the COMET and CS-COUSIN taxonomies.[23,24]. Lay definitions will be
190 appended to all outcomes and reviewed by the melasma steering group patient representative to
191 assure that patient stakeholders can actively participate in the forthcoming Delphi consensus
192 process.

193

194 Delphi Participants

195 Two separate groups, consisting of physicians and patients, respectively, will be invited
196 to take part in the Delphi process. A global context will be provided by inviting physicians from
197 the United States and from other countries on various continents, including a range of ethnicities.

50 Drug and device safety regulators from the countries most represented in the systematic review will be contacted for
51 interviews. When their names are publicly available, officials from dermatology or cosmetic-related offices within
52 these regulatory agencies will be contacted first.

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54 ⁵ US Food and Drug Administration, European Medicines Agency, Ministry of Food and Drug Safety (Korean),
55 Pharmaceuticals and Medical Devices Agency (Japan), Health Canada, Brazilian Health Regulatory Agency
56 (ANVISA).
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3 198 To include the perspective of researchers, the senior authors of all clinical trials extracted in our
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5 199 literature review will be included in the physician group. Eligible physician stakeholders will
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7 200 include dermatologists, clinical researchers, primary care providers, and other medical specialists
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9 201 who have experience treating melasma. Demographic information, including participants'
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11 202 ethnicity, gender, and specialty will be recorded. To account for potential dropouts, at least 100
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13 203 physicians meeting any of the following criteria will be invited: corresponding author of a
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15 204 clinical trial of melasma included in our systematic review; among the most frequently
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17 205 published authors on melasma treatment, as identified through electronic databases; recent
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19 206 lecturer on the topic of melasma at national or international dermatology professional society
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21 207 meetings in any country; or a member of a national or international dermatologic society⁶ with
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23 208 clinical expertise in melasma treatment, as demonstrated by committee or other affiliations.
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25 209 Physicians who agree to participate will be asked to identify one or more melasma patients who
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27 210 may be invited to join the patient Delphi group.
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212 Delphi Process

213 From the long list of potential outcomes vetted by the steering committee, a core set of
214 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 Venereology; Asian Academy of Dermatology and Venereology; Arab Academy of Dermatology and Aesthetics; Argentine Society of Dermatology; Brazilian Society of Dermatology; British Association of Dermatologists; Canadian Dermatology Association; European Academy of Dermatology and Venereology; French Society of Dermatology; Mexican Society of Dermatology; Skin of Color Society; World Congress of Dermatology.

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3 215 recommended by the COMET and CS-COUSIN initiatives [17,18, 24]. Specifically, each
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5 216 Delphi participant will be asked to rate each outcome for its level of importance on a scale from
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7 217 1-9. Average ratings for each outcome, and relevant participant comments, will then be
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9 218 redistributed to each survey participant, who will have the option of changing his or her earlier
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11 219 ratings based on the additional information surfaced in this process. Prior to a consensus
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13 220 meeting, at least two Delphi rounds will be conducted using DelphiManager software available
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15 221 for this purpose from COMET.
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23 223 Delphi Rounds

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26 224 During each Delphi round, the provisional outcomes in the long list will be presented to
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28 225 each participant for rating. Participants will rate each outcome on a 9-point scale developed by
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30 226 the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working
31
32 227 group, with “9” denoting “critically important” and “1,” “not that important.” [25] In each
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34 228 round, each participant will have the option to select “10” if they are uncertain about an
35
36 229 outcome’s need for inclusion. Also in each round, each participant will have the option to
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38 230 identify new outcomes that they feel should be added in the subsequent round. All previously
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40 231 included outcomes will be carried to the next round. Participants will have 3 weeks to complete
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42 232 each Delphi round, and will receive weekly reminders until they do or time expires.
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47 233 Results from Round 1 will be analyzed by outcome and for each stakeholder group.
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49 234 After Round 1, a virtual meeting will be held with participants to discuss the results of the first
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51 235 round, and to allow participants to share their thoughts about items they found particularly
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53 236 salient or controversial. Then, Round 2 will commence. In Round 2, participants will be
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3 237 graphically shown the distribution of scores for each item for each stakeholder group from
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5 238 Round 1, and also their own individual ratings for each outcome from the previous round, and
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8 239 asked to score each item again. New outcomes will be added to Round 2 if suggested by two or
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10 240 more participants in Round 1, with any uncertainties addressed by the steering committee.
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12 241 Summarized scores from Round 2, analyzed by outcome and for each stakeholder group, will be
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15 242 presented at the consensus meeting.
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17 243 18 19 244 Definition of Provisional Consensus

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22 245 Outcomes will be *retained* in the provisional consensus pool if 70% of the participants
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24 246 score 7, 8, or 9 with less than 15% scoring 1-3.[26] Outcomes will be *removed* from the
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27 247 provisional consensus pool if 70% or more of the participants score 1, 2, or 3 and less than 15%
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29 248 score 7- 9. Outcomes that have not reached consensus will also be retained for discussion during
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31 249 the consensus meeting.
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33 34 250 35 36 37 251 Consensus Meeting

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40 252 A consensus meeting will be held to discuss the results of Delphi, to review the
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42 253 provisional core outcome set as well as the outcomes for which consensus has not be reached,
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45 254 and to move towards selection of a final core outcome set. This meeting will be moderated by an
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47 255 independent facilitator, and invited participants will include all physicians and patients who
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49 256 participated in both rounds of the Delphi. If time constraints and other limitations preclude a
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51 257 single consensus meeting, multiple virtual consensus meetings will be held, with each having
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258 balanced representation across stakeholder groups and geographic regions to ensure the result is
259 development of a global COS.

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

268

269 **Timeline**

270 The expected timeline from the start of the study to full development of the core set of
271 outcome domains will be one year. Identification of an initial list of outcomes, including
272 systematic review and qualitative interviews, will span approximately five months. An additional
273 seven months will be dedicated to conducting the Delphi survey and convening the consensus
274 meeting.

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276 **Patient and Public Involvement**

277 The patient and public perspective will be sought at multiple points in this study. Patient
278 stakeholders will review plain language summaries of outcome definitions. A minimum of one

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3 279 patient representative will be included in the research team, as described earlier in this protocol.
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5 280 Additionally, patients will be recognized as key stakeholders during the identification and
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7 281 prioritization of outcomes, with fully one-half of the Delphi process reserved for patients.
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10 282 Patients will be encouraged to provide feedback before (semi-structured interviews), during, and
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12 283 after (at the consensus meeting) the Delphi process to ensure that patient-centered outcomes are
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14 284 incorporated. Lastly, with their consent, patient representatives will be named as contributors in
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16 285 any published work that arises from the study.
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23 287 **ETHICS AND DISSEMINATION**

24 25 288 **Dissemination and Implementation of Results**

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28 289 The full development of this COS and the results of the study will be reported in peer-
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30 290 reviewed journals. The main results of the study, including the core outcome set, will be
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32 291 disseminated to all participants through email at the time of study publication. Researchers will
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34 292 be encouraged to use the COS when performing future trials.
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41 294 **Ethical Approval and Consent to Participate**

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44 295 Ethical approval and consent to participate for the study has been granted from the
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46 296 Northwestern University Institutional Review Board (IRB) (protocol ID: STU00201637).
47

48 297 Informed consent will be obtained from all participants prior to their involvement in the study.
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54 299 **DISCUSSION**

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3 300 Despite the numerous completed and ongoing clinical trials of treatments for melasma,
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5 301 there is currently no COS informing such investigations. The proposed core outcome set for
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7 302 melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus
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10 303 standardizing future outcomes reporting. Investigators would be free to consider and include
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12 304 additional outcomes beyond the core set, but their use of at least the core set would allow
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14 305 aggregation and comparison of data across melasma trials. Cross-trial comparisons of
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17 306 treatments and large-scale meta-analyses would, in turn, enable more definitive conclusions on
18
19 307 the merits of available treatments.
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25 309 **Trial Registration and Status**

28 310 This study has been registered with both the COMET and CS-COUSIN initiatives for
29
30 311 core outcome set development, and the development of this protocol is in accordance with the
31
32 312 guidelines for protocol development of both groups. The development of the core outcome set is
33
34
35 313 currently in its initial phase of outcome extraction.
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3 317 **DECLARATIONS:**
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8 319 **Abbreviations**
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10 320 **COMET:** Core Outcome Measures in Effectiveness Trials
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12 321 **COS:** Core outcome set
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14 322 **CS-COUSIN:** Cochrane Skin - Core Outcome Set Initiative
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16 323 **HOME:** Harmonising Outcome Measures for Eczema
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18 324 **IMPROVED:** Measurement of Priority Outcome Variables in Dermatologic Surgery Group
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24 326 **Consent for publication**
25

26 327 All authors consent.
27

28 328
29

30
31 329 I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as
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11 346 **Data availability statement**

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13
14 347 There are no data in this work.
15
16 348

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20
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22
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24
25 352 Dermatologic Surgery) Group.
26
27
28 353

29 30 354 **Competing Interests**

31
32 355 None of the authors have personal or financial relationships with other people or organizations that may
33
34 356 influence their interpretation of data or presentation of information. Several of the authors (JFS, TVC,
35
36 357 IAN, JJK, KS, MA) have been involved also in the development of other core outcome sets, and several
37
38 358 (JJK, JS, MA) are members of the CS-COUSIN Methods group.
39
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44
45 361 None
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47
48 362

49 50 363 **Author Contributions**

51
52 364 *Study concept and design:* SAI, BYK, DIS, JT, JJK, JS, EP, IAM, JFS, TVC, and MA. *Drafting*
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54 365 *of the manuscript:* SAI, BYK, SCG, EP, TVC, and MA. *Critical revision of the manuscript for*
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366 *important intellectual content:* SAI, BYK, DIS, JJK, EP, and MA. *Obtained funding:* MA. *Study*
367 *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 <u>identification</u> of	9	Provide a detailed plan for the identification of the core outcome domains (e.g. literature searches, focus groups, interviews).	Pg 9

core outcome domains			
Consensus Process and Definition, Method for the <u>definition</u> 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

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

	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

BMJ Open

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

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Manuscripts

1 Protocol for Development of a Core Outcome Set for Clinical Trials in 2 Melasma

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3 49 **ABSTRACT**

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5 50 **Introduction:** Melasma is a pigmentation disorder of the skin. Characterized by brown to gray-
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7 brown patches on the face and neck, the condition predominantly affects women and has been
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9 associated with pregnancy, hormonal variation, and sun exposure. Melasma can be disfiguring
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11 52 associated with pregnancy, hormonal variation, and sun exposure. Melasma can be disfiguring
12
13 53 and anxiety-provoking, and quality of life is often adversely impacted. Management includes sun
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15 54 protection, laser and energy device therapy, topical and oral skin-bleaching agents, and chemical
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17 55 peels. While clinical trials of melasma exist, there is a lack of consistency in reported outcomes,
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19 56 which has been a barrier to the aggregation of data in systematic reviews and meta-analyses. This
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21 57 protocol describes a planned process for development of a minimum set of outcomes (i.e., “core
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23 58 outcome set”) that should be measured in all clinical trials of melasma.

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26 59 **Methods and Analysis:** An exhaustive list of potential outcomes will be extracted from four
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28 60 sources: 1) systematic literature review of outcomes in clinical trials; 2) semi-structured patient
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30 61 interviews; 3) brochures, pamphlets, clinical trial registries, and other published and unpublished
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32 62 sources and documentation; and 4) interviews with non-patient, non-physician stakeholders,
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34 63 including federal regulators, industry scientists, and non-physician providers. An international
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36 64 two-round Delphi process will then be performed to identify the outcomes deemed most
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38 65 important to patients and physicians. Subsequently, a consensus meeting will be convened to
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40 66 review and process the results, and to vote on a final set of core outcomes.

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44 67 **Ethics and Dissemination:** Ethics approval was provided by the Northwestern University
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46 68 Institutional Review Board (IRB) (protocol ID: STU00201637). This study is registered with
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48 69 both the COMET and CS-COUSIN initiatives, and this protocol is in accordance with the
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50 70 guidelines for protocol development of both groups. All findings from the study described in this
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3 71 protocol will be disseminated to all stakeholders involved in the development process and will be
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5 72 submitted for publication in peer-reviewed journals.
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3 74 **ARTICLE SUMMARY**
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5 75 **Strengths and Limitations of This Study**
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- 8 76 • This protocol describes a planned process for the development of a minimum set of
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10 77 outcomes (i.e., “core outcome set”) that should be measured in all clinical trials of
11
12 78 melasma.
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14 79 • A long list of potential outcomes will be extracted from a systematic literature review,
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16 80 semi-structured interviews, brochures and pamphlets, clinical trial registries, and other
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18 81 published and unpublished sources and documentation.
19
20 82 • An international group of stakeholders, including patients, physicians, federal regulators,
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22 83 industry scientists, pharmacologists and pharmacists, nurses, and non-physician providers
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24 84 will be included in the process.
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26 85 • At least two rounds of Delphi process will then be performed to identify a provisional list
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28 86 of outcomes meeting a 70% consensus level for patient and physicians, followed by the
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30 87 convening of a consensus meeting to review and process the results, and to vote on a final
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32 88 set of core outcomes.
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34 89 • This COS will establish “what” should be measured, but not “how” or “when,” which
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36 90 will be defined in later development of core outcome measure set for melasma.
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92 INTRODUCTION

93 Melasma is a chronic hyperpigmentation disorder primarily occurring in women.^{1,2} The
94 condition is characterized by brown, irregularly shaped macules and patches, commonly of the
95 bilateral upper cheeks, mid forehead, and upper lip. Predisposing risk factors for the
96 development of melasma include darker skin types III and IV, genetic predisposition, ultraviolet
97 radiation, and hormonal changes due to pregnancy, menopause, or medications.³⁻⁵ However,
98 melasma remains a poorly understood condition that also arises in the absence of traditional risk
99 factors, with a significant minority of cases occurring in men.⁶ Histologically, there is an
100 increase of melanocytes and solar elastosis in the epidermis of melasma lesions compared to
101 normal skin.^{2,4,7} Due to its sometimes striking impact on cosmetic appearance, melasma can
102 cause psychological distress, thereby negatively affecting quality of life.³

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

110 Systematic reviews of treatments for melasma are limited in utility by the lack of
111 standardization in outcomes across trials.⁸ The selective inclusion of outcomes in publications,
112 so-called selective outcome reporting bias, remains a problem in the reporting of clinical trials.
113 In particular, the heterogeneity of outcomes reported across trials may affect the
114 recommendations and conclusions of systematic reviews.⁹ In order to address the heterogeneity

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3 115 of outcomes in clinical trials of the same disease or condition, The Core Outcome Measures in
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5 116 Effectiveness Trials (COMET) initiative was created, with the goal of providing methodological
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8 117 support to facilitate development of standardized core outcome sets to be measured in health-
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10 118 related research.¹⁰ A core outcome set (COS) is defined as a consensus-derived set of outcomes
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12 119 that are measured at minimum in all clinical studies of a given condition or disease. Similarly,
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14 120 another group, the Cochrane Skin - Core Outcome Set Initiative (CS-COUSIN), was developed
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16 121 specifically to address core outcome sets in dermatology.¹¹ CS-COUSIN provides
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18 122 methodological support, and much of its approach is based on the experience of the Harmonizing
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20 123 Outcome Measures for Eczema (HOME) initiative.¹²⁻¹⁶

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24 124 To date, there has been no core outcome set published specifically for melasma. The data
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26 125 obtained from the investigation described in this protocol will define the minimum set of
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28 126 outcomes that should be reported in future clinical trials of melasma interventions.

31 127 **Objective**

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34 128 The aim of this study will be to develop a COS through an international consensus
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36 129 process, for use in future clinical trials of melasma. The objective is to determine what outcomes
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38 130 should be reported as a minimum in future clinical trials of melasma.

41 131 **Scope of this COS**

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45 132 This COS is envisioned as the global standard for all clinical trials examining the efficacy
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47 133 and safety of all melasma interventions, including both early and late phase trials. The COS to be
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49 134 developed is intended to apply to all individuals with melasma, regardless of age, gender, and
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51 135 ethnicity.

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3 136 This COS will establish “what” should be measured, but not “how” or “when,” which
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6 137 will be defined in a later consensus study specific to outcome measures.
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8 138 **METHODS AND ANALYSIS**

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10 139 This study was designed using guidance provided by the CS-COUSIN and COMET
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13 140 initiatives and has been registered with both organizations.^{17–20} Additional guidance was
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15 141 provided by the Harmonising Outcome Measures for Eczema (HOME) roadmap.¹⁶ The reporting
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17 142 of this protocol conforms to the COS-STAP (The Core Outcome Set-STANDARDISED Protocol
18
19 143 Items) Statement checklist and the CS-COUSIN Core Domain Development Process
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22 144 guidance.^{18,21} This protocol is also based on prior work in protocol development by the
23
24 145 Measurement of Priority Outcome Variables in Dermatologic Surgery (IMPROVED) Group, a
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26 146 core outcome set development organization for dermatologic surgery-related conditions.²²
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29 147 **Study Oversight**

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31 148 The international study steering committee developing this COS will include four
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33 149 physicians (MA, IAM, JFS, TVC) as well as a patient representative. The latter, who will also
34
35 150 have melasma, will represent others with this condition by providing input at key points to
36
37 151 ensure that the patient perspective is incorporated. The four physicians have prior experience in
38
39 152 developing core outcome sets in dermatology and therefore also act as researchers in COS
40
41 153 development. The steering committee will lead each stage of COS development and ensure
42
43 154 methodological quality throughout the study. In addition, an independent member of the CS-
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45 155 COUSIN Methods Group (JJK) will provide guidance on the most current methodological
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47 156 recommendations for COS development.
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51 157 **Study Design**

52 158 *Identification of Outcomes*

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3 159 A long list of outcomes will be generated from four sources. First, a systematic review of
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5 160 the literature, which has been registered prospectively with the International Prospective Register
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7 161 of Systematic Reviews (PROSPERO, CRD42020214189), will be performed to identify and
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10 162 extract outcomes measured in randomized controlled trials of melasma. Specifically, with the
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12 163 help of a medical librarian, PubMed/Medline and Embase will be searched for the period 2006-
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14 164 16 to detect English language human RCTs including, but not limited to, the following terms:
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17 165 [(melasma [title/abstract]) AND (randomized controlled trial [publication type]) AND (treatment
18
19 166 OR therapy OR therapeutics)]. RCTs will be used to identify outcomes of interest, since it is
20
21 167 usual and customary in COS methodology to focus on RCTs when they are available in
22
23 168 sufficient variety and quantity.²³⁻²⁶ Inclusion criteria will be studies that: (1) are randomized and
24
25 169 controlled; (2) assess the efficacy and/or safety of one or more interventions for treatment of
26
27 170 melasma; (3) are available in the English language; (4) and involve human subjects. Articles will
28
29 171 be excluded if they: (1) were published as a poster or conference abstract; or (2) the full text of
30
31 172 the article is unavailable. Articles will be independently screened for eligibility by two
32
33 173 investigators, and disagreements will be resolved by a third investigator. Two independent
34
35 174 reviewers will then extract outcomes from individual studies. During extraction, quality of life
36
37 175 (QoL) outcomes will be separated into distinct categories to ensure all of the various components
38
39 176 of QoL that have been measured in previous investigations are included as possible core
40
41 177 outcomes. Outcome measures will also be extracted during this step, and this data will be
42
43 178 recorded for the future development of a core outcome measure set for melasma.²⁷ The results of
44
45 179 the systematic review will be published separately from the COS.
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3 180 Second, other printed and electronic sources, including clinical trial registries,¹ patient
4
5 181 pamphlets,² medical society brochures, and relevant FDA/EMA guidance documents, will be
6
7 182 reviewed to identify any additional outcomes not detected in the systematic review. Third,
8
9
10 183 outcomes valued by patients will be identified by conducting semi-structured interviews with
11
12 184 patients diagnosed with melasma.³ These interviews will be audio-recorded, transcribed, and
13
14 185 analyzed by the methods of qualitative research to find outcomes considered relevant by patients.
15
16
17 186 Fourth, semi-structured interviews will be performed to identify any remaining outcomes
18
19 187 deemed relevant by representatives of key non-physician, non-patient stakeholder classes,
20
21 188 including industry scientists,⁴ pharmacologists and pharmacists, drug and device safety
22
23 189 regulators⁵, nurses, and physician assistants. Semi-structured interviews with patients and other
24
25 190 stakeholders will be conducted by investigators who have been trained in this qualitative
26
27 191 research technique. Specifically, such interviews will be comprised of a series of open-ended
28
29 192 questions, followed by pre-established prompts, in the event that respondents are unclear as to
30
31 193 the primary question. At the end of the semi-structured interview, stakeholders will be asked to
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36
37 ¹ Clinicaltrials.gov searched for “melasma”, 2017-2021, no exclusion criteria.

38
39 ² American Academy of Dermatology website searched for “melasma”, with inclusion criteria being “all patient
40 education material”, and no exclusion criteria.

41
42 ³ The Electronic Data Warehouse (EDW) of outpatient dermatology clinics at Northwestern University will be
43 searched to identify patients who have received consultations or treatments for melasma. At least 20 patients will be
44 contacted by telephone for interviews. Those who agree to respond will each be scheduled via email for a 30-minute
45 interview.

46
47 ⁴ Leaders at a purposive sample of large, medium-sized, and small US drug, device, and cosmetic companies
48 involved in research on products for melasma will be contacted to ask for identification of qualified industry
49 scientists in their employ who can help identify additional outcomes. In total, up to 20 industry scientists will be
50 contacted.

51
52 Drug and device safety regulators from the countries most represented in the systematic review will be contacted for
53 interviews. When their names are publicly available, officials from dermatology or cosmetic-related offices within
54 these regulatory agencies will be contacted first.

55
56 ⁵ US Food and Drug Administration, European Medicines Agency, Ministry of Food and Drug Safety (Korean),
57 Pharmaceuticals and Medical Devices Agency (Japan), Health Canada, Brazilian Health Regulatory Agency
58 (ANVISA).
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3 194 volunteer any additional information about the topic that they may wish to share. Interviewers
4
5 195 will be strictly prohibited from using off-script leading questions that may bias data collection.
6
7 196 After the semi-structured interviews are completed, they will be transcribed, and the iterative
8
9
10 197 methods of qualitative methods will be used to extract common themes. These themes, if not
11
12 198 already present in the list of outcomes, will then be used to create new outcomes that will be
13
14 199 appended to the long list. Non-physician, non-patient stakeholders will not be invited to
15
16
17 200 participate in the subsequent Delphi process but will be invited to the final consensus meeting.
18
19

20 *Final Review of Long List of Outcomes*

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23 202 The outcomes obtained from the sources above will be collated into a long list of
24
25 203 provisional outcomes. Members of the steering committee will review and condense this list,
26
27 204 eliminating duplicate items and combining items when possible, without loss of content. In
28
29 205 accordance with the proposed definition of a unique outcome by Young et al., unique outcomes
30
31 206 (i.e., outcomes with “original meaning and context”) will be preserved, and other outcomes (i.e.,
32
33 207 those “with different words, phrasing, or spelling addressing the same concept and context”) will
34
35
36 208 be lumped together.²⁸ The list of outcomes will then be placed into appropriate domains by two
37
38 209 steering committee members using the COMET and CS-COUSIN taxonomies.^{29,30} Lay
39
40 210 definitions will be appended to all outcomes and reviewed by the melasma steering group patient
41
42
43 211 representative to assure that patient stakeholders can actively participate in the forthcoming
44
45
46 212 Delphi consensus process.
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48

49 *Delphi Participants*

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52 214 Two separate groups, consisting of physicians and patients, respectively, will be invited
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54 215 to take part in the Delphi process. A global context will be provided by inviting physicians from
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3 216 the United States and from other countries on various continents, including a range of ethnicities.
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5 217 To include the perspective of researchers, the senior authors of all clinical trials extracted in our
6
7 218 literature review will be included in the physician group. Eligible physician stakeholders will
8
9 219 include dermatologists, clinical researchers, primary care providers, and other medical specialists
10
11 220 who have experience treating melasma. Demographic information, including participants'
12
13 221 ethnicity, gender, and specialty will be recorded. To account for potential dropouts, at least 100
14
15 222 physicians meeting any of the following criteria will be invited: corresponding author of a
16
17 223 clinical trial of melasma included in our systematic review; among the most frequently
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19 224 published authors on melasma treatment, as identified through electronic databases; recent
20
21 225 lecturer on the topic of melasma at national or international dermatology professional society
22
23 226 meetings in any country; or a member of a national or international dermatologic society⁶ with
24
25 227 clinical expertise in melasma treatment, as demonstrated by committee or other affiliations.
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31 228 Physicians who agree to participate will be asked to identify one or more melasma
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33 229 patients who may be invited to join the patient Delphi group, with a goal of 15 patient
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35 230 stakeholders participating in the Delphi. All recruitment will be done by our study team and will
36
37 231 be approved by our ethics committee. However, this will not entail limiting patient recruitment
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39 232 from our site only, since we will be asking physician Delphi participants located elsewhere to
40
41 233 volunteer patients who may choose to participate in the study. Such patient volunteers will
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47 ⁶ Representative board members of the following societies will be invited to participate as individuals in the Delphi
48 to ensure inclusion of the perspectives of expert clinicians and researchers who may not have recently published in
49 the literature: American Academy of Dermatology Association; American Society for Laser Medicine and Surgery;
50 African Society of Dermatology and Venerology; Asian Academy of Dermatology and Venereology; Arab
51 Academy of Dermatology and Aesthetics; Argentine Society of Dermatology; Brazilian Society of Dermatology;
52 British Association of Dermatologists; Canadian Dermatology Association; European Academy of Dermatology and
53 Venereology; French Society of Dermatology; Mexican Society of Dermatology; Skin of Color Society; World
54 Congress of Dermatology.
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3 234 contact the research staff at our site, who will consent and enroll them, if appropriate. Additional
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5 235 methods will be taken to ensure patient involvement throughout the study, including: (1)
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7 236 specifying patient involvement in the Institutional Review Board (IRB) protocol; (2) seeking
8
9 237 relevant input from patients; (3) maintenance of investigator open-mindedness to the patient
10
11 238 perspective; (4) careful reviewing of all outcomes with patient representatives; (5) thorough note
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13 239 taking; (6) taking time to reflect on patient feedback; and (7) identifying and engaging a diverse
14
15 240 group of patient participants.³¹
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20 241 *Modified Delphi Process*

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23 242 From the long list of potential outcomes vetted by the steering committee, a core set of
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25 243 outcomes will be provisionally selected by stakeholders through a Delphi process, as
26
27 244 recommended by the COMET and CS-COUSIN initiatives.^{17,18,30} Specifically, each Delphi
28
29 245 participant will be asked to rate each outcome for its level of importance on a scale from 1-9.
30
31 246 Average ratings for each outcome, and relevant participant comments, will then be redistributed
32
33 247 to each survey participant, who will have the option of changing his or her earlier ratings based
34
35 248 on the additional information surfaced in this process. Prior to a consensus meeting, at least two
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37 249 Delphi rounds will be conducted using DelphiManager software available for this purpose from
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39 250 COMET.
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44 251 *Delphi Rounds*

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47 252 During each Delphi round, the provisional outcomes in the long list will be presented to
48
49 253 each participant for rating. Participants will rate each outcome on a 9-point scale developed by
50
51 254 the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working
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53 255 group, with “9” denoting “critically important” and “1,” “not that important.”³² In each round,
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3 256 each participant will have the option to select “10” if they are uncertain about an outcome’s need
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5 257 for inclusion. Also in each round, each participant will have the option to identify new outcomes
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7 258 that they feel should be added in the subsequent round. All previously included outcomes will be
8
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10 259 carried to the next round. Participants will have 3 weeks to complete each Delphi round, and will
11
12 260 receive weekly reminders until they do, or time expires.
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15 261 Results from Round 1 will be analyzed by outcome and for each stakeholder group.
16
17 262 After Round 1, a virtual meeting will be held with participants to discuss the results of the first
18
19 263 round, and to allow participants to share their thoughts about items they found particularly
20
21 264 salient or controversial. Then, Round 2 will commence. In Round 2, participants will be
22
23 265 graphically shown the distribution of scores for each item for each stakeholder group from
24
25 266 Round 1, and also their own individual ratings for each outcome from the previous round, and
26
27 267 asked to score each item again. New outcomes will be added to Round 2 if suggested by two or
28
29 268 more participants in Round 1, if the steering committee determines the suggested outcome(s) to
30
31 269 be unique from existing outcomes.²⁸
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36 270 Summarized scores from Round 2, analyzed by outcome and for each stakeholder group,
37
38 271 will be presented at the consensus meeting. Attrition is possible between Delphi rounds, and
39
40 272 although numeric data (e.g., mean, median, and range of scores) from Round 2 alone will be
41
42 273 analyzed and presented at the consensus meeting, written feedback from both rounds will be
43
44 274 collated and discussed at the consensus meeting, as well.
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48 275 *Definition of Provisional Consensus*

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50 276 Outcomes will be *retained* in the provisional consensus pool if 70% of the participants
51
52 277 score 7, 8, or 9 with less than 15% scoring 1-3.³³ Outcomes will be *removed* from the provisional
53
54 278 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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3 279 The definition of consensus is based on previous, published COS consensus methodology, and
4
5 280 guidance of the COMET Methodology Group.^{17,34–36} Outcomes that have not reached consensus
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7
8 281 will also be retained for discussion during the consensus meeting.
9

10 282 *Consensus Meeting*

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14 283 A virtual consensus meeting will be held to discuss the results of Delphi, to review the
15
16 284 provisional core outcome set as well as the outcomes for which consensus has not be reached,
17
18 285 and to move towards selection of a final core outcome set. This meeting will be moderated by an
19
20 286 independent facilitator, and invited participants will include all physicians and patients who
21
22 287 participated in at least the first round of the Delphi. If time constraints and other limitations
23
24 288 preclude a single consensus meeting, multiple virtual consensus meetings will be held, with each
25
26 289 having balanced representation across stakeholder groups and geographic regions to ensure the
27
28 290 result is development of a global COS. In total, the meeting(s) will aim to include 30 to 60
29
30 291 physicians and at least 5 patients. Other non-physician, non-patient stakeholders will be invited,
31
32 292 as well.
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37 293 Informed by the Delphi results, feedback regarding the consensus-derived set of
38
39 294 provisional outcomes and outcomes for which consensus has not been reached will be elicited
40
41 295 from the consensus meeting participants with the assistance of the facilitator. Using live polling
42
43 296 software, participants will vote to include or not include outcomes into the final core set of
44
45 297 outcomes. If multiple consensus meetings are held, and if there is any inconsistency between the
46
47 298 outcomes selected in these, a final email ballot will be circulated to all consensus meeting
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49 299 participants to confirm the final COS. The result will be a core outcome set that reflects the
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51 300 priorities and concerns of all stakeholders.
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301 **Timeline**

302 The expected timeline from the start of the study to full development of the core set of
303 outcome domains will be 18 to 24 months. Identification of an initial list of outcomes, via
304 systematic review followed by qualitative interviews, will span approximately seven to eight
305 months. An additional seven to ten months will be dedicated to conducting the Delphi survey and
306 convening the consensus meeting, followed by approximately four to six months for analyzing
307 feedback and drafting, circulating, and finalizing the manuscript.

308

309 **Patient and Public Involvement**

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

319

320 **ETHICS AND DISSEMINATION**

321 **Dissemination and Implementation of Results**

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2
3 322 The full development of this COS and the results of the study will be reported in peer-
4
5 323 reviewed journals. The main results of the study, including the core outcome set, will be
6
7 324 disseminated to all participants through email at the time of study publication. Researchers will
8
9 325 be encouraged to use the COS when performing future trials.
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16 327 **Ethical Approval and Consent to Participate**

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19 328 Ethical approval and consent to participate for the study has been granted from the
20
21 329 Northwestern University IRB (protocol ID: STU00201637). Informed consent will be presented
22
23 330 before registering for the Delphi. The Northwestern University IRB has waived written informed
24
25 331 consent and has approved verbal consent for interviews, and online consent for the Delphi
26
27
28 332 process.
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31 333

34 334 **DISCUSSION**

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37 335 Despite the numerous completed and ongoing clinical trials of treatments for melasma,
38
39 336 there is currently no COS informing such investigations. The proposed core outcome set for
40
41 337 melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus
42
43 338 standardizing future outcomes reporting. Investigators would be free to consider and include
44
45 339 additional outcomes beyond the core set, but their use of at least the core set would allow
46
47 340 aggregation and comparison of data across melasma trials. Cross-trial comparisons of
48
49 341 treatments and large-scale meta-analyses would, in turn, enable more definitive conclusions on
50
51 342 the merits of available treatments.
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56 344 **Trial Registration and Status**
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8
9 345 This study has been registered with both the COMET and CS-COUSIN initiatives for
10
11 346 core outcome set development, and the development of this protocol is in accordance with the
12
13 347 guidelines for protocol development of both groups. The development of the core outcome set is
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15 348 currently in its initial phase of outcome extraction.
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3 352 **DECLARATIONS:**
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8 354 **Abbreviations**
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10 355 **COMET:** Core Outcome Measures in Effectiveness Trials
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12 356 **COS:** Core outcome set
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14 357 **CS-COUSIN:** Cochrane Skin - Core Outcome Set Initiative
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16
17 358 **HOME:** Harmonising Outcome Measures for Eczema
18

19 359 **IMPROVED:** Measurement of Priority Outcome Variables in Dermatologic Surgery Group
20
21

22 360
23

24 361 **Consent for publication**
25

26 362 All authors consent.
27
28

29 363
30

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11 381 **Data availability statement**

12 382 There are no data in this work.
13

14 383

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17
18 386 Dermatologic Surgery and the IMPROVED (Measurement of Priority Outcome Variables in
19
20 387 Dermatologic Surgery) Group.
21
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23 388

24 389 **Competing Interests**

25 390 None of the authors have personal or financial relationships with other people or organizations that may
26
27 391 influence their interpretation of data or presentation of information. Several of the authors (JFS, TVC,
28
29 392 IAN, JJK, KS, MA) have been involved also in the development of other core outcome sets, and several
30
31 393 (JJK, JS, MA) are members of the CS-COUSIN Methods group.
32
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34 394

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36 396 None
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39 397

40 398 **Author Contributions**

41 399 *Study concept and design:* SAI, BYK, DIS, JT, JJK, JS, EP, IAM, JFS, TVC, and MA. *Drafting*
42
43 400 *of the manuscript:* SAI, BYK, SCG, EP, TVC, and MA. *Critical revision of the manuscript for*
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402 *supervision: MA. All authors read and approved the final manuscript.*

403

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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

1				
2		5d	Composition, roles, and	Page 8
3			responsibilities of the coordinating	
4			centre, steering committee,	
5			endpoint adjudication committee,	
6			data management team, and other	
7			individuals or groups overseeing	
8			the trial, if applicable (see Item 21a	
9			for data monitoring committee)	
10				
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12				
13	Introduction			
14				
15	Background and	6a	Description of research question	Page 6
16	rationale		and justification for undertaking	
17			the trial, including summary of	
18			relevant studies (published and	
19			unpublished) examining benefits	
20			and harms for each intervention	
21				
22				
23		6b	Explanation for choice of	N/A
24			comparators	
25				
26	Objectives	7	Specific objectives or hypotheses	N/A
27				
28	Trial design	8	Description of trial design including	N/A
29			type of trial (eg, parallel group,	
30			crossover, factorial, single group),	
31			allocation ratio, and framework	
32			(eg, superiority, equivalence,	
33			noninferiority, exploratory)	
34				
35				
36				
37	Methods: Participants, interventions, and outcomes			
38				
39	Study setting	9	Description of study settings (eg,	N/A
40			community clinic, academic	
41			hospital) and list of countries	
42			where data will be collected.	
43			Reference to where list of study	
44			sites can be obtained	
45				
46				
47	Eligibility criteria	10	Inclusion and exclusion criteria for	N/A
48			participants. If applicable, eligibility	
49			criteria for study centres and	
50			individuals who will perform the	
51			interventions (eg, surgeons,	
52			psychotherapists)	
53				
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55	Interventions	11a	Interventions for each group with	N/A
56			sufficient detail to allow replication,	
57			including how and when they will	
58			be administered	
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2		11b	Criteria for discontinuing or	N/A
3			modifying allocated interventions	
4			for a given trial participant (eg,	
5			drug dose change in response to	
6			harms, participant request, or	
7			improving/worsening disease)	
8				
9				
10		11c	Strategies to improve adherence	N/A
11			to intervention protocols, and any	
12			procedures for monitoring	
13			adherence (eg, drug tablet return,	
14			laboratory tests)	
15				
16				
17		11d	Relevant concomitant care and	N/A
18			interventions that are permitted or	
19			prohibited during the trial	
20				
21	Outcomes	12	Primary, secondary, and other	N/A
22			outcomes, including the specific	
23			measurement variable (eg, systolic	
24			blood pressure), analysis metric	
25			(eg, change from baseline, final	
26			value, time to event), method of	
27			aggregation (eg, median,	
28			proportion), and time point for	
29			each outcome. Explanation of the	
30			clinical relevance of chosen	
31			efficacy and harm outcomes is	
32			strongly recommended	
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37	Participant	13	Time schedule of enrolment,	N/A
38	timeline		interventions (including any run-ins	
39			and washouts), assessments, and	
40			visits for participants. A schematic	
41			diagram is highly recommended	
42			(see Figure)	
43				
44				
45	Sample size	14	Estimated number of participants	N/A
46			needed to achieve study	
47			objectives and how it was	
48			determined, including clinical and	
49			statistical assumptions supporting	
50			any sample size calculations	
51				
52				
53	Recruitment	15	Strategies for achieving adequate	N/A
54			participant enrolment to reach	
55			target sample size	
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Methods: Assignment of interventions (for controlled trials)

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

1				
2	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
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18			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
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26	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
27				
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37	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
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43		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
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48		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
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57	Methods: Monitoring			
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2	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure;	N/A
3			statement of whether it is	
4			independent from the sponsor and	
5			competing interests; and reference	
6			to where further details about its	
7			charter can be found, if not in the	
8			protocol. Alternatively, an	
9			explanation of why a DMC is not	
10			needed	
11				
12		21b	Description of any interim analyses	N/A
13			and stopping guidelines, including	
14			who will have access to these	
15			interim results and make the final	
16			decision to terminate the trial	
17				
18	Harms	22	Plans for collecting, assessing,	N/A
19			reporting, and managing solicited	
20			and spontaneously reported	
21			adverse events and other	
22			unintended effects of trial	
23			interventions or trial conduct	
24				
25	Auditing	23	Frequency and procedures for	N/A
26			auditing trial conduct, if any, and	
27			whether the process will be	
28			independent from investigators	
29			and the sponsor	
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39	Ethics and dissemination			
40	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 15
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45	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
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54	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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2		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
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7	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
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 17
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21	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
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28	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
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34	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
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46		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 18
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51		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 15
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56	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.

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 <u>identification</u> 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

Consensus Process and Definition, Method for the <u>definition</u> 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

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

	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

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046953.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Dec-2021
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Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Research methods
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Clinical trials < THERAPEUTICS, DERMATOLOGY

SCHOLARONE™
Manuscripts

1 Protocol for Development of a Core Outcome Set for Clinical Trials in 2 Melasma

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Word Count Abstract: 298 Manuscript: 3557/4000

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

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For peer review only

1
2
3 49 **ABSTRACT**

4
5 50 **Introduction:** Melasma is a pigmentation disorder of the skin. Characterized by brown to gray-
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7 brown patches on the face and neck, the condition predominantly affects women and has been
8
9 associated with pregnancy, hormonal variation, and sun exposure. Melasma can be disfiguring
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11 52 associated with pregnancy, hormonal variation, and sun exposure. Melasma can be disfiguring
12
13 53 and anxiety-provoking, and quality of life is often adversely impacted. Management includes sun
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15 54 protection, laser and energy device therapy, topical and oral skin-bleaching agents, and chemical
16
17 55 peels. While clinical trials of melasma exist, there is a lack of consistency in reported outcomes,
18
19 56 which has been a barrier to the aggregation of data in systematic reviews and meta-analyses. This
20
21 57 protocol describes a planned process for development of a minimum set of outcomes (i.e., “core
22
23 58 outcome set”) that should be measured in all clinical trials of melasma.

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26 59 **Methods and Analysis:** An exhaustive list of potential outcomes will be extracted from four
27
28 60 sources: 1) systematic literature review of outcomes in clinical trials; 2) semi-structured patient
29
30 61 interviews; 3) brochures, pamphlets, clinical trial registries, and other published and unpublished
31
32 62 sources and documentation; and 4) interviews with non-patient, non-physician stakeholders,
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34 63 including federal regulators, industry scientists, and non-physician providers. An international
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36 64 two-round Delphi process will then be performed to identify the outcomes deemed most
37
38 65 important to patients and physicians. Subsequently, a consensus meeting will be convened to
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40 66 review and process the results, and to vote on a final set of core outcomes.

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44 67 **Ethics and Dissemination:** Ethics approval was provided by the Northwestern University
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46 68 Institutional Review Board (IRB) (protocol ID: STU00201637). This study is registered with
47
48 69 both the COMET and CS-COUSIN initiatives, and this protocol is in accordance with the
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50 70 guidelines for protocol development of both groups. All findings from the study described in this
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3 71 protocol will be disseminated to all stakeholders involved in the development process and will be
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5 72 submitted for publication in peer-reviewed journals.
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For peer review only

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3 74 **ARTICLE SUMMARY**
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5 75 **Strengths and Limitations of This Study**
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- 8 76 • This protocol describes a planned process for the development of a minimum set of
9
10 77 outcomes (i.e., “core outcome set”) that should be measured in all clinical trials of
11
12 78 melasma.
13
14 79 • A long list of potential outcomes will be extracted from a systematic literature review,
15
16 80 semi-structured interviews, brochures and pamphlets, clinical trial registries, and other
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18 81 published and unpublished sources and documentation.
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20 82 • An international group of stakeholders, including patients, physicians, federal regulators,
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22 83 industry scientists, pharmacologists and pharmacists, nurses, and non-physician providers
23
24 84 will be included in the process.
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26 85 • At least two rounds of Delphi process will then be performed to identify a provisional list
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28 86 of outcomes meeting a 70% consensus level for patient and physicians, followed by the
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30 87 convening of a consensus meeting to review and process the results, and to vote on a final
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32 88 set of core outcomes.
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34 89 • This COS will establish “what” should be measured, but not “how” or “when,” which
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36 90 will be defined in later development of core outcome measure set for melasma.
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92 INTRODUCTION

93 Melasma is a chronic hyperpigmentation disorder primarily occurring in women.^{1,2} The
94 condition is characterized by brown, irregularly shaped macules and patches, commonly of the
95 bilateral upper cheeks, mid forehead, and upper lip. Predisposing risk factors for the
96 development of melasma include darker skin types III and IV, genetic predisposition, ultraviolet
97 radiation, and hormonal changes due to pregnancy, menopause, or medications.³⁻⁵ However,
98 melasma remains a poorly understood condition that also arises in the absence of traditional risk
99 factors, with a significant minority of cases occurring in men.⁶ Histologically, there is an
100 increase of melanocytes and solar elastosis in the epidermis of melasma lesions compared to
101 normal skin.^{2,4,7} Due to its sometimes striking impact on cosmetic appearance, melasma can
102 cause psychological distress, thereby negatively affecting quality of life.³

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

110 Systematic reviews of treatments for melasma are limited in utility by the lack of
111 standardization in outcomes across trials.⁸ The selective inclusion of outcomes in publications,
112 so-called selective outcome reporting bias, remains a problem in the reporting of clinical trials.
113 In particular, the heterogeneity of outcomes reported across trials may affect the
114 recommendations and conclusions of systematic reviews.⁹ In order to address the heterogeneity

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3 115 of outcomes in clinical trials of the same disease or condition, The Core Outcome Measures in
4
5 116 Effectiveness Trials (COMET) initiative was created, with the goal of providing methodological
6
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8 117 support to facilitate development of standardized core outcome sets to be measured in health-
9
10 118 related research.¹⁰ A core outcome set (COS) is defined as a consensus-derived set of outcomes
11
12 119 that are measured at minimum in all clinical studies of a given condition or disease. Similarly,
13
14 120 another group, the Cochrane Skin - Core Outcome Set Initiative (CS-COUSIN), was developed
15
16 121 specifically to address core outcome sets in dermatology.¹¹ CS-COUSIN provides
17
18 122 methodological support, and much of its approach is based on the experience of the Harmonizing
19
20 123 Outcome Measures for Eczema (HOME) initiative.¹²⁻¹⁶

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24 124 To date, there has been no core outcome set published specifically for melasma. The data
25
26 125 obtained from the investigation described in this protocol will define the minimum set of
27
28 126 outcomes that should be reported in future clinical trials of melasma interventions.

31 127 **Objective**

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34 128 The aim of this study will be to develop a COS through an international consensus
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36 129 process, for use in future clinical trials of melasma. The objective is to determine what outcomes
37
38 130 should be reported as a minimum in future clinical trials of melasma.

41 131 **Scope of this COS**

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45 132 This COS is envisioned as the global standard for all clinical trials examining the efficacy
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47 133 and safety of all melasma interventions, including both early and late phase trials. The COS to be
48
49 134 developed is intended to apply to all individuals with melasma, regardless of age, gender, and
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51 135 ethnicity.

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3 136 This COS will establish “what” should be measured, but not “how” or “when,” which
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5
6 137 will be defined in a later consensus study specific to outcome measures.
7

8 138 **METHODS AND ANALYSIS**

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10 139 This study was designed using guidance provided by the CS-COUSIN and COMET
11
12 140 initiatives and has been registered with both organizations.^{17–20} Additional guidance was
13
14 141 provided by the Harmonising Outcome Measures for Eczema (HOME) roadmap.¹⁶ The reporting
15
16 142 of this protocol conforms to the COS-STAP (The Core Outcome Set-STANDARDISED Protocol
17
18 143 Items) Statement checklist and the CS-COUSIN Core Domain Development Process
19
20 144 guidance.^{18,21} This protocol is also based on prior work in protocol development by the
21
22 145 Measurement of Priority Outcome Variables in Dermatologic Surgery (IMPROVED) Group, a
23
24 146 core outcome set development organization for dermatologic surgery-related conditions.²²
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29 147 **Study Oversight**

30
31 148 The international study steering committee developing this COS will include four
32
33 149 physicians (MA, IAM, JFS, TVC) as well as a patient representative. The latter, who will also
34
35 150 have melasma, will represent others with this condition by providing input at key points to
36
37 151 ensure that the patient perspective is incorporated. The four physicians have prior experience in
38
39 152 developing core outcome sets in dermatology and therefore also act as researchers in COS
40
41 153 development. The steering committee will lead each stage of COS development and ensure
42
43 154 methodological quality throughout the study. In addition, an independent member of the CS-
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45 155 COUSIN Methods Group (JJK) will provide guidance on the most current methodological
46
47 156 recommendations for COS development.
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52 157 **Study Design**

53 54 55 158 *Identification of Outcomes*

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3 159 A long list of outcomes will be generated from four sources. First, a systematic review of
4
5 160 the literature, which has been registered prospectively with the International Prospective Register
6
7 161 of Systematic Reviews (PROSPERO, CRD42020214189), will be performed to identify and
8
9
10 162 extract outcomes measured in randomized controlled trials of melasma. Specifically, with the
11
12 163 help of a medical librarian, PubMed/Medline and Embase will be searched for the period 2006-
13
14 164 16 to detect English language human RCTs including, but not limited to, the following terms:
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16
17 165 [(melasma [title/abstract]) AND (randomized controlled trial [publication type]) AND (treatment
18
19 166 OR therapy OR therapeutics)]. RCTs will be used to identify outcomes of interest, since it is
20
21 167 usual and customary in COS methodology to focus on RCTs when they are available in
22
23 168 sufficient variety and quantity.²³⁻²⁶ Inclusion criteria will be studies that: (1) are randomized and
24
25 169 controlled; (2) assess the efficacy and/or safety of one or more interventions for treatment of
26
27 170 melasma; (3) are available in the English language; (4) and involve human subjects. Articles will
28
29 171 be excluded if they: (1) were published as a poster or conference abstract; or (2) the full text of
30
31 172 the article is unavailable. Articles will be independently screened for eligibility by two
32
33 173 investigators, and disagreements will be resolved by a third investigator. Two independent
34
35 174 reviewers will then extract outcomes from individual studies. During extraction, quality of life
36
37 175 (QoL) outcomes will be separated into distinct categories to ensure all of the various components
38
39 176 of QoL that have been measured in previous investigations are included as possible core
40
41 177 outcomes. Outcome measures will also be extracted during this step, and this data will be
42
43 178 recorded for the future development of a core outcome measure set for melasma.²⁷ The results of
44
45 179 the systematic review will be published separately from the COS.
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3 180 Second, other printed and electronic sources, including clinical trial registries,¹ patient
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5 181 pamphlets,² medical society brochures, and relevant FDA/EMA guidance documents, will be
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7 182 reviewed to identify any additional outcomes not detected in the systematic review. Third,
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10 183 outcomes valued by patients will be identified by conducting semi-structured interviews with
11
12 184 patients diagnosed with melasma.³ These interviews will be audio-recorded, transcribed, and
13
14
15 185 analyzed by the methods of qualitative research to find outcomes considered relevant by patients.
16
17 186 Fourth, semi-structured interviews will be performed to identify any remaining outcomes
18
19 187 deemed relevant by representatives of key non-physician, non-patient stakeholder classes,
20
21 188 including industry scientists,⁴ pharmacologists and pharmacists, drug and device safety
22
23
24 189 regulators⁵, nurses, and physician assistants. Semi-structured interviews with patients and other
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26 190 stakeholders will be conducted by investigators who have been trained in this qualitative
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28 191 research technique. Specifically, such interviews will be comprised of a series of open-ended
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31 192 questions, followed by pre-established prompts, in the event that respondents are unclear as to
32
33 193 the primary question. At the end of the semi-structured interview, stakeholders will be asked to

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37 ¹ Clinicaltrials.gov searched for “melasma”, 2017-2021, no exclusion criteria.

38
39 ² American Academy of Dermatology website searched for “melasma”, with inclusion criteria being “all patient
40 education material”, and no exclusion criteria.

41
42 ³ The Electronic Data Warehouse (EDW) of outpatient dermatology clinics at Northwestern University will be
43 searched to identify patients who have received consultations or treatments for melasma. At least 20 patients will be
44 contacted by telephone for interviews. Those who agree to respond will each be scheduled via email for a 30-minute
45 interview.

46
47 ⁴ Leaders at a purposive sample of large, medium-sized, and small US drug, device, and cosmetic companies
48 involved in research on products for melasma will be contacted to ask for identification of qualified industry
49 scientists in their employ who can help identify additional outcomes. In total, up to 20 industry scientists will be
50 contacted.

51
52 Drug and device safety regulators from the countries most represented in the systematic review will be contacted for
53 interviews. When their names are publicly available, officials from dermatology or cosmetic-related offices within
54 these regulatory agencies will be contacted first.

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56 ⁵ US Food and Drug Administration, European Medicines Agency, Ministry of Food and Drug Safety (Korean),
57 Pharmaceuticals and Medical Devices Agency (Japan), Health Canada, Brazilian Health Regulatory Agency
58 (ANVISA).

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3 194 volunteer any additional information about the topic that they may wish to share. Interviewers
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5 195 will be strictly prohibited from using off-script leading questions that may bias data collection.
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7 196 After the semi-structured interviews are completed, they will be transcribed, and the iterative
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10 197 methods of qualitative methods will be used to extract common themes. These themes, if not
11
12 198 already present in the list of outcomes, will then be used to create new outcomes that will be
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14 199 appended to the long list. Non-physician, non-patient stakeholders will not be invited to
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16
17 200 participate in the subsequent Delphi process but will be invited to the final consensus meeting.
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20 201 *Final Review of Long List of Outcomes*

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23 202 The outcomes obtained from the sources above will be collated into a long list of
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25 203 provisional outcomes. Members of the steering committee will review and condense this list,
26
27 204 eliminating duplicate items and combining items when possible, without loss of content. In
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29
30 205 accordance with the proposed definition of a unique outcome by Young et al., unique outcomes
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32 206 (i.e., outcomes with “original meaning and context”) will be preserved, and other outcomes (i.e.,
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34 207 those “with different words, phrasing, or spelling addressing the same concept and context”) will
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37 208 be lumped together.²⁸ The list of outcomes will then be placed into appropriate domains by two
38
39 209 steering committee members using the COMET and CS-COUSIN taxonomies.^{29,30} Lay
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41 210 definitions will be appended to all outcomes and reviewed by the melasma steering group patient
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43 211 representative to assure that patient stakeholders can actively participate in the forthcoming
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46 212 Delphi consensus process.
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49 213 *Delphi Participants*

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52 214 Two separate groups, consisting of physicians and patients, respectively, will be invited
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54 215 to take part in the Delphi process. A global context will be provided by inviting physicians from
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3 216 the United States and from other countries on various continents, including a range of ethnicities.
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5 217 To include the perspective of researchers, the senior authors of all clinical trials extracted in our
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7 218 literature review will be included in the physician group. Eligible physician stakeholders will
8
9 219 include dermatologists, clinical researchers, primary care providers, and other medical specialists
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11 220 who have experience treating melasma. Demographic information, including participants'
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13 221 ethnicity, gender, and specialty will be recorded. To account for potential dropouts, at least 100
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15 222 physicians meeting any of the following criteria will be invited: corresponding author of a
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17 223 clinical trial of melasma included in our systematic review; among the most frequently
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19 224 published authors on melasma treatment, as identified through electronic databases; recent
20
21 225 lecturer on the topic of melasma at national or international dermatology professional society
22
23 226 meetings in any country; or a member of a national or international dermatologic society⁶ with
24
25 227 clinical expertise in melasma treatment, as demonstrated by committee or other affiliations.
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31 228 Physicians who agree to participate will be asked to identify one or more melasma
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33 229 patients who may be invited to join the patient Delphi group, with a goal of 15 patient
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35 230 stakeholders participating in the Delphi. All recruitment will be done by our study team and will
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37 231 be approved by our ethics committee. However, this will not entail limiting patient recruitment
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39 232 from our site only, since we will be asking physician Delphi participants located elsewhere to
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41 233 volunteer patients who may choose to participate in the study. Such patient volunteers will
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47 ⁶ Representative board members of the following societies will be invited to participate as individuals in the Delphi
48 to ensure inclusion of the perspectives of expert clinicians and researchers who may not have recently published in
49 the literature: American Academy of Dermatology Association; American Society for Laser Medicine and Surgery;
50 African Society of Dermatology and Venereology; Asian Academy of Dermatology and Venereology; Arab
51 Academy of Dermatology and Aesthetics; Argentine Society of Dermatology; Brazilian Society of Dermatology;
52 British Association of Dermatologists; Canadian Dermatology Association; European Academy of Dermatology and
53 Venereology; French Society of Dermatology; Mexican Society of Dermatology; Skin of Color Society; World
54 Congress of Dermatology.
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3 234 contact the research staff at our site, who will consent and enroll them, if appropriate. Additional
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5 235 methods will be taken to ensure patient involvement throughout the study, including: (1)
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7 236 specifying patient involvement in the Institutional Review Board (IRB) protocol; (2) seeking
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9 237 relevant input from patients; (3) maintenance of investigator open-mindedness to the patient
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11 238 perspective; (4) careful reviewing of all outcomes with patient representatives; (5) thorough note
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13 239 taking; (6) taking time to reflect on patient feedback; and (7) identifying and engaging a diverse
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15 240 group of patient participants.³¹
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20 241 *Modified Delphi Process*

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23 242 From the long list of potential outcomes vetted by the steering committee, a core set of
24
25 243 outcomes will be provisionally selected by stakeholders through a Delphi process, as
26
27 244 recommended by the COMET and CS-COUSIN initiatives.^{17,18,30} Specifically, each Delphi
28
29 245 participant will be asked to rate each outcome for its level of importance on a scale from 1-9.
30
31 246 Average ratings for each outcome, and relevant participant comments, will then be redistributed
32
33 247 to each survey participant, who will have the option of changing his or her earlier ratings based
34
35 248 on the additional information surfaced in this process. Prior to a consensus meeting, at least two
36
37 249 Delphi rounds will be conducted using DelphiManager software available for this purpose from
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39 250 COMET.
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44 251 *Delphi Rounds*

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47 252 During each Delphi round, the provisional outcomes in the long list will be presented to
48
49 253 each participant for rating. Participants will rate each outcome on a 9-point scale developed by
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51 254 the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working
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53 255 group, with “9” denoting “critically important” and “1,” “not that important.”³² In each round,
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3 256 each participant will have the option to select “10” if they are uncertain about an outcome’s need
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5 257 for inclusion. Also in each round, each participant will have the option to identify new outcomes
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7 258 that they feel should be added in the subsequent round. All previously included outcomes will be
8
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10 259 carried to the next round. Participants will have 3 weeks to complete each Delphi round, and will
11
12 260 receive weekly reminders until they do, or time expires.

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14
15 261 Results from Round 1 will be analyzed by outcome and for each stakeholder group.
16
17 262 After Round 1, a virtual meeting will be held with participants to discuss the results of the first
18
19 263 round, and to allow participants to share their thoughts about items they found particularly
20
21 264 salient or controversial. Then, Round 2 will commence. In Round 2, participants will be
22
23 265 graphically shown the distribution of scores for each item for each stakeholder group from
24
25 266 Round 1, and also their own individual ratings for each outcome from the previous round, and
26
27 267 asked to score each item again. New outcomes will be added to Round 2 if suggested by two or
28
29 268 more participants in Round 1, if the steering committee determines the suggested outcome(s) to
30
31 269 be unique from existing outcomes.²⁸

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34 270 Summarized scores from Round 2, analyzed by outcome and for each stakeholder group,
35
36 271 will be presented at the consensus meeting. Attrition is possible between Delphi rounds, and
37
38 272 although numeric data (e.g., mean, median, and range of scores) from Round 2 alone will be
39
40 273 analyzed and presented at the consensus meeting, written feedback from both rounds will be
41
42 274 collated and discussed at the consensus meeting, as well.

43 275 *Definition of Provisional Consensus*

44
45
46 276 Outcomes will be *retained* in the provisional consensus pool if 70% of the participants
47
48 277 score 7, 8, or 9 with less than 15% scoring 1-3.³³ Outcomes will be *removed* from the provisional
49
50 278 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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3 279 To avoid having a core outcome set that entails too many items, if the provisional list of included
4
5 280 outcomes is longer than expected, participants at the consensus meeting will be urged to further
6
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8 281 refine and abbreviate this list. The definition of consensus is based on previous, published COS
9
10 282 consensus methodology, and guidance of the COMET Methodology Group.^{17,34–36} Outcomes
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12 283 that have not reached consensus will also be retained for discussion during the consensus
13
14
15 284 meeting.

17 285 *Consensus Meeting*

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20 286 A series of virtual consensus meetings will be held to discuss the results of the Delphi, to
21
22 287 review the provisional core outcome set as well as the outcomes for which consensus has not
23
24
25 288 been reached, and to move towards selection of a final core outcome set. The reason to have more
26
27 289 than one consensus meeting is to avoid the scenario in which the loudest voices dominate, and patients in
28
29 290 particular are not heard as clearly and to the extent that they should be. Since we anticipate 30-60
30
31 291 healthcare professionals, and approximately five patients to participate in the process, we anticipate three
32
33 292 virtual consensus meetings of 15-20 participants each, with each meeting also including patient
34
35
36 293 participants. An additional benefit of having multiple consensus meetings is that different schedules and
37
38 294 time zones can be accommodated. Finally, if the outcomes of the different consensus meetings are not
39
40 295 fully consistent, an email ballot will be sent to all participants individually to resolve any remaining
41
42 296 issues. Each meeting will be moderated by an independent facilitator, and invited participants will
43
44 297 include all physicians and patients who participated in at least the first round of the Delphi. Each
45
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47 298 meeting will have balanced representation across stakeholder groups and geographic regions to
48
49 299 ensure the result is development of a global COS. Other non-physician, non-patient stakeholders
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51 300 will be invited, as well.

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3 301 Informed by the Delphi results, feedback regarding the consensus-derived set of
4
5 302 provisional outcomes and outcomes for which consensus has not been reached will be elicited
6
7 303 from the consensus meeting participants with the assistance of the facilitator. Using live polling
8
9 304 software, participants will vote to include or not include outcomes into the final core set of
10
11 305 outcomes. If multiple consensus meetings are held, and if there is any inconsistency between the
12
13 306 outcomes selected in these, a final email ballot will be circulated to all consensus meeting
14
15 307 participants to confirm the final COS. The result will be a core outcome set that reflects the
16
17 308 priorities and concerns of all stakeholders.
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22 309 **Timeline**

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25 310 The expected timeline from the start of the study to full development of the core set of
26
27 311 outcome domains will be 18 to 24 months. Identification of an initial list of outcomes, via
28
29 312 systematic review followed by qualitative interviews, will span approximately seven to eight
30
31 313 months. An additional seven to ten months will be dedicated to conducting the Delphi survey and
32
33 314 convening the consensus meeting, followed by approximately four to six months for analyzing
34
35 315 feedback and drafting, circulating, and finalizing the manuscript.
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43 317 **Patient and Public Involvement**

44
45 318 The patient and public perspective will be sought at multiple points in this study. Patient
46
47 319 stakeholders will review plain language summaries of outcome definitions. A minimum of one
48
49 320 patient representative will be included in the research team, as described earlier in this protocol.
50
51 321 Additionally, patients will be recognized as key stakeholders during the identification and
52
53 322 prioritization of outcomes, with fully one-half of the Delphi process reserved for patients.
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3 323 Patients will be encouraged to provide feedback before (semi-structured interviews), during, and
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5 324 after (at the consensus meeting) the Delphi process to ensure that patient-centered outcomes are
6
7 325 incorporated. Lastly, with their consent, patient representatives will be named as contributors in
8
9 326 any published work that arises from the study.
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13 327

16 328 **ETHICS AND DISSEMINATION**

18 329 **Dissemination and Implementation of Results**

21 330 The full development of this COS and the results of the study will be reported in peer-
22
23 331 reviewed journals. The main results of the study, including the core outcome set, will be
24
25 332 disseminated to all participants through email at the time of study publication. Researchers will
26
27 333 be encouraged to use the COS when performing future trials.
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34 335 **Ethical Approval and Consent to Participate**

37 336 Ethical approval and consent to participate for the study has been granted from the
38
39 337 Northwestern University IRB (protocol ID: STU00201637). Informed consent will be presented
40
41 338 before registering for the Delphi. The Northwestern University IRB has waived written informed
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43 339 consent and has approved verbal consent for interviews, and online consent for the Delphi
44
45 340 process.
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52 342 **DISCUSSION**

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3 343 Despite the numerous completed and ongoing clinical trials of treatments for melasma,
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5 344 there is currently no COS informing such investigations. The proposed core outcome set for
6
7 345 melasma would provide a minimum set of outcomes to be reported in all trials of melasma, thus
8
9
10 346 standardizing future outcomes reporting. Investigators would be free to consider and include
11
12 347 additional outcomes beyond the core set, but their use of at least the core set would allow
13
14 348 aggregation and comparison of data across melasma trials. Cross-trial comparisons of
15
16 349 treatments and large-scale meta-analyses would, in turn, enable more definitive conclusions on
17
18 350 the merits of available treatments.
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25 352 **Trial Registration and Status**

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28 353 This study has been registered with both the COMET and CS-COUSIN initiatives for
29
30 354 core outcome set development, and the development of this protocol is in accordance with the
31
32 355 guidelines for protocol development of both groups. The development of the core outcome set is
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34
35 356 currently in its initial phase of outcome extraction.
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3 360 **DECLARATIONS:**
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5 361

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8 362 **Abbreviations**
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10 363 **COMET:** Core Outcome Measures in Effectiveness Trials
11

12 364 **COS:** Core outcome set
13

14 365 **CS-COUSIN:** Cochrane Skin - Core Outcome Set Initiative
15

16
17 366 **HOME:** Harmonising Outcome Measures for Eczema
18

19 367 **IMPROVED:** Measurement of Priority Outcome Variables in Dermatologic Surgery Group
20

21 368
22

23
24 369 **Consent for publication**
25

26 370 All authors consent.
27

28 371
29

30
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11 389 **Data availability statement**

12
13
14 390 There are no data in this work.
15
16 391

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18
19 393 This publication was supported by Merz Center for Quality and Outcomes Research in
20
21 394 Dermatologic Surgery and the IMPROVED (Measurement of Priority Outcome Variables in
22
23 395 Dermatologic Surgery) Group.
24
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26 396

27 397 **Competing Interests**

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29
30 398 None of the authors have personal or financial relationships with other people or organizations that may
31
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