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## A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure

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## A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure Frederike Fransen<sup>1</sup>, Phyllis I. Spuls<sup>1</sup>, Murad Alam<sup>2,3</sup>, Ashraf Badawi<sup>4</sup>, Pablo Boixeda<sup>5</sup>, Merete Haedersdal<sup>6,7</sup>, Iltevat Hamzavi<sup>8</sup>, Lene Hedelund<sup>9</sup>, Kristen Kelly<sup>10</sup>, Taro Kono<sup>11</sup>, Hans-Joachim Laubach<sup>12</sup>, Woraphong Manuskiatti<sup>13</sup>, Leonardo Marini<sup>14</sup>, Keyvan Nouri<sup>15</sup>, Uwe Paasch<sup>16</sup>, Thierry Passeron<sup>17,18</sup>, Cecilia A.C. Prinsen<sup>19</sup>, Ines Verner<sup>20</sup>, Albert Wolkerstorfer<sup>1</sup> <sup>1</sup> Department of Dermatology, Amsterdam Public Health, Infection and Immunity, Amsterdam University Medical Center, Amsterdam, the Netherlands <sup>2</sup>Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. <sup>3</sup>Department of Dermatology, Northwestern Memorial Hospital, Arkes Family Pavilion, 676 N Saint Clair Suite 1600, Chicago, IL, 60611, USA. <sup>4</sup>Dermatology Unit, Department of Medical Applications of Lasers (MAL), National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt. <sup>5</sup>Dermatology Department, Ramón y Cajal Hospital, Madrid, Spain. <sup>6</sup>Massachusetts General Hospital, Harvard Medical School Boston, USA. <sup>7</sup>University of Copenhagen, Bispebjerg Hospital, Denmark.<sup>8</sup>Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA. <sup>9</sup>Department of Dermatology, Aarhus University Hospital, Denmark. <sup>10</sup>Beckman Laser Institute, University of California, Irvine, California, USA. <sup>11</sup>Department of Plastic and Reconstructive Surgery, Tokai University School of Medicine, Isehara, Japan. <sup>12</sup>Department of Dermatology and Venereology, Geneva University Hospitals (HUG), Switzerland. <sup>13</sup>Faculty of Medicine Siriraj Hospital, Department of Dermatology, Mahidol University, Bangkok, Thailand. <sup>14</sup>SDC - The Skin Doctors' Center, Trieste, Italy. <sup>15</sup>Dermatology and Cutaneous Surgery, University of Miami School of Medicine, 1475 NW 12th Ave., Miami, FL, 33136, USA. <sup>16</sup>Department of Dermatology, Venereology and Allergy, University of Leipzig. <sup>17</sup>University of Côte d'Azur, University Hospital Nice, Department of Dermatology, Nice, France. <sup>18</sup>University of Côte d'Azur, Centre Méditéranéen de Médecine Moléculaire (C3M), INSERM 52 27 U1065, team 12, Nice, France. <sup>19</sup>Department of Epidemiology and Biostatistics, Amsterdam Public Health research institute, Amsterdam UMC, The Netherlands. <sup>20</sup>Verner Clinic, Tel Aviv,

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ABSTRACT

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Introduction: While laser technology has expanded the armamentarium of treatment for various skin diseases during the past years, heterogeneity in study outcomes hampers comparability and appropriate evidence synthesis. Part of these issues can be addressed by developing a generic outcome set. Using the Delphi method, this study aims to seek consensus between key stakeholders on relevant generic outcomes (*what* to measure) for implementation in the international registry on Laser trEAtments in Dermatology (LEAD). The registry is focused on collecting research data on various laser treatments for skin disorders.

Methods and analysis: By reviewing the literature and involvement of key stakeholder groups and adult patients in need or after laser surgery and health professionals, a preliminary list of outcomes will be generated and categorized into domains. Using these outcomes, an international three-round Delphi study will be performed to rate the importance of outcomes in the selection of a generic outcome set. Participants are allowed to provide new outcomes to the prelimary list for revisions during the first Delphi round. Finally, results will be discussed during a consensus meeting to agree on generic outcomes to be used in the LEAD Registry.

Ethics and Dissemination: An ethics approval was not applicable (W19\_290 # 18.336). The study is registered with the CS-COUSIN (Cochrane Skin Core OUtcome Set INitiative) and the Core Outcome Measures in Effectiveness Trials (COMET) initiative. Procedures will be conducted according to the Declaration of Helsinki. The findings will be disseminated through peer-reviewed publications and conference presentations.

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3	91	
4 5	~ <b>~</b>	
6 7	92	<b>Keywords:</b> Laser Therapy, Dermatology, Consensus study, Delphi study, Disease registry, Generic
8	93	Outcome Set
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18	00	Change with a good line in this stands
19 20	96 97	Strengths and limitations of this study
21 22		
23	98	•This protocol outlines the first international consensus effort to develop a generic outcome
24 25	99	set for use in the international LEAD laser registry.
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28 <sup>1</sup> 20	00	• With advances in laser technology, considering outcomes of importance ( <i>what</i> to measure) to
29 30 1	01	patients and health professionals is crucial.
31 32 1	02	• A comprehensive systematic review will evalure which outcomes are used and reported in
33 <sup>1</sup> 34	02	•A comprehensive systematic review will explore which outcomes are used and reported in
35 1	03	existing studies on laser treatments.
36 37 1	∩4	• The Delphi procedure requires three survey rounds and involves a large group of stakeholders
38 <sup>-</sup> 39	01	The Delphi procedure requires three survey rounds and involves a large group of stationalers
40 1	05	across various disciplines and geographical areas including patients, reflecting different
41 42 1	06	viewpoints.
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2 3 114	INRODUCTION
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5 6 115 7	During the past decades, modifications in laser technology have further widened its scope and
8 <sub>9</sub> 116	greatly expanded the cutaneous laser surgeon's armamentarium [1,2]. Today, there are many
10 11 <b>117</b> 12	medical indications in dermatology, encompassing vascular, pigmented, inflammatory,
<sup>13</sup> 118 14	metabolic or infectious lesions, benign tumours, scars, and hair follicle- related skin conditions
15 16 119 17	that are regularly - and sometimes exclusively - treated with lasers [1–3]. Many of these
18 <b>120</b> 19	disorders meet the criteria of an orphan disease.
<sup>20</sup>	
21 22 <b>122</b> 23	The diversity in laser devices and the spectrum of medical indications pose unique research
<sup>24</sup> 123 25	challenges for clinical decision-making in laser therapy. Because most laser physicians are not
26 27 124 28	exposed to large numbers of patients receiving laser treatments for uncommon indications,
29 <b>125</b> 30	knowledge on the most effective laser treatment, including safety and used regimen, is unclear.
<sup>31</sup> 32 33	The current evidence for most of these specific skin conditions is sporadic at best, consisting
34 <b>127</b> 35	mostly of case reports and case series and only a very small number of randomized controlled
<sup>36</sup> 37 38	trials (RCTs) [4,5]. Moreover, most often only isolated successes are reported while cases that
39 129 40	failed to respond are not published, leading to publication bias [6].
41 42 43	Another issue hampering evidence synthesis is heterogeneity of outcome definition,
44 131 45	measurement and reporting in laser research. Patient-reported outcomes (PROs), such as
46 132 47 48	'patient experience of laser treatments' and 'health-related quality of life', are often not
49 49 50	reported and together with selective outcome reporting in laser research, it is all a serious
51 <b>134</b> 52	threat to comparative effectiveness research as it limits the ability to compare, contrast, and
53 54 55	combine individual studies [7,8]. As a result, this hampers to draw meaningful conclusions and
56 136 57 58 59 60	guidance to inform clinical decision-making [9,10].

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137 To overcome this issue in the field of laser dermatology, the development of the International 138 Laser Treatment (LEAD) Registry has been proposed to initiate collaborative data pooling of a 139 wide range of skin disorders. The development of a registry may be the key to the lack of solid 140 evidence for laser treatments in dermatology, however, well-defined standardized and generic outcomes are required for its establishment.

<sub>17</sub> 143 To address the variations in outcome reporting, organizations such as the Core Outcome 19 144 Measures in Effectiveness Trials Initiative (COMET) bring together researchers interested in developing a standardized set of core outcomes in various health-related fields [11]. A core 145 24 1 4 6 outcome set (COS) is defined as an agreed minimum set of outcomes that should be measured <sup>26</sup> 147 and reported in all clinical trials for a specific health condition, including methods used to 29 1 4 8 measure these core outcomes[10,12]. Throughout this report, the definition of "outcome" <sup>31</sup> 149 refers to a single construct that can be measured as a standalone item (e.g. 'erythema'), while <sub>34</sub> 150 the term "outcome domain" or "domain" is an umbrella term for a group of associated <sup>36</sup> 151 outcomes (e.g. 'signs as assessed by physician'). Furthermore, the outcome instrument refers <sub>39</sub> 152 to how the outcomes are measured. Although a COS is recommended for clinical trials, they can 41 153 also be developed for routine clinical practice, and for registries [10,12]. In 2015, the 154 international, multidisciplinary working group, the Cochrane Skin Group- Core OUtcome Set 46 155 INitiative (CS-COUSIN) has been established [13]. The organization supports dermatology-156 specific initiatives to develop and implement a COS by building upon experiences of the Harmonizing Outcome Measures for Eczema (HOME) initiative, which developed a roadmap to 51 157 <sup>53</sup> 158 guide the process of COS development and implementation [14]. Currently, 17 COS initiatives 55 <sub>56</sub> 159 have been supported by CS-COUSIN in dermatology. These projects involve 26 different skin 57 <sup>58</sup> 160 diseases, such as acne, atopic eczema, hidradenitis suppurativa, melanoma, nail psoriasis, 59 60

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<sup>3</sup> 161 4	rosacea, and vitiligo [11,15]. However, with hundreds of different and mostly unrelated
5 6 162 7	dermatoses that are treated with lasers in the field of laser dermatology, the need for a generic
8 163 9	outcome set (GOS) is commanding. Therefore we focus on developing a GOS ( <i>what</i> to measure)
10 11 164	for the purpose of the LEAD registry. The GOS is intended to be applied for the assessment of
13 165 14 <sup>15</sup> 166	various, unrelated skin diseases that are treated with different types of lasers.
16 17 18	In summary, there is an urgency of using the same generic outcomes in laser therapy. Hence,
19 168 20	establishing consensus on the relevant outcomes for the LEAD registry will promote clinical
<sup>21</sup> 22 23	researchers to use outcomes chosen by consensus that are relevant to patients and clinicians.
24 170 25	The use of generic outcomes support data synthesis for many diseases in dermatology. The
<sup>26</sup> 27 28	protocol outlines the context, scope and methods for the development of a GOS to be
29 172 30 31	implemented in the LEAD registry.
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<sup>33</sup> 173 <sup>34</sup> 174	Aims and objectives
36 175 37	Aim
<sup>38</sup> 176 39	The aim of this study is to reach consensus between various stakeholders on generic outcomes
40 41 42 43	relevant for the LEAD registry.
44 178 45 179	Objectives
46 17 5 47 180 48	Our study objectives are:
49 181 50	1. To identify outcomes that have previously been used and reported in RCTs, cohort
<sup>51</sup> 182	studies, case-control studies and case series from a literature review and classify these
53 54 183 55 56	outcomes into domains according to the COMET taxonomy;
<sup>57</sup> 184 58	2. To reach consensus between stakeholders on the outcomes of a GOS to be implemented
<sub>60</sub> 185	in the LEAD registry.

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## Scope and applicability of outcomes

The registry is envisioned to suit all types of laser interventions for skin disorders in dermatology including vascular, pigmented or inflammatory lesions, benign tumours, scars, and hair folliclerelated skin conditions treated with lasers. The GOS is intended for use in the LEAD registry, with the focus on prospectively recording the effectiveness and safety of cutaneous non cosmetic laser interventions. Therefore we excluded laser assisted drug delivery, low laser level therapy, body- contouring, skin tightening, hair removal, rejuvenation and anti-aging procedures. Furthermore, because of the distinctive mode of action and use in daily clinical practice, laser assisted drug delivery, low laser level therapy and laser procedures for (leg) veins were excluded.

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6 METHODS AND ANALYSIS

## 198 Research group

The steering committee (FF, PS, AW, MA, AB, PB, IH, MH, LH, KK, TK, HL, WM, LM, KN, UP, TP, CP, V) provide input at critical points of the study such as protocol development, stakeholder recruitment, consensus process and the consensus meeting. Three members of the steering committee (FF,PS,AW) coordinate the overall project, ensure methodological quality of the project and make key decisions. All members of the steering committee will participate in the Delphi procedure as well as in the final consensus meeting. The steering committee has representatives from The Netherlands, Denmark, Egypt, France, Germany, Israel, Italy, Japan, Spain, Switzerland, Thailand and USA, with extensive expertise in various laser treatments, outcomes research and clinical research. A list of all members of the steering committee is given in supplementary file 1.

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<sup>3</sup> 209	Study design
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6	Figure 1 provides a brief querview of the stanuise approach with different research methods
7 210	rigule 1 provides a brief overview of the stepwise approach with different research methods.
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<sup>9</sup> 211	The study consists of the following two phases:
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12 212	Dhann 4. Islandification of a stanticlass terms in a stant in large twenty outs by assess of a
13 212	Phase 1: Identification of potential outcomes important in laser treatments by means of a
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16 <b>21</b> 3	1. A systematic review to form the preliminary list of outcomes for the Delphi survey
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19 214	2. Classification of outcomes into domains according to the COMET taxonomy [10]
20 214	2. Classification of outcomes into domains according to the COMET taxonomy [19]
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26 216	Phase 2: A consensus process involving key stakeholders who are able to suggest additional
27 210	rhase 2. A consensus process involving key stakeholders who are able to suggest additional
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<sub>29</sub> 217	outcomes during the first round and who will rate the importance of outcome for reaching
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<sup>31</sup> 218	consensus on the GOS by means of a
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38 220	2. Expert consensus meeting. attended by representatives of all stakeholder groups.
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<sup>41</sup> 221	
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45 222	This study is registered with the CS-COUSIN and COMET initiative [11,16]. Results of the
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<sup>47</sup> 223	consensus study will be reported according to the Core Outcome Set-STAndards for Reporting
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50 2 2 4	(COS-STAR) [17].
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## 227 Phase 1: Identification of potential outcomes and domains

## 228 Phase 1.1: Systematic literature review

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10 229 The first phase of the study is to identify which outcomes should be measured and reported in a 11 12 13 2 3 0 registry on laser treatments for skin disorders (what to measure: the GOS, see definitions in 14 15 231 supplementary file 2). A SR will be performed to explore existing outcomes that are used in laser 16 17 18 2 3 2 studies. According to the COMET guidelines [18], searches will be performed in the following 19 <sup>20</sup> 233 database: MEDLINE and EMBASE. Articles between January 2013 and December 2017 will be 21 22 retrieved. The electronic search strategy is detailed in supplementary file 3. A recent 5-year time <sub>23</sub> 234 24 <sup>25</sup> 235 period has been selected for the search so that outcomes extracted represent the practice of 26 27 \_, 28 236 present-day laser research. The inclusion and exclusion criteria are presented in Table 1. Two 29 30 2 37 reviewers will select articles and extract the data independently. Disagreement will be resolved 31 32 238 by discussion and by consulting a third review author if necessary. The following data will be 33 34 extracted from the selected articles in data extraction tables : authors, years of publication, 35 2 39 36 <sup>37</sup> 240 country, cutaneous indications for treatment and type of laser treatments. We will assess what 38 39 outcomes and outcome measurement instrument are used, consistency in outcomes, number of 40 2 4 1 41 <sup>42</sup> 242 times an outcome was used, consistency in classification used. 43 44

# <sup>3</sup> 251 **Table 1** Inclusion and exclusion criteria for literature review

	Inclusion criteria	Exclusion criteria
Patient population and indication	Studies including patients age 18 and older with vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours and hair follicle-related skin conditions treated with lasers	Non-humans flebological skin conditions Laser assisted drug delivery, low laser leve therapy, body- contouring, skin tightening, hair remova rejuvenation and anti- aging
Study design	RCTs, cohort studies, case- control studies, case series	In vitro studies, systematic reviews, abstracts and expert opinions, case reports
Intervention	Any type of laser treatment for vascular, pigmented or inflammatory lesions, benign tumours, and hair follicle- related skin conditions.	Laser assisted drug delivery, low laser leve therapy, laser therapy for leg veins and cosmetic interventions (see scope of outcome
Outcomes		Non-clinical outcomes e.g. biochemical outcomes, imaging, confocal laser, histolog
Publication	All studies are conducted between 2013-2017	

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<sup>2</sup> 3 262 4	Phase 1.2: Classification of outcomes into domains
5 <b>263</b> 6	Subsequently, data will be classified according to the standardized taxonomy for outcomes
7 8 264	proposed by the COMET initiative [19]. This taxonomy encompasses 38 domains within 5 core
10 265 11 12	areas: mortality/survival; physiological/clinical; life impact; resource use; adverse events.
<sup>13</sup> 266	Outcomes and their classification in domains will be discussed with three members (FF, PS, AW)
15 16 267 17	of the steering committee. The preliminary list of outcomes classified to domains will be included
18 268 19 20 21 22 269 23 24	in the consensus process.
25 26 <b>27</b> 0 27 28	Phase 2: Consensus process
<sup>29</sup> 30	Phase 2.1: Delphi procedure
31 32 272 33	For investigating crucial outcomes in context of the LEAD registry, a Delphi study will be
<sup>34</sup> 273 35	conducted. The Delphi is based on a structured process for gathering and condensing knowledge
36 37 274 38	from key stakeholder groups by means of 3 rounds with a series of questionnaires [20]. The
<sup>39</sup> 275 40 41	procedure will consist of three online rounds (Figure 1).
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45 46 <b>277</b> 47	Participants
<sup>48</sup> 49278	The involvement of a variety of stakeholders is a key part for the identification of outcomes and
50 51 <b>279</b> 52 53	strongly recommended by methodologists [21].
<sup>54</sup> 280	The following representatives from four international key stakeholder groups are involved in the
57 281 58 59 60	process of reaching consensus on outcomes:

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282 1. Patients of age 18 with vascular, pigmented, inflammatory, metabolic or infectious lesions, 283 benign tumours and hair follicle-related skin conditions treated by lasers.

284 2. Patient representatives involved in patient associations that raise awareness on the impact of 285 vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours and hair follicle-related skin conditions.

287 3. Health care professionals – Laser experts who treat patients with vascular, pigmented or inflammatory, metabolic or infectious lesions, benign tumours, hair follicle-related skin conditions and who are involved in research on laser treatments.

<sub>26</sub> 290 4. Health care professionals –General physicians who treat patients with dermatological <sup>28</sup> 291 indications. revie

Panel size and recruitment

There is no robust guidance for calculating the number of participants needed for a Delphi study 39 40 295 and expectations are based on COMET Initiative guidelines and previous literature [16,22,23]. As 41 <sup>42</sup> 296 there are various stakeholder groups involved in the Delphi procedure, we will recruit as many 43 44 45 297 international representatives as possible from each group. All potential participants will be 46 <sup>47</sup> 298 invited with a letter explaining the aims and details of the study and the rationale and importance 48 49 <sub>50</sub> 299 of completing the entire Delphi process. Respondents who agree to take part will be assigned a 51 52 300 unique identification number. Furthermore, each member of the steering committee will be 53 54 301 asked to cascade the link of the survey to 3 other physicians in their network. Patients and patient 55 56 57 302 representatives will be recruited from national and international support groups for skin diseases 58 59 303 treated with lasers and can be found in supplemental file 4. In addition, laser experts from the 60

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steering committee will be asked to recruit 3 patients with different skin conditions treated with lasers in their center. To make sure that we involve skin diseases of different categories, laser experts will indicate the diagnosis of the patients that are recruited. By sending the survey invitation to experts and patient support groups from different continents, we aim to reflect a broad range of patients and health professionals with diverse backgrounds and experiences. For each round, the number of participants invited and those who completed the surveys will be documented. The participants will have 3 weeks to complete each round. We will send personal reminder emails to those who did not respond after 7 and 14 days to increase the response rate. **Delphi survey** Participants will be divided into a group of patient and a group of health professional, leading to separate scoring of outcomes. All participants will be asked to rate the importance of each of the outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluations) approach. The scale will range from 1 to 9 and will be categorized as follows: 1–3 'not important'; 4–6 'important but not critical'; and 7–9 'critical' [24,25]. If participants feel unable to rate or provide feedback they can select 'unable to score'. **Delphi rounds** Delphi round 1 During the first round of the Delphi survey, baseline characteristics (age, gender, country of practice) will be obtained from all participants. Patients will be asked for their medical indication and type of laser treatment, and whether any complications have occurred during treatment.

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2 3 326 Health professionals will be asked their specialty (laser dermatology, general dermatology or 4 5 327 other), workplace (academic, teaching hospital or non-teaching hospital) and years in practice. 6 8 328 Next, participants will be asked to score listed outcomes and will have the option to suggest any 9 10 11 329 additional outcomes that are not yet presented in the preliminary list. 12 13 Delphi round 2 and 3 14330 15 <sup>16</sup> --- 331 In the second and third Delphi rounds, all participants will receive feedback on the scores of the 17 18 previous round in both the patient and the health professional group. The outcomes from the 19 332 20 <sup>21</sup> 333 22 previous rounds will be presented with the median scores from each stakeholder group 23 <sub>24</sub> 334 combined with a histogram showing the scoring distribution. Subsequently, participants will be 25 <sup>26</sup> 335 asked to score all outcomes for which consensus has not been reached, in the same manner as 27 28 29 336 in the first Delphi round. Outcomes for which there was only consensus within a single 30 31 337 stakeholder group will also be shown to the other stakeholder group to evaluate whether 32 33 33 34 338 consensus can be achieved in both stakeholder groups. 35 36 37 339 38 39 <sup>40</sup> 340 **Definition of consensus** 41 42 43 341 The definition of consensus is presented in Table 2. 'Consensus in' is defined as approval of the 44 <sup>45</sup> 342 outcome by the vast majority (70 %) of all stakeholder groups that score 7, 8, or 9 with fewer 46 47 <sub>48</sub> 343 than the minority (15%) of panelists scoring 1–3. On the contrary, 'consensus out' is defined as 49 50 344 70% or more of all stakeholder groups scoring as 1 to 3 and less than 15% scoring as 7 to 9 [12]. 51 52 53 345 After three e-Delphi rounds, outcomes will be classified as 'consensus in' (consensus on the 54 55 346 importance of the outcome), 'consensus out' (no consensus on the importance, or consensus on 56

<sup>57</sup> 347 nonimportance) or 'no consensus' (consensus on the importance in only one or or no consensus).

#### Table 2: Definitions of consensus for identifying generic outcomes for the LEAD registry

Consensus category		
	Clarification	Definition
Consensus in	Outcome should be included in the registry	70% of stakeholder group scoring as 7 to 9 and < 159 stakeholder groups scorin 1 to 3
Consensus out	Outcome should not be included in the registry	70% or more of stakehold groups scoring as 1 to 3 a 15% of stakeholder group scoring as 7 to 9
No consensus	Hesitation about relevance of outcome to be included in the registry	Anything other
with three members of Delphi method and t	of the steering committee (FF. PS, AW)	to check misconceptions i
with three members of Delphi method and t	of the steering committee (FF. PS, AW)	to check misconceptions in
	Delphi has not been reached, we invite	15 participants from acro
definition during the		15 participants from acro
definition during the stakeholder groups to	participate in an online expert consensu	s meeting within 2 months
definition during the stakeholder groups to the close of round 3. Tl	participate in an online expert consensu he primary goal of the meeting is discussi	s meeting within 2 months
definition during the stakeholder groups to the close of round 3. The Consensus results from	participate in an online expert consensu he primary goal of the meeting is discussi n the Delphi can be reversed in this meetin	ng the 'no consensus' outco ng if reasons are very stron

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26 27	371
28 29 30	
31 32	372
33 34 35	272
36 37	3/3
38 39 40	374
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48 49	377
50 51 52	378
53 54	379
55 56 57	200
58 59 60	380

Patient and public involvement Patient and public were not involved in the development of this study protocol. However, patients will be involved and included within the Delphi procedure as expert group. Consensus methodology will ensure that the opinions and preferences of patients will be given the same weighting as those of the laser experts and health professionals. Furthermore, patients will participate in the final consensus meeting. We disseminate the main results to study participants and patients by email which will include a copy of the final outcomes of the GOS. In addition, where approval has been given, participants (including members of the public) will be named as contributors in the acknowledgments section.

372 **DISCUSSION** 

By the end of this study, we hope to reach consensus on a GOS that could be implemented in an international registry with a research focus, that collects data of rare skin diseases treated by lasers. Analysis of registry data provides insight into effectiveness and safety of different laser treatments across many skin diseases, laser centers and countries.

There are several strengths using the Delphi method for this study. First, the Delphi method allows to recruit a large number of laser experts, physicians and patients from diverse regions globally. The diversity in the experts' backgrounds and expertise ensures maximum impact of the results. Secondly, the Delphi method is the accurate tool in consensus processes in various

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stakeholder groups as individuals are able to express their own opinions and feedback can be provided in a controlled anonymous way. This means that there is room for individual disagreement but also consideration of the answers given by other individuals and stakeholder groups as a whole. However, there are also limitations of the Delphi method. Results are dependent upon the composition of the participants. There is a risk of relative uneven representations among patients, but also health professionals. Especially, when focusing on a specific group of rare skin diseases, selection bias could result in insufficient representation of other skin disorders. We request health professionals of the steering committee to recruit patients with 3 different skin disorders. Through this method, we hope to ensure that all subgroups including vascular, pigmented, metabolic, inflammatory lesions, benign tumours and hair follicle-related skin conditions, will be adequately involved. For patients it might be a barrier to imagine what is important to be included in a registry for a broad range of diseases, rather than one disease that is important to themselves. We will stress the importance of agreeing on a GOS for all diseases in each round of the Delphi survey and consensus meetings. Photographs will be included to illustrate the variety of skin disorders that are involved. To provide the highest possible input we will extend our invitation to take part in the Delphi survey to patients and health professionals in Africa, Asia, South-America, Australia, in addition to Europe and North-America. With support from all panel members we hope to ensure that the LEAD registry will be 58 399 internationally relevant, accepted and ready to use.

1	
2 3 400 4	Trial status
5 6 401 7	The identification of generic outcomes for registry use is ongoing and in the initial phase. A
8 402 9	systematic review has been performed to explore current outcomes used and reported in laser
<sup>10</sup> 11 12	dermatology. We are currently preparing to recruit participants for the Delphi study. The generic
13 404 14 15	outcomes s are expected to be implemented in the laser registry in 2020.
<sup>16</sup> 405 17 18 19	
20 406 21	ETHICS AND DISSEMINATION
<sup>22</sup> 407 23	The medical research ethics committee of the Academic Medical Center Amsterdam confirmed
24 25 408 26	that the Dutch Medical Research Involving Human Subjects Act does not apply to this study
<sup>27</sup> 409 28	(W19_290 # 18.336) and that complete approval of this study by the committee is not necessary.
<sub>30</sub> 410 31	All participants involved in the Delphi study will be asked for their consent before taking part. All
32 411 33	procedures will be conducted according to the Declaration of Helsinki. All results from the
<sup>34</sup> 35 36	consensus study will be reported in peer-reviewed indexed journals. The data will be presented
37 413 38 39	at conferences chosen to reach a wide range of knowledge users.
40 41 41	Abbreviations
42 43 415 44	COMET: Core Outcome Measures for Effectiveness Trials; GOS: Generic Outcome Set; CSG-
<sup>45</sup> 416 46	COUSIN: Cochrane Skin Group—Core Outcome Set Initiative; COSMIN: COnsensus-based
47 48 417 49	Standards for the selection of health Measurement Instruments; GOS: Generic Outcome Set;
<sup>50</sup> 418 51	GRADE: Grading of Recommendations Assessment; LEAD registry: Laser TrEAtment
<sup>52</sup> 53 419 54 <sup>55</sup> 420	Dermatology registry; RCT: Randomized controlled trial.
57 58 <b>421</b>	Contributors
<sup>59</sup> 60 422	FF initiated the protocol, designed the study, wrote the manuscript and reviewed it for

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<sup>3</sup> 423 4	important intellectual content. PS contributed significantly to the study design and reviewed
5 6 424	the manuscript for important intellectual content. CP contributed to the study design and
7 8 425 9	reviewed the manuscript for important intellectual content. AW initiated the protocol,
<sup>10</sup> 11 12	designed the study and reviewed it for important intellectual content. All authors (FF, PS, AW,
13 <b>427</b> 14	MA, AB, PB, IH, MH, LH ,KK, TK, HL, WM, LM, KN, UP, TP, CP, IV) read and approved the final
<sup>15</sup> 428 16	manuscript.
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<sup>19</sup> 429	
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<sup>23</sup> 430	Acknowledgements
24 25	
<sub>26</sub> 431	We are grateful to Jan Kottner of the CS-COUSIN methods group for providing advice for
27	
<sup>28</sup> 432 29	methodological issues during the protocol development. We acknowledge Marjolein van Kessel
30	as noticest advances of Nearrow International for her averaget in preparing the Dalphi rounds
31 433	as patient advocate of Naevus international for her support in preparing the Delphi rounds.
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34	Supplementary Files
35 4 5 4	
37 125	1 List of members of the LEAD registry steering committee
38	1. List of members of the LEAD registry steering committee
<sup>39</sup> ₄₀ 436	2. A glossary on the definitions of terminology
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<sup>42</sup> 438	3. Search strategy for the systematic review of literature
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44 45 439	<ol><li>A list of invited patient support groups for the Delphi survey</li></ol>
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40 49 41	REFERENCES
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31 22 521	Figur	e legends
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34 5 2 3	Figur	e 1. Flow diagram outlining the development of a generic outcome set for the LEAD
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36 525		Droparatory stages and process of consensus for relevant generic outcomes
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Dr. Adrian Aldcroft London, UK Editor-in-Chief BMJ Open

December 21<sup>th</sup>, 2019

Dear Editor-in-Chief Dr. Adrian Aldcroft,

Re: Manuscript ID bmjopen-2018-025361 (previously) entitled "Study Protocol for the Identification of Outcomes in Skin Laser Therapy: A Starting Point for the European Laser Treatment Registry"

We would like to thank you for considering the above titled paper for publication in BMJ open.

We have made the major and necessary revisions. An itemized response to each suggested revision is enclosed. We assert that each named author has approved the final version of this enclosed manuscript.

We hope that this clarification and revision persuade you to accept our submission. Thank you for your consideration of our revised manuscript, we would be glad to respond to any further questions and comments that you may have.

We look forward to hearing from you.

On behalf of the authors, yours sincerely,

Frederike Fransen, MD Department of Dermatology, Amsterdam UMC Phone: +31 6 51 99 38 31 Email: frederikefransen@gmail.com/f.fransen@amc.uva.nl

#### Dear Reviewers,

We thank you for taking the time to carefully read our manuscript that is currently entitled " A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure " and for the valuable comments you have provided. Please find below our detailed response to each of the comments..

On behalf of all co-authors,

Yours sincerely,

Frederike Fransen, MD Department of Dermatology, Amsterdam UMC Phone: +31 6 51 99 38 31 Email: frederikefransen@gmail.com/f.fransen@amc.uva.nl

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#### **Editor Comments to Author:**

We would like to thank the Editor for the feedback and we appreciate the valid assessment of our protocol.

#### Please include the study design in title.

We changed the title of the protocol, including the study design (Delphi consensus).

The initial title 'Study Protocol for the Identification of Outcomes in Skin Laser Therapy: A Starting Point for the European Laser Treatment Registry' has been changed to 'A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure'

Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions:

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?

How did you involve patients in the design of this study?

Were patients involved in the recruitment to and conduct of the study?

How will the results be disseminated to study participants?

For randomised controlled trials, was the burden of the intervention assessed by patients themselves?

We included a statement in the methods section of the manuscript under the sub-heading 'Patient and Public involvement' covering the responses to the questions above.

In the methods section we added, line 362-370:

"Patient and public were not involved in the development of this study protocol. However, patients will be involved and included within the Delphi procedure as expert group. Consensus methodology will ensure that the opinions and preferences of patients will be given the same weighting as those of the other laser experts and health professionals. Furthermore, patients will participate in the final consensus meeting. To make sure the Delphi questionnaire is understandable and has no ambiguities, we received input from a patient representative. Also, the questionnaire is tested by a group of patients and health professionals before the start of the Delphi study. Part of the Delphi study is giving feedback to all its participants after each round; this will also be done with the final study results. We intend to disseminate the main results to study participants and patients. On completion of the Delphi study, all participants (experts, health professionals and patients) will be sent an email with a copy of the final outcomes for the LEAD. In addition, where consent has been given, participants (including members of the public) will be named as contributors in the results publication."

#### Patient advisers should also be thanked in the contributorship statement/acknowledgements.

We added the patient advocate to our acknowledgements. See line 435-438 "We acknowledge Marjolein van Kessel as patient advocate of Naevus International for her support in drafting the protocol."

#### If patients and or public were not involved please state this.

Patients are involved in the Delphi consensus study, however, as reported in methods section line 369, they are not involved in drafting the protocol.

Please provide a more detailed contributorship statement. It needs to mention all the names/initials of authors along with their specific contribution/participation for the article.

A more detailed contributorship statement including names and initials of authors has been included. Section Contributors, line 420-427.

Please provide another copy of your figures with better qualities and please ensure that Figures are of better quality or not pixelated when zooming in. NOTE: They can be in TIFF or JPG format and make sure that they have a resolution of at least 300 dpi and at least 90mm x 90m of width. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable.

The figure has been changed with details of the Delphi study with a better quality. We will provide the figure in JPG format with a resolution of a least 300 dpi.

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## 1. Reviewer: 1 **Reviewer Name: Travis Blalock** Institution and Country: Emory University SOM

We would like to thank the reviewer for the suggestions and we appreciate the valid assessment of our protocol.

#### Line 86: you cannot say that lasers are the treatment of choice for these entities... surely great treatments, but "treatment of choice" is incorrect for tumors and others.

We agree with the reviewer that laser treatments are not in all cases the treatment of choice, especially in cases focusing on skin tumors. We have made the changes accordingly. Introduction section, manuscript page 5, line 115-119, words: "Today, there are many medical indications in dermatology, encompassing vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours, scars, and hair follicle- related skin conditions that are regularly - and sometimes exclusively - treated with lasers [1–3]."

#### Line 149: delete "a long list of"

"a long list of" has been deleted.

### Line 152: Is the goal 'expert' or 'provider?'

Our goals is here to create a list of outcomes from a laser expert perspective.

### **Reviewer: 2**

#### Reviewer Name: Dr Freedom Gumedze

Institution and Country: University of Cape Town, Department of Statistical Sciences, P D Hahn Building, Room 6.63, Private Bag, Rondebosch 7701, South Africa

We would like to thank for the recommendations of the reviewer and we appreciate the valid assessment.

#### Please leave your comments for the authors below

#### Page 1, Table 1: Under study design would registries be included? If no, why not?

To our knowledge, there have not been any registries focusing exclusively on uncommon dermatological diseases that are treated by lasers.

### Page 1, Table 1: Can the authors justify the study period of 2013-2017. Would this include studies that are ongoing or completed after 2017 with preliminary findings or final results?

We started our study and protocol in the beginning of 2018. This means that also studies that are completed after 2017 with final results are included in the review. Our goal is to show the outcomes used in the past years. Due to time limitations it is not our intention to create the most up-to-date (all articles of 2018 and 2019) version.

#### Page 6, line 104: Rephrase as [RCTs) [10,11]. Here and everywhere in the text fullstop must be inserted after the references.

Thank you for mentioning the in-text citations details. We inserted full stops after all references throughout the manuscript.

### Page 25, Figure 1: Can the authors give an indication of the duration of each phase or Delphi round and the entire duration of the study.

Figure 1 has been changed to provide an indication of the duration of each Delphi round (3 weeks). This has also been reported in the manuscript

Page 14, Methods section, 'Panel size and recruitment) Line 309-310, words: "Participants will have 3 weeks to complete each round, depending on the response rate. Furthermore, we will send personal reminder emails to those who did not respond after 7 and 14 days to increase the response rate."

The expectations of the entire duration of the study is indicated in the manuscript text, see below.

Section 'Trial status', page 19, line 400, words "The generic outcomes are expected to be implemented in the laser registry by the beginning of 2020".

### Reviewer: 3

#### Reviewer Name: Jennifer Zuccaro

Institution and Country: Hospital for Sick Children, Division of Plastic and Reconstructive Surgery, Toronto, Canada

Thank you for supporting us by reviewing the manuscript. We appreciate the dedication and efforts for correcting the manuscript as well.

### **General Comments:**

This is an important protocol that highlights the need for standardized outcome reporting in the field of laser medicine. In addition to the comments below, the following points should be considered:

# Provide further background and justification for why it is crucial that outcomes for laser therapy be identified for patients with skin conditions specifically as opposed to other indications.

In accordance with the suggestions of the reviewer, we now adjusted the introduction section of the manuscript and clearly explained the importance of standardized generic outcomes for dermatological diseases treated with lasers in context of a core outcome set for specific skin diseases.

Introduction section: line 152" In 2015, the international, multidisciplinary working group, the Cochrane Skin Group- Core Outcome Set Initiative (CS-COUSIN) has been established" until line 161-164 "Therefore we focus on developing a generic set of outcomes (GOS) for the purpose of the LEAD registry. The GOS is intended to be applied to the assessment of various, unrelated skin diseases that are treated with different types of lasers."

Provide further information for how the e-Delphi will actually run and clarify how long each round will take. Please specify if the length of each round will be determined by time or by participant saturation and when you expect the process to be complete.

We changed figure 1 and clarified the length of each Delphi round, determined by time (3 weeks for each round). The expectations of the entire duration of the study is indicated in the manuscript text. The expectations of the entire duration of the manuscript text, see below.

Section 'Trial status', page 19, line 404, words "The generic outcomes are expected to be implemented in the laser registry by the beginning of 2020".

## All spelling and grammar corrections are included on the attached protocol.

Thank you for supporting us with the corrections. We appreciate the dedication and efforts for reviewing the manuscript. We corrected the spelling and grammar.

# 1. Line 59/60: Please clarify what meant by "rapidly evolving laser treatments." Specifically, what aspect is evolving?

We mean with 'rapidly evolving laser treatments' that refinements in laser technology have progressed so rapidly during the past decade that successful treatment of many cutaneous can be achieved. We changed the part of the sentence to "<u>With modifications in laser technology</u>, considering outcomes of importance (what to measure) to patients and health professionals is crucial."

Page 4, Article summary 'Strengths and limitations of this study', line 102.

# 2. Lines 90-94: "A growing number of laser treatments facilitates" must be clarified. Also, provide further justification for why it is relevant to include the etiologies of the selected skin conditions.

Due to the word count of the introduction, we deleted this section of the introduction.

# 3. Line 96: Clarify what is meant by "diversity in laser devices." Are you referring to types of lasers? Settings? Etc.

We mean with 'diversity in laser devices' that there are many types of lasers. This is indicated on page 11, table 1, Inclusion criteria 'intervention' described as 'any type of laser treatment for vascular, pigmented or inflammatory lesions, tumours, scars, hair-related and (pre)malignant skin conditions'.

# 4. Line 106: Reference 11 refers to a paper that discusses intense pulsed light therapy as opposed to laser therapy for treating dermatologic conditions. Given that IPL differs from laser therapy, this reference must be corrected or the protocol must clearly state that the registry will be developed for laser therapy and IPL.

We agree with this statement of the reviewer. We removed this reference and corrected for another reference in which a great number of case reports in shown in the field of laser dermatology.

### 5. Line 107: Provide an example or reference to justify opinion that only successful studies are published.

We included an example of a reference to justify this statement : see references Atakpo P, Vassar M. Publication bias in dermatology systematic reviews and meta-analyses. J Dermatol Sci. 2016;82:69–74, reference number 6.

#### 6. Line 110/111: Provide references/justification for the mentioned PROs.

We provided references (7,8) for the justification of the mentioned PROs

#### 7. Line 114/115: This statement is unclear as is, please re-word.

We removed the sentence.

#### 8. Line 117: Please specify what the "evidence-based approach" is for ...?

We removed the sentence and changed the sentence to 'To address the variations in outcome reporting, organizations such as the Core Outcome Measures in Effectiveness Trials Initiative (COMET) bring together researchers interested in developing a standardized set of core outcomes (COS) in various health-related fields. (Introduction, page 6, line 145)

#### 9. Line 124: Please clarify which "comparisons" you are referring to and their significance.

We clarified in the following sentence which comparisons I am referring to and their significance:

Currently, 17 COS initiatives have been supported by CS-COUSIN in dermatology. These projects involve 26 different skin diseases, such as acne, atopic eczema, hidradenitis suppurativa, melanoma, nail psoriasis, rosacea, and vitiligo. However, with hundreds of different and mostly unrelated dermatoses that are treated with lasers in the field of laser dermatology, the need for a generic set of outcomes (GOS) is commanding. (introduction, page 6, line 157)

#### 10. Line 129: Please clarify if "different laser treatments" refers to treatments with different types of lasers.

See scope page 8, sentence 188-190. The sentence has been changed to "The GOS is intended for use in the LEAD registry, with the focus on prospectively recording the effectiveness and safety of cutaneous non cosmetic laser interventions.".

# 11. Lines 168-173: Overall, the scope and applicability of outcomes is unclear. The authors should provide further justification for exclusions and must also clarify what is meant by "distinctive mode of action."

We adjusted the scope and added more detailed information, see page 8 line 185-193. The distincitive mode of actions refers to energy based devices with more than one wavelength and the role of drug delivery. Our focus is the effect of laser on skin conditions by means of one wavelength without the action of drug delivery or any other component.

**12.** Line 201- Table- Please clarify the inclusion criteria for the patient population. Also, provide further justification for the exclusion criteria for the intervention.

 We changed the protocol and included patients with age 18 and older with vascular, pigmented or inflammatory lesions, benign tumours, scars, and hair follicle-related skin conditions treated by lasers. With these inclusion criteria we refer to all medical indications for which laser could be an effective treatment. With the excluision criteria 'Non-humans, flebological skin conditions, laser assisted drug delivery, low laser level therapy, body-contouring, skin tightening, hair removal, rejuvenation and anti-aging' we justify that we do not focus on cosmetic indications and energy based devices with more than one wavelength, additional drug delivery and focusing on cosmetic outcomes, see methods, table 1, page 11.

13. Lines 248-250: Please clarify if participants will be invited via mail or email. If an email is used, will the email provide a link to the questionnaires or will a subsequent email be provided? Also, please specify where information related to consenting to participate will be included.

Those who want to participate will be asked to respond with their name, country of origin and email address. We described now that 'Participants will be invited to participate in web-based anonymized electronic questionnaires. The surveys will be administered using Lime Survey and will be accessible via a direct hyperlink from the invitation email'.

**14.** Lines 259-266: Please provide further explanation for the potential outcomes listed. We removed the alinea of potential outcomes.

15. Lines 274-275: The authors' state that participants will be recruited from Europe for "ensuring an international context" however, one could argue that this is misleading as participants from other parts of the world will not be included. Could consider re-wording to state "diverse context."

We reconsidered the European scope. A major change is that we have changed the scope registry from European to international scope. By sending the survey invitation to experts and advocacy groups from different continents, we aim to reflect a broad range of patients and health professionals with diverse backgrounds and experiences. Our steering committee now consists of laser experts from all continents to ensure the international context.

# 16. Lines 310-313: Please explain how the results will be "fed-back." Also, elaborate on who the included feedback will be from and how it will be presented (i.e. individual comments, summary of findings, etc.) Results will be a feedback given in the form of charts. In these charts, summary of findings, votings, of each of the Delphi questions will be given to both groups of patients and health care professionals by email.

17. Line 331: Please specify who the target audience is for the international conference.

The target audience will be experts in the field of laser dermatology and physicians who work with lasers.

18. Line 334-367: Overall, a greater level of detail must be provided in the discussion section (i.e. provide examples of identified outcomes; specify what methodological guidelines you are referring to; clarify if "multiple treatments" means several treatments with the same device or treatments with different devices; clarify what is meant by "a diversity of outcome items;" elaborate on what you will gain from having a diverse sample of participants)

Examples of identified outcomes are given in the manuscript. We elaborated on strengths of methodological guidelines and the gain form having a divers sample of participant in the discussion section, see line 377-380, words "There are several strengths using the Delphi method for this study. First, the Delphi method allows to recruit a large number of laser experts, physicians and patients from diverse regions globally. The diversity in the experts' backgrounds and expertise ensures maximum impact of the results."

# **19.** Line **379**: Please specify how you will ensure that the email from each participant will be kept separate from the online survey.

Only the investigator has a code that relates to the email of the participant, to make sure that the participant receives a reminder when not completing the survey. However, the answers of the survey will relate to the code and not directly to the email.

# 20. Line 382: Please specify how consent will be obtained and if consent will be repeated for each round of the process.

The process of how consent will be obtained is described under the section of 'Definition of consensus', page 15, line 339-346. The definition of consensus is presented in Table 2. 'Consensus in' is defined as approval of the outcome by the vast majority (70 %) of all stakeholder groups that score 7, 8, or 9 with fewer than the minority (15 %) of panelists scoring 1–3. On the contrary, 'consensus out' is defined as 70% or more of all stakeholder groups scoring as 1 to 3 and less than 15% scoring as 7 to 9 [12] After three e-Delphi rounds, outcomes will be classified as 'consensus in' (consensus on the importance of the outcome), 'consensus out' (no consensus on the importance, or consensus on nonimportance) or 'no consensus' (consensus on the importance in only one or or no consensus.

#### <u>Reviewer: 4</u>

#### Reviewer Name: Daniel Schlessinger

Institution and Country: Northwestern University Feinberg School of Medicine

#### Please leave your comments for the authors below

This is a well-written protocol for an important topic - the generation of a Core Outcome Set. I have a few questions, however:

1) Page 9, Line 193-194: the authors state that their literature search will be of the MEDLINE and EMBASE databases, "between January 2013 and December 2017". Why does the literature search terminate in December 2017? Certainly this will miss a number of important articles published in laser research between 12/2017 and the present date. At the earliest, the literature search should terminal in December 2018.

We thank the reviewer for studying our paper and providing positive feedback and comments. The literature search terminates in December 2017 as our study on outcome reporting started in January 2018. We performed a literature review which was in January 2018 the most updated version. For more details we refer to the systematic review which has recently been published:

Fransen F, Tio D, Prinsen CA, Haedersdal M, Hedelund L, Laubach HJ, Marini L, Paasch U, Passeron T, Wolkerstorfer A. A Systematic Review of Outcome Reporting in Laser Treatments for Dermatological Diseases. J Eur Acad Dermatol Venereol. 2019 Aug 30. doi: 10.1111/jdv.15928

2) The majority of Core Outcome Sets have been developed for a specific medical condition - not a medical treatment. This makes sense, as the most important outcomes are generally condition-specific. The author's proposal is fundamentally different, however. Lasers are used for an extremely diverse set of conditions and I expect the resultant outcomes generated in their long list to be multifarious and in some cases unrelated. How can one COS encompass all laser-related outcomes? Wouldn't it be better to focus this (e.g., for lasers as used for vascular malformations or abnormalities)?

We would like to thank the suggestion of the reviewer and we appreciate the valid assessment. Regarding the comments on the manuscript, the reviewer has raised an important issue on the methodological approach. One COS could simply not encompass all laser-related outcomes indeed.

However, the current COSs development suggest that the outcomes are most likely very similar for specific different skin conditions and their different treatments (see CS-COUSIN projects such as Vascular Malformations, Atopic Eczema, Vitiligo and Acne. However, given the long duration and huge effort of the COS development and validation process, it is impossible to reach consensus on the COS for each skin condition apart. All the more as there are hundreds of uncommon dermatological conditions for which laser treatments have been documented and published. Due to overlapping outcomes and the long process of development of a COS for each disease, we propose a generic set of outcomes for various skin diseases treated by laser.

To clarify the aforesaid purpose of the development generic outcomes for a registry, the following changes to the text in the manuscript:

Introduction section, page 6: line 153 " Since 2015, the international, multidisciplinary working group, the Cochrane Skin Group- Core Outcome Set Initiative (CS-COUSIN) has been established" until line 164 "Therefore we focus on developing a generic set of outcomes (GOS) for the purpose of the LEAD registry. The GOS is intended to be applied to the assessment of various, unrelated skin diseases that are treated with different lasers."

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## **SUPPLEMENTARY FILE 1**

# LEAD Registry : Steering Committee

Coordination team

Frederike Fransen (the Netherlands)

Albert Wolkerstorfer (the Netherlands)

Phyllis Spuls (the Netherlands)

In addition to the coordinaton team , the LEAD registry Steering Committee includes:

Murad Alam (US), Ashraf Badawi (Egypt), Pablo Boixeda (Spain), Iltefat Hamzavi (US), Merete Haedersdal (Denmark), Lene Hedelund (Denmark), Kristen Kelly (US), Taro Kono (Japan), Hans-Joachim Laubach (Switzerland), Woraphong Manuskiatti (Thailand), Leonardo Marini (Italy), Keyvan Nouri (US), Uwe Paasch (Germany), Thierry Passeron (France), Sanna Prinsen (The Netherlands), Ines Verner (Israel)

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### **SUPPLEMENTARY FILE 2**

The definitions for COS, outcome, outcome instruments and outcome parameters according to Prinsen *et al.* (2014). [1]

## Definitions

Similar constructs are defined differently across several research groups such as COMET, OMERACT, and HOME. As there is currently no consensus on the definitions, we would like to explicitly state the definitions that are being used in the COMET Delphi study in order to avoid any possible misinterpretations.

## Core outcome set (COS)

A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. A COS includes all relevant outcomes of a specific health condition within a specified setting (the OMERACT definition refers to 'core domain set' whereas the HOME definition refers to 'core outcome domains').

## Generic core outcome set (GOS)

A GOS is an agreed minimum set of *generic* outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. In this study, the GOS is intended to be applied for the assessment of various, unrelated skin diseases that are treated with different types of lasers.

## Outcome and outcome domain.

Throughout this report, the definition of "outcome" refers to a single construct that can be measured as a standalone item (e.g. 'erythema'), while the term "outcome domain" or "domain" is an umbrella term for a group of associated outcomes (e.g. 'signs as assessed by physician').

### **Outcome measurement instrument**

An outcome measurement instrument refers to how the outcome is being measured (the tool used to assess the outcome). An outcome measurement instrument can be a single question, a questionnaire, a performance-based test, a physical examination, a laboratory measurement, an imaging technique, and so forth (the HOME definition refers to 'outcome measure').

### Reference

1 Prinsen CAC, Vohra S, Rose MR, *et al.* Core Outcome Measures in Effectiveness Trials (COMET) initiative: Protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. *Trials* 2014;**15**. doi:10.1186/1745-6215-15-247

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3	SUPPLEMENTARY FILE 3
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5	Systematic review search strategies
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# 24."Humans[Mesh]

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### **SUPPLEMENTARY FILE 4**

A list of invited patient support groups for the Delphi survey

Name of Society Hidradenitis Patiëntenvereniging (NL) Nevus Netwerk Nederland (NL) Nevus Outreach (US) Nevus Support (AU) Neurofibromatose Vereniging Nederland (NL) The Neuro Foundation (UK) Neurofibromatose Ireland Association (IE) Vereniging Wijnvlek Sturgeweber syndroom (NL) Schweizerischen Nuerofibromatose Vereinigung (CH) Interessengemeinschaf Sturge-Weber-Syndrom (DE) Sturge Weber Foundation Great Britain (UK) iez on Sturge-Weber-Foundation (US) Vitiligo patientenvereniging (NL) National Vitiligo Foundation (US)

# **BMJ Open**

### A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure

Journal:	BMJ Open
Manuscript ID	bmjopen-2020-038145.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Mar-2020
Complete List of Authors:	Fransen, Frederike; Amsterdam UMC , Dermatology Spuls, Phyllis; Department of Dermatology, Amsterdam Public Health, Infection and Immunity, Amsterdam University Medical Center Alam, Murad; Northwestern Medical Faculty Foundation, Badawi, Ashraf; Dermatology Unit, Department of Medical Applications of Lasers (MAL), National Institute of Laser Enhanced Sciences, Cairo University Boixeda, Pablo; Dermatology Department, Ramón y Cajal Hospital Haedersdal, Merete; Copenhagen University Hospital Bispebjerg, Dermatology Hamzavi, Iltefat; Department of Dermatology, Henry Ford Hospital, Detroit Hedelund, Lene; Aarhus Universitetshospital, Dermatology Kelly, Kristen ; Beckman Laser Institute, University of California Kono, Tara; Department of Plastic and Reconstructive Surgery, Tokai University School of Medicine Laubach, Hans Joachim; Hopitaux Universitaires de Geneve, Dermatology and Venereology Manuskiatti, Woraphong; Faculty of Medicine Siriraj Hospital, Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, 1475 NW 12th Ave., Paasch, Uwe; University of Leipzig Passeron, Thierry; Centre Hospitalier Universitaire de Nice, Dermatology Prinsen, C; VU University Medical Center, 19Department of Epidemiology and Biostatistics, Amsterdam Public Health research institute, Amsterdam UMC Verner, Ines; Verner Clinic Wolkerstorfer, Albert; Academic Medical Center (AMC), Dermatology
<b>Primary Subject Heading</b> :	Dermatology
Secondary Subject Heading:	Evidence based practice
Keywords:	Laser therapy < DERMATOLOGY, DERMATOLOGY, Surgical dermatology < DERMATOLOGY

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A generic outcome set for the international registry on Laser TrEAtments in Dermatology (LEAD): a protocol for a Delphi study to achieve consensus on what to measure Frederike Fransen<sup>1</sup>, Phyllis I. Spuls<sup>1</sup>, Murad Alam<sup>2,3</sup>, Ashraf Badawi<sup>4</sup>, Pablo Boixeda<sup>5</sup>, Merete Haedersdal<sup>6,7</sup>, Iltefat Hamzavi<sup>8</sup>, Lene Hedelund<sup>9</sup>, Kristen M. Kelly<sup>10</sup>, Taro Kono<sup>11</sup>, Hans-Joachim Laubach<sup>12</sup>, Woraphong Manuskiatti<sup>13</sup>, Leonardo Marini<sup>14</sup>, Keyvan Nouri<sup>15</sup>, Uwe Paasch<sup>16</sup>, Thierry Passeron<sup>17,18</sup>, Cecilia A.C. Prinsen<sup>19</sup>, Ines Verner<sup>20</sup>, Albert Wolkerstorfer<sup>1</sup> <sup>1</sup> Department of Dermatology, Amsterdam Public Health, Infection and Immunity, Amsterdam University Medical Center, Amsterdam, the Netherlands <sup>2</sup>Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, 

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1 2		
3 ∡	54	
5	55	Competing interests
6 7	56	There are no competing interests for any author.
8 9	57	
10 11	58	
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27 28	68	
29 30		
31	69	ABSTRACT
32 33	70	
34 35		
36 37	71	Introduction: While laser technology has expanded the armamentarium of treatment for various
38	70	
39 40	12	skin diseases during the past years, neterogeneity in study outcomes nampers comparability and
41 42	73	appropriate evidence synthesis. Part of these issues can be addressed by developing a generic
43 44	74	outcome set. Using the Delphi method, this study aims to seek consensus between key
45		
40 47	75	stakeholders on relevant generic outcomes (what to measure) for implementation in the
48 49	76	international registry on Laser trEAtments in Dermatology (LEAD). The registry is focused on
50 51	77	collection records data an unique la contractor ente for allin discurdant
52	//	collecting research data on various laser treatments for skin disorders.
53 54	78	
55 56		
57 58	79	Methods and analysis: By reviewing the literature and involvement of key stakeholder groups
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and adult patients in need or after laser surgery and health professionals, a preliminary list of outcomes will be generated and categorized into domains. Using these outcomes, an international three-round Delphi study will be performed to rate the importance of outcomes in the selection of a generic outcome set. Participants are allowed to provide new outcomes to the prelimary list for revisions during the first Delphi round. Finally, results will be discussed during a consensus meeting to agree on generic outcomes to be used in the LEAD Registry.

37 Ethics and Dissemination: An ethics approval was not applicable (W19 290 # 18.336). The study is registered with the CS-COUSIN (Cochrane Skin Core OUtcome Set INitiative) 38 and the Core Outcome Measures in Effectiveness Trials (COMET) initiative. Procedures 39 90 will be conducted according to the Declaration of Helsinki. The findings will be disseminated through peer-reviewed publications and conference presentations. 91 92 93 Keywords: Laser Therapy, Dermatology, Consensus study, Delphi study, Disease registry, **Generic Outcome Set** 94

1		
2 3 4 5 6	95	
0 7 8 9	96	ARTICLE SUMMARY
10 11 12 13	97 98	Strengths and limitations of this study
14 15 16	99	•This protocol outlines the first international consensus effort to develop a generic outcome
17 18	100	set for use in the international LEAD laser registry.
19 20 2 21	101	• With advances in laser technology, considering outcomes of importance ( <i>what</i> to measure) to
22 <u>^</u> 23	102	patients and health professionals is crucial.
24 25 26	103	•A comprehensive systematic review will explore which outcomes are used and reported in
27 <u>^</u> 28	104	existing studies on laser treatments.
29 30 - 31	105	• The Delphi procedure requires three survey rounds and involves a large group of stakeholders
32 <u>^</u> 33	106	across various disciplines and geographical areas including patients, reflecting different
34 35 36 37 38 39 40 41	107 108 109	viewpoints.
42	110	
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116 During the past decades, modifications in laser technology have further widened its scope and 117 greatly expanded the cutaneous laser surgeon's armamentarium [1,2]. Today, there are many 118 medical indications in dermatology, encompassing vascular, pigmented, inflammatory, 119 metabolic or infectious lesions, benign tumours, scars, and hair follicle- related skin conditions 13 120 that are regularly - and sometimes exclusively - treated with lasers [1–3]. Many of these 121 disorders meet the criteria of an orphan disease. 18 122 19 123 The diversity in laser devices and the spectrum of medical indications pose unique research challenges for clinical decision-making in laser therapy. Because most laser physicians are not 124 exposed to large numbers of patients receiving laser treatments for uncommon indications, 24 1 2 5 126 knowledge on the most effective laser treatment, including safety and used regimen, is unclear. 29 127 The current evidence for most of these specific skin conditions is sporadic at best, consisting <sup>31</sup> 128 mostly of case reports and case series and only a very small number of randomized controlled <sub>34</sub> 129 trials (RCTs) [4,5]. Moreover, most often only isolated successes are reported while cases that <sup>36</sup> 130 failed to respond are not published, leading to publication bias [6]. <sub>39</sub> 131 Another issue hampering evidence synthesis is heterogeneity of outcome definition, 41 132 measurement and reporting in laser research. Patient-reported outcomes (PROs), such as 133 'patient experience of laser treatments' and 'health-related quality of life', are often not 46 1 34 reported and together with selective outcome reporting in laser research, it is all a serious 135 threat to comparative effectiveness research as it limits the ability to compare, contrast, and combine individual studies [7,8]. As a result, this hampers to draw meaningful conclusions and 51 136 <sup>53</sup> 137 guidance to inform clinical decision-making [9,10]. 54 55 <sub>56</sub> 138 To overcome this issue in the field of laser dermatology, the development of the International 57 <sup>58</sup> 139 Laser Treatment (LEAD) Registry has been proposed to initiate collaborative data pooling of a

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<sup>3</sup> 140 4	wide range of skin disorders. The development of a registry may be the key to the lack of solid
5 6 141 7	evidence for laser treatments in dermatology, however, well-defined standardized and generic
8 142 9	outcomes are required for its establishment.
<sup>10</sup>	
11 - 13 12 144 13	To address the variations in outcome reporting, organizations such as the Core Outcome
<sup>14</sup> 145 15	Measures in Effectiveness Trials Initiative (COMET) bring together researchers interested in
16 17 146 18	developing a standardized set of core outcomes in various health-related fields [11]. A core
19 147 20	outcome set (COS) is defined as an agreed minimum set of outcomes that should be measured
<sup>21</sup> 22 148	and reported in all clinical trials for a specific health condition, including methods used to
24 149 25	measure these core outcomes[10,12]. Throughout this report, the definition of "outcome"
<sup>26</sup> 27 150	refers to a single construct that can be measured as a standalone item (e.g. 'erythema'), while
28 29 151 30	the term "outcome domain" or "domain" is an umbrella term for a group of associated
<sup>31</sup> 152 32	outcomes (e.g. 'signs as assessed by physician'). Furthermore, the outcome instrument refers
33 34 153 35	to how the outcomes are measured. Although a COS is recommended for clinical trials, they can
<sup>36</sup> 154 37	also be developed for routine clinical practice, and for registries [10,12]. In 2015, the
<sup>38</sup> 39 155 40	international, multidisciplinary working group, the Cochrane Skin Group- Core OUtcome Set
41 156 42	INitiative (CS-COUSIN) has been established [13]. The organization supports dermatology-
<sup>43</sup> 44 45	specific initiatives to develop and implement a COS by building upon experiences of the
46 158 47	Harmonizing Outcome Measures for Eczema (HOME) initiative, which developed a roadmap to
48 49 50	guide the process of COS development and implementation [14]. Currently, 17 COS initiatives
50 51 160 52	have been supported by CS-COUSIN in dermatology. These projects involve 26 different skin
<sup>53</sup> 161 54	diseases, such as acne, atopic eczema, hidradenitis suppurativa, melanoma, nail psoriasis,
<sup>55</sup> 56 162 57	rosacea, and vitiligo [11,15]. However, with hundreds of different and mostly unrelated
58 163 59 60	dermatoses that are treated with lasers in the field of laser dermatology, the need for a generic

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<sup>3</sup> 164 4	outcome set (GOS) is commanding. Therefore we focus on developing a GOS (what to measure)
5 6 165	for the purpose of the LEAD registry. The GOS is intended to be applied for the assessment of
8 166 9	various, unrelated skin diseases that are treated with different types of lasers.
10 11 <b>167</b>	
<sup>12</sup> 13 168 14	In summary, there is an urgency of using the same generic outcomes in laser therapy.
15 16 169 17 18	Hence, establishing consensus on the relevant outcomes for the LEAD registry will
<sup>19</sup> 20 <b>170</b> 21	promote clinical researchers to use outcomes chosen by consensus that are relevant to
22 23 171 24 25	patients and clinicians. The use of generic outcomes support data synthesis for many
<sup>26</sup> 27 28 28	diseases in dermatology. The protocol outlines the context, scope and methods for the
29 30 173 31 32 33 34	development of a GOS to be implemented in the LEAD registry.
<sup>35</sup> 36 174 37 175	Aims and objectives
<sup>38</sup> 176 39	Aim
40 41 47 42	The aim of this study is to reach consensus between various stakeholders on generic outcomes
43 178 44 45	relevant for the LEAD registry.
<sup>46</sup> 47 48 180	Objectives
<sup>49</sup> 181 50	Our study objectives are:
<sup>51</sup> 182 52	1. To identify outcomes that have previously been used and reported in RCTs, cohort
54 183 55	studies, case-control studies and case series from a literature review and classify these
<sup>56</sup> 184 57 58 59 60	outcomes into domains according to the COMET taxonomy;

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<sup>2</sup> <sup>3</sup> 185	2. To reach consensus between stakeholders on the outcomes of a GOS to be implemented
4 5	
6 186 7	in the LEAD registry.
8	
9 <sup>10</sup> 11187	Scope and applicability of outcomes
12 13 188 14	The registry is envisioned to suit all types of laser interventions for skin disorders in dermatology
<sup>15</sup> 189 16 17	including vascular, pigmented or inflammatory lesions , benign tumours, scars, and hair follicle-
17 18 190 19	related skin conditions treated with lasers. The GOS is intended for use in the LEAD registry, with
20 191 21	the focus on prospectively recording the effectiveness and safety of cutaneous non cosmetic
<sup>22</sup> 23 24	laser interventions. Therefore we excluded laser assisted drug delivery, low laser level therapy,
25 193 26	body- contouring, skin tightening, hair removal, rejuvenation and anti-aging procedures.
<sup>27</sup> 28 194 29	Furthermore, because of the distinctive mode of action and use in daily clinical practice, laser
30 <b>195</b> 31	assisted drug delivery, low laser level therapy and laser procedures for (leg) veins were excluded.
32 33	
34 35 196	
36	
<sup>38</sup> 197	METHODS AND ANALYSIS
39 ± 57 40	
41 198 42	
42 43 44 49	Research group
45 46 200 47	The steering committee (FF, PS, AW, MA, AB, PB, IH, MH, LH ,KK, TK, HL, WM, LM, KN,
<sup>48</sup> 201 49	UP, TP, CP, IV) provide input at critical points of the study such as protocol development,
<sup>50</sup> 51 202	stakeholder recruitment, consensus process and the consensus meeting. Three members of the
53 203 54	steering committee (FF,PS,AW) coordinate the overall project, ensure methodological quality of
<sup>55</sup> 204 56 204	the project and make key decisions. All members of the steering committee will participate in
58 205 59 60	the Delphi procedure as well as in the final consensus meeting. The steering committee has

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<sup>3</sup> 206 4	representatives from The Netherlands, Denmark, Egypt, France, Germany, Israel, Italy, Japan,
5 6 207 7	Spain, Switzerland, Thailand and USA, with extensive expertise in various laser treatments,
, 8 208 9	outcomes research and clinical research. A list of all members of the steering committee is given
<sup>10</sup> 11 209	in supplementary file 1.
12 13	
14 210	Study design
15 16	
<sup>17</sup> 18 10	Figure 1 provides a brief overview of the stepwise approach with different research methods.
20 <b>212</b>	The study consists of the following two phases:
21	
22	
23 213 24	Phase 1: Identification of potential outcomes important in laser treatments by means of a
25	
20 27 <b>2</b> 14	1. A systematic review to form the preliminary list of outcomes for the Delphi survey
28	
29 30 <b>2</b> 4 F	2. Classification of autoemos into domains according to the CONJET tours and
31	2. Classification of outcomes into domains according to the COMET taxonomy
32	
<sup>33</sup> 34 216	
35	
36 37 <b>21 7</b>	Phase 2. A concensus process involving key stakeholders who are able to suggest additional
38	Phase 2: A consensus process involving key stakeholders who are able to suggest additional
<sup>39</sup> 10 218	outcomes during the first round and who will rate the importance of outcome for reaching
40 41	
42 219	consensus on the GOS by means of a
43 44	
44 45 220	1 Three round Delphi curren
46 220	1. Three-round Delphi survey.
47 48	
49 221	2. Expert consensus meeting. attended by representatives of all stakeholder groups.
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52 <b>777</b>	
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2	
<sup>3</sup> 223	This study is registered with the CS-COUSIN and COMET initiative [11,16]. Results of the
4	
5 c 224	consensus study will be reported according to the Core Outcome Set-STAndards for Reporting
7	
, 8 225	(COS-STAR) [17]
9	
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16 <sup>227</sup>	
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<sup>19</sup> 228	Phase 1: Identification of potential outcomes and domains
20	
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24 229	Phase 1.1: Systematic literature review
25	
26	
2/ 20 230	The first phase of the study is to identify which outcomes should be measured and reported in a
20 29	
30 231	registry on laser treatments for skin disorders (what to measure: the GOS, see definitions in
31	
<sup>32</sup> 232	supplementary file 2) A SR will be performed to explore existing outcomes that are used in laser
33 - 5 -	supplementary me 2/. Non win be performed to explore existing outcomes that are used in laser
34 35 <b>733</b>	studies According to the COMET guidelines [18] searches will be performed in the following
36	studies. According to the cower guidelines [10], searches will be performed in the following
37 221	database: MEDLINE and EMRASE Articles between January 2012 and December 2017 will be
38 234	ualabase. MEDLINE and EMBASE. Articles between January 2013 and December 2017 will be
39	ratriaved. The electronic coarch strategy is detailed in supplementary file 2. A recent E year time
40 235	retrieved. The electronic search strategy is detailed in supplementary file 3. A recent 5-year time
42 226	united has been colored for the second of that outcomes outworked references the marking of
43	period has been selected for the search so that outcomes extracted represent the practice of
44	
45 237	present-day laser research. The inclusion and exclusion criteria are presented in Table 1. Two
46	
47 238 48	reviewers will select articles and extract the data independently. Disagreement will be resolved
40	
<sub>50</sub> 239	by discussion and by consulting a third review author if necessary. The following data will be
51	
52 <b>240</b>	extracted from the selected articles in data extraction tables : authors, years of publication,
53	
<sup>54</sup> 241	country, cutaneous indications for treatment and type of laser treatments. We will assess what
55 56	
57 <b>242</b>	outcomes and outcome measurement instrument are used, consistency in outcomes, number of
58	· · · · ·
<sup>59</sup> 243	times an outcome was used, consistency in classification used.
60	

Table 1 Inclusion and 6	exclusion criteria for literature revie	W
	Inclusion criteria	Exclusion criteria
Patient population	Studies including patients age	Non-humans
and indication	18 and older with vascular,	flebological skin
	metabolic or infectious lesions.	Laser assisted drug
	benign tumours and hair	delivery, low laser level
	follicle-related skin conditions	therapy, body-
	treated with lasers	contouring, skin
		tightening, hair remova
		aging
Study design	RCTs, cohort studies, case-	In vitro studies,
	control studies, case series	systematic reviews,
		abstracts and expert
		opinions, case reports
Intervention	Any type of laser treatment for	Laser assisted drug
	vascular, pigmented or	delivery, low laser level
	inflammatory lesions, benign	therapy, laser therapy
	related skin conditions.	cosmetic interventions
		(see scope of outcomes
Outcomes		Non-clinical outcomes
		e.g. biochemical
		outcomes, imaging,
		confocal laser, histology
Publication	All studies are conducted	

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<sup>17</sup> 262	
18 19 263	Phase 1.2: Classification of outcomes into domains
20	
21 264 22	Subsequently, data will be classified according to the standardized taxonomy for outcomes
<sup>23</sup> 265	proposed by the COMET initiative [19]. This taxonomy encompasses 38 domains within 5 core
24	
25 26 266	areas: mortality/survival: physiological/clinical: life impact: resource use: adverse events.
20	
28	
29 267	Outcomes and their classification in domains will be discussed with three members (FF
30 207	
31	
32 33 268	PS_AW/) of the steering committee. The preliminary list of outcomes classified to domains
34	To, rev or the steering committee. The preiminary ist or outcomes classified to domains
35	
<sup>36</sup>	will be included in the consensus process
37 205	
38 30	
40	
41 270	
42	
43	
44 ⊿⊑ 271	Phase 2: Consensus process
45 <b>-</b> 7 - 46	
47	
48 272	Phase 2.1. Delphi procedure
49 272	
50	For investigating grucial autoemes in context of the LEAD registry a Delphi study will be
51 273	For investigating crucial outcomes in context of the LEAD registry, a Delphi study will be
52 53	
55 274 54	conducted. The Delphi is based on a structured process for gathering and condensing knowledge
55	
<sub>56</sub> 275	from key stakeholder groups by means of 3 rounds with a series of questionnaires [20]. The
57	
<sup>58</sup> 276	procedure will consist of three online rounds (Figure 1).
59 60	
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- 3 277 4 5	
5 7 <b>27</b> 8	Participants
8 9 <b>27</b> 9 10	The involvement of a variety of stakeholders is a key part for the identification of outcomes and
11 12 <b>2</b> 80 13	strongly recommended by methodologists [21].
14 15 <b>281</b> 16	The following representatives from four international key stakeholder groups are involved in the
<sup>17</sup> 282 18 19	process of reaching consensus on outcomes:
20 21 <b>283</b> 22	1. Patients of age 18 with vascular, pigmented, inflammatory, metabolic or infectious lesions,
<sup>23</sup> 284 24 25	benign tumours and hair follicle-related skin conditions treated by lasers.
26 27 <b>28</b> 5 28	2. Patient representatives involved in patient associations that raise awareness on the impact of
<sup>29</sup> 286 <sup>30</sup>	vascular, pigmented, inflammatory, metabolic or infectious lesions, benign tumours and hair
31 32 287 33 34	follicle-related skin conditions.
35 <b>288</b> 36	3. Health care professionals – Laser experts who treat patients with vascular, pigmented or
<sup>37</sup> 38 289	inflammatory, metabolic or infectious lesions, benign tumours, hair follicle-related skin
40 <b>290</b> 41 42	conditions and who are involved in research on laser treatments.
<sup>43</sup> 291 44	4. Health care professionals –General physicians who treat patients with dermatological
46 <b>292</b> 47 48	indications.
<sup>49</sup> 293 50 51	
52 53 <b>2</b> 94 54	Panel size and recruitment
55 <b>295</b> 56	There is no robust guidance for calculating the number of participants needed for a Delphi study
57 58 59	and expectations are based on COMET Initiative guidelines and previous literature [16,22,23]. As
60 297	there are various stakeholder groups involved in the Delphi procedure, we will recruit as many
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2 <sup>3</sup> 298	international representatives as possible from each group. All potential participants will be
4 5	invited with a latter eveloping the sime and details of the study and the rationale and importance
6 299 7	invited with a letter explaining the aims and details of the study and the rationale and importance
8 300 9	of completing the entire Delphi process. Respondents who agree to take part will be assigned a
<sup>10</sup> 11 301 12	unique identification number. Furthermore, each member of the steering committee will be
13 <b>302</b> 14	asked to cascade the link of the survey to 3 other physicians in their network. Patients and patient
<sup>15</sup> 303 16 17	representatives will be recruited from national and international support groups for skin diseases
<sup>18</sup> 304 19 20	treated with lasers and can be found in supplemental file 4. In addition, laser experts from the
21 22 305 23 24	steering committee will be asked to recruit 3 patients with different skin conditions treated
<sup>25</sup> 306 26 27	with lasers in their center. To make sure that we involve skin diseases of different categories,
<sup>28</sup> 307 29 30	laser experts will indicate the diagnosis of the patients that are recruited. By sending the survey
31 308 32	invitation to experts and patient support groups from different continents, we aim to reflect a
<sup>33</sup> 309 34 25	broad range of patients and health professionals with diverse backgrounds and experiences. For
36 36 37	each round, the number of participants invited and those who completed the surveys will be
38 311 39	documented. The participants will have 3 weeks to complete each round. We will send personal
<sup>40</sup> 41 42	reminder emails to those who did not respond after 7 and 14 days to increase the response rate.
43 44 313 45 46	
47 48 314	Delphi survey
49 50 315 51	Participants will be divided into a group of patient and a group of health professional , leading to
<sup>52</sup> 316	separate scoring of outcomes. All participants will be asked to rate the importance of each of the
54 55 317 56	outcomes using the GRADE (Grading of Recommendations Assessment, Development and
57 318 58 59 60	Evaluations) approach. The scale will range from 1 to 9 and will be categorized as follows: 1–3

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During the first round of the Delphi survey, baseline characteristics (age, gender, country of

practice) will be obtained from all participants. Patients will be asked for their medical indication

and type of laser treatment, and whether any complications have occurred during treatment.

Health professionals will be asked their specialty (laser dermatology, general dermatology or

other), workplace (academic, teaching hospital or non-teaching hospital) and years in practice.

Next, participants will be asked to score listed outcomes and will have the option to suggest any

In the second and third Delphi rounds, all participants will receive feedback on the scores of the

previous round in both the patient and the health professional group. The outcomes from the

previous rounds will be presented with the median scores from each stakeholder group

combined with a histogram showing the scoring distribution. Subsequently, participants will be

asked to score all outcomes for which consensus has not been reached, in the same manner as

in the first Delphi round. Outcomes for which there was only consensus within a single

stakeholder group will also be shown to the other stakeholder group to evaluate whether

additional outcomes that are not yet presented in the preliminary list.

consensus can be achieved in both stakeholder groups.

319 'not important'; 4–6 'important but not critical'; and 7–9 'critical' [24,25]. If participants feel
320 unable to rate or provide feedback they can select 'unable to score'.

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**Delphi rounds** 

Delphi round 1

Delphi round 2 and 3

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The definition of consensus is presented in Table 2. 'Consensus in' is defined as approval of the outcome by the vast majority (70 %) of all stakeholder groups that score 7, 8, or 9 with fewer than the minority (15 %) of panelists scoring 1–3. On the contrary, 'consensus out' is defined as 70% or more of all stakeholder groups scoring as 1 to 3 and less than 15% scoring as 7 to 9 [12]. After three e-Delphi rounds, outcomes will be classified as 'consensus in' (consensus on the importance of the outcome), 'consensus out' (no consensus on the importance, or consensus on nonimportance) or 'no consensus' (consensus on the importance in only one or or no consensus).

Table 2: Definitions of consensus for identifying generic outcomes for the LEAD registry

Consensus category	Clarification	Definition
Consensus in	Outcome should be included in the registry	70% of stakeholder groups scoring as 7 to 9 and < 15% of stakeholder groups scoring as 1 to 3
Consensus out	Outcome should not be included in the registry	70% or more of stakeholder groups scoring as 1 to 3 and < 15% of stakeholder groups scoring as 7 to 9
No consensus	Hesitation about relevance of outcome to be included in the registry	Anything other
Phase 2.2: Determinat	tion of the GOS during the expert consen	sus meeting
In case complete cons	ensus is reached in the Delphi procedure	on the outcomes of the GOS , no
formal consensus mee	ting will be organized. However, the resul	ts of the Delphi will be discussed

354 with three members of the steering committee (FF. PS, AW) to check misconceptions in the

<sup>0</sup>355 Delphi method and to safeguard a well-defined GOS. For outcomes for which consensus

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definition during the Delphi has not been reached, we invite 15 participants from across all
stakeholder groups to participate in an online expert consensus meeting within 2 months after
the close of round 3. The primary goal of the meeting is discussing the 'no consensus' outcomes.
Consensus results from the Delphi can be reversed in this meeting if reasons are very strong and
clear.

363 Patient and public involvement

Patient and public were not involved in the development of this study protocol. However, patients will be involved and included within the Delphi procedure as expert group. Consensus methodology will ensure that the opinions and preferences of patients will be given the same weighting as those of the laser experts and health professionals. Furthermore, patients will participate in the final consensus meeting. We disseminate the main results to study participants and patients by email which will include a copy of the final outcomes of the GOS. In addition, where approval has been given, participants (including members of the public) will be named as contributors in the acknowledgments section.

<sup>1</sup>373 **DISCUSSION** 

<sup>55</sup> 374 By the end of this study, we hope to reach consensus on a GOS that could be implemented in an
 <sup>57</sup>
 <sup>58</sup> 375 international registry with a research focus, that collects data of rare skin diseases treated by

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<sup>3</sup> 376 4 5	lasers. Analysis of registry data provides insight into effectiveness and safety of different laser
6 377 7 8 9	treatments across many skin diseases, laser centers and countries.
<sup>10</sup> 378 11 12	There are several strengths using the Delphi method for this study. First, the Delphi method
<sup>13</sup> 379 14 15	allows to recruit a large number of laser experts, physicians and patients from diverse regions
<sup>16</sup> 380 17 18	globally. The diversity in the experts' backgrounds and expertise ensures maximum impact of the
<sup>19</sup> 381 20 381 21	results. Secondly, the Delphi method is the accurate tool in consensus processes in various
<sup>22</sup> 23 382 24	stakeholder groups as individuals are able to express their own opinions and feedback can be
<sup>25</sup> 26 <b>383</b> 27	provided in a controlled anonymous way. This means that there is room for individual
<sup>28</sup> 29 384 30	disagreement but also consideration of the answers given by other individuals and stakeholder
31 32 385 33	groups as a whole. However, there are also limitations of the Delphi method. Results are
34 35 386 36	dependent upon the composition of the participants. There is a risk of relative uneven
37 38 387 39	representations among patients, but also health professionals. Especially, when focusing on a
40 41 388 42 43	specific group of rare skin diseases, selection bias could result in insufficient representation of
44 389 45 46	other skin disorders. We request health professionals of the steering committee to recruit
47 390 48 49	patients with 3 different skin disorders. Through this method, we hope to ensure that all
50 <b>391</b> 51 52	subgroups including vascular, pigmented, metabolic, inflammatory lesions, benign tumours and
53 <b>392</b> 54 55	hair follicle-related skin conditions, will be adequately involved. For patients it might be a barrier
56 393 57 58	to imagine what is important to be included in a registry for a broad range of diseases, rather
59 394 60	than one disease that is important to themselves. We will stress the importance of agreeing on

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2 3 395 4 5	a GOS for all diseases in each round of the Delphi survey and consensus meetings. Photographs
6 396 7	will be included to illustrate the variety of skin disorders that are involved. To provide the highest
9 10 11	possible input we will extend our invitation to take part in the Delphi survey to patients and
<sup>12</sup> 398 13 14	health professionals in Africa, Asia, South-America, Australia, in addition to Europe and North-
<sup>15</sup> 399 16 17	America. With support from all panel members we hope to ensure that the LEAD registry will be
<sup>18</sup> 400 19 20 21	internationally relevant, accepted and ready to use.
<sup>22</sup> 23401 24	Trial status
25 402 26	The identification of generic outcomes for registry use is ongoing and in the initial phase. A
<sup>27</sup> 403 28 29	systematic review has been performed to explore current outcomes used and reported in laser
30 404 31	dermatology. We are currently preparing to recruit participants for the Delphi study. The generic
<sup>32</sup> 405 33 34 35	outcomes s are expected to be implemented in the laser registry in 2020.
36 406 37 38	
<sup>39</sup> 407 40	ETHICS AND DISSEMINATION
41 42 408 43	The medical research ethics committee of the Academic Medical Center Amsterdam confirmed
44 409 45	that the Dutch Medical Research Involving Human Subjects Act does not apply to this study
46 47 48	(W19_290 # 18.336) and that complete approval of this study by the committee is not necessary.
49 411 50	All participants involved in the Delphi study will be asked for their consent before taking part. All
<sup>51</sup> 412 52	procedures will be conducted according to the Declaration of Helsinki. All results from the
54 413 55	consensus study will be reported in peer-reviewed indexed journals. The data will be presented
<sup>56</sup> 414 57 58 59 60	at conferences chosen to reach a wide range of knowledge users.

2	
<sup>3</sup> 415	Abbreviations
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5 416	COMET: Core Outcome Measures for Effectiveness Trials: GOS: Generic Outcome Set: CSG-
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, 8 <u>4</u> 17	COLISIN: Cochrane Skin Group—Core Outcome Set Initiative: COSMIN: COnsensus-based
9	coosini. cocinane skin croup core outcome set initiative, cosinini. consensas sasca
10 110	Standards for the selection of health Measurement Instruments, COS, Conoris Outcome Set
11 410	Standards for the selection of health Measurement instruments, GOS. Generic Outcome Set,
12	
13 419	GRADE: Grading of Recommendations Assessment; LEAD registry: Laser Treatment
15	
16 <sup>13</sup> 420	Dermatology registry; RCT: Randomized controlled trial.
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<sup>18</sup> 421	
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27 422	Contributors
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<sup>25</sup> 423	FE initiated the protocol, designed the study, wrote the manuscript and reviewed it for
26	
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29 424	important intellectual content. PS contributed significantly to the study design and reviewed
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31 425	the manuscript for important intellectual content. CP contributed to the study design and
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$^{33}_{34}$ 426	reviewed the manuscript for important intellectual content. AW initiated the protocol,
35	
36 427	designed the study and reviewed it for important intellectual content. All authors (FF, PS, AW,
37	
<sup>38</sup> 428	MA, AB, PB, IH, MH, LH ,KK, TK, HL, WM, LM, KN, UP, TP, CP, IV) read and approved the final
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50 431	Acknowledgements
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55 54 432	We are grateful to Jan Kottner of the CS-COUSIN methods group for providing advice
55	
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57 433	for methodological issues during the protocol development. We acknowledge Marjolein
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<sup>14</sup> 437	1	List of members of the LEAD registry steering committee	
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patients



## **SUPPLEMENTARY FILE 1**

# LEAD Registry : Steering Committee

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### **SUPPLEMENTARY FILE 2**

The definitions for COS, outcome, outcome instruments and outcome parameters according to Prinsen *et al.* (2014). [1]

## Definitions

Similar constructs are defined differently across several research groups such as COMET, OMERACT, and HOME. As there is currently no consensus on the definitions, we would like to explicitly state the definitions that are being used in the COMET Delphi study in order to avoid any possible misinterpretations.

# Core outcome set (COS)

A COS is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. A COS includes all relevant outcomes of a specific health condition within a specified setting (the OMERACT definition refers to 'core domain set' whereas the HOME definition refers to 'core outcome domains').

# Generic core outcome set (GOS)

A GOS is an agreed minimum set of *generic* outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. In this study, the GOS is intended to be applied for the assessment of various, unrelated skin diseases that are treated with different types of lasers.

## Outcome and outcome domain.

Throughout this report, the definition of "outcome" refers to a single construct that can be measured as a standalone item (e.g. 'erythema'), while the term "outcome domain" or "domain" is an umbrella term for a group of associated outcomes (e.g. 'signs as assessed by physician').

## **Outcome measurement instrument**

An outcome measurement instrument refers to how the outcome is being measured (the tool used to assess the outcome). An outcome measurement instrument can be a single question, a questionnaire, a performance-based test, a physical examination, a laboratory measurement, an imaging technique, and so forth (the HOME definition refers to 'outcome measure').

## Reference

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SUPPLEMENTARY FILE 3
Systematic review search strategies
Pubmed
1."Skin" [Majr MeSH]
2."cutaneous" [Majr MeSH]
3."dermatology" [Majr MeSH]
4. "Skin Diseases"
5. 1 or 2 or 3 or 4
6."laser" [Majr MeSH]
7. "alexandrite laser" [MeSH Terms]
8 "laser, pulsed dye" [MeSH Terms]
9. "er yag" [MeSH Terms]
10. "laser, nd yag" [MeSH Terms]
11. "laser, ruby" [MeSH Terms]
12. "laser, ysgg" [MeSH Terms]
13. "laser, argon" [MeSH Terms]
14. "laser, ktp" [MeSH Terms]
15. "laser, q switched" [MeSH Terms]
16. "laser, carbon dioxide" [MeSH Terms]
17. "laser, co2" [MeSH Terms]
18. "laser, diode" [MeSH Terms]
19. "thullium laser"
20. "fluoride laser"
21. "fractional laser"
22. "fractional CO2 laser"
23. "non-ablative fractional laser"

### 24."Humans[Mesh]

 25. "last 5 years" [PDat]

#### 26. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

26. 5 and 26

#### Embase:

- 1. #1, Skin.mp. or exp skin/
- 2. #2, cutaneous.mp.
- 3. #3, dermatology.mp. or exp dermatology/
- 4. #4, skin diseases.mp. or exp skin disease/
- 5. #5, laser.mp. or exp laser/
- 6. #6, laser treatment.mp.
- 7. #7, laser therapy.mp.
- 8. #8, skin laser therapy.mp.

9. #9, exp argon laser/ or exp frequency doubled neodymium YAG laser/ or exp thulium YAG laser/ or exp dye laser/ or exp gallium aluminum arsenide laser/ or exp neodymium laser/ or exp pulsed dye laser/ or exp carbon dioxide laser/ or exp excimer laser/ or exp YAG laser/ or exp alexandrite laser/ or exp argon fluoride laser/ or exp gas laser/ or exp laser surgery/ or exp erbium YAG laser/

10. #10, nd YAG laser.mp.

- 11. #11, non-ablative fractional laser.mp.
- 12. #12, CO2 laser.mp.
- 13. #13, fractional CO2 laser.mp.
- 14. #14, carbon dioxide laser.mp. or exp carbon dioxide laser/
- 15. #15, q switched laser.mp.
- 16. #16, nd YAG laser.mp.
- 17. #17, exp symptom assessment/ or exp symptom/ or symptoms.mp.
- 18. #18, outcome assessment.mp. or exp outcome assessment/
- 19. #19, treatment outcome.mp. or exp treatment outcome/

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20. #20, exp treatment outcome/ or exp outcome assessment/ or outcome.mp.

- 21. #1 or #2 or #3 or #4
- 22. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
- 23. #17 or # 18 or #19 or #20
- 24. #21 and #22
- 25. #23 and #24
- 26. 25 and 2013:2017.(sa\_year).
  - 27. 26 and "human" [Subjects]

# SUPPLEMENTARY FILE 4

A list of invited patient support groups for the Delphi survey

Name of Society Hidradenitis Patiëntenvereniging (NL) Nevus Netwerk Nederland (NL) Nevus Outreach (US) Nevus Support (AU) Neurofibromatose Vereniging Nederland (NL) The Neuro Foundation (UK) Neurofibromatose Ireland Association (IE) Vereniging Wijnvlek Sturgeweber syndroom (NL) Schweizerischen Nuerofibromatose Vereinigung (CH) Interessengemeinschaf Sturge-Weber-Syndrom (DE) Sturge Weber Foundation Great Britain (UK) Sturge-Weber-Foundation (US) ez-Vitiligo patientenvereniging (NL) National Vitiligo Foundation (US)