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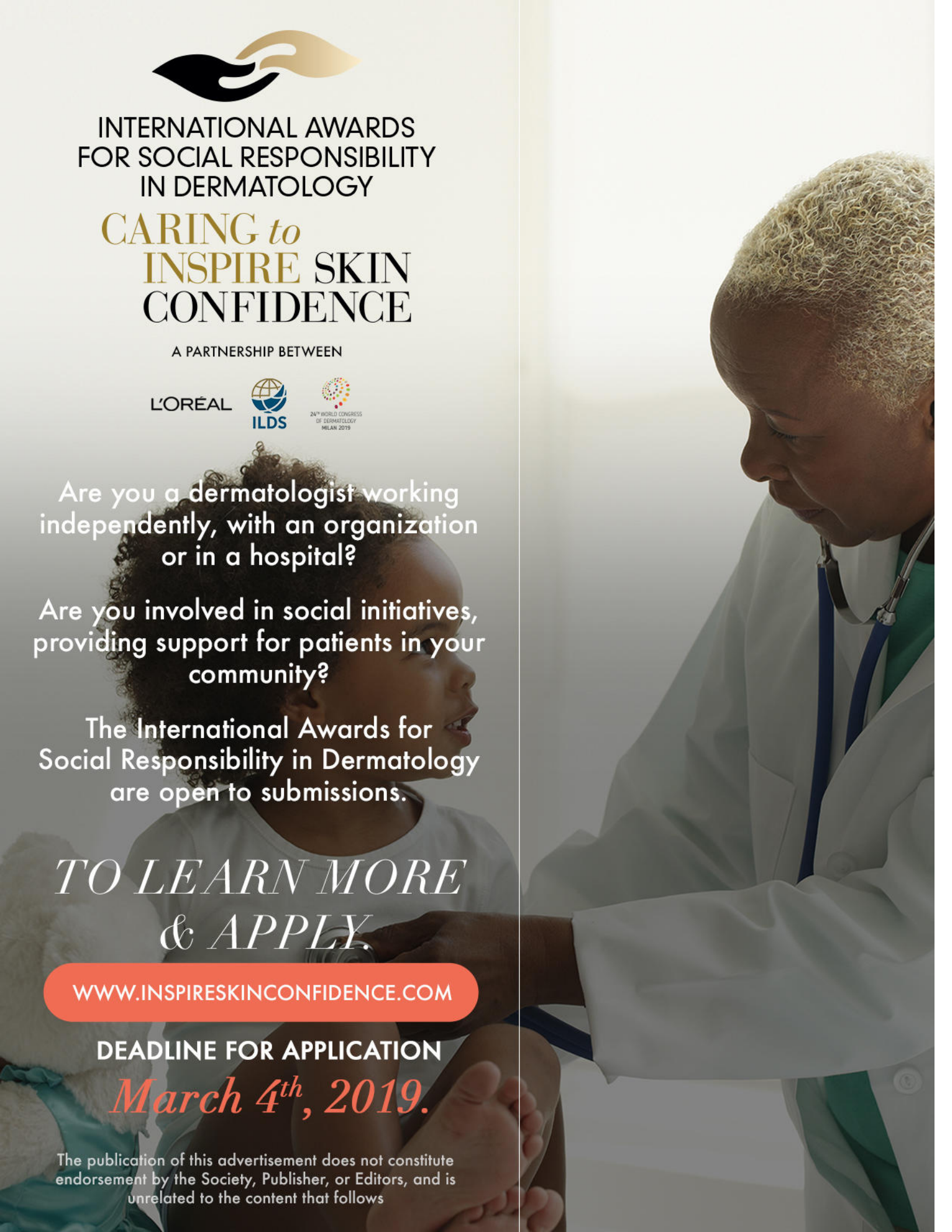

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Which outcomes have been measured in hand eczema trials? A systematic review

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Conflict of interest

We disclose that AB was involved in three and UM was involved in one of the included hand eczema trials. CA and AB lead the HECOS initiative and HR is the coordinator of the HECOS initiative. However, none of the authors has any conflict of interest or any financial interests that could potentially be relevant for this review.

Abstract

The considerable heterogeneity of outcomes and measurement instruments in hand eczema trials substantially limits the evidence synthesis concerning therapeutic and preventive interventions. Therefore, the Hand Eczema Core Outcome Set (HECOS) initiative is developing a core outcome set for future trials. The first objective was to identify outcomes that were measured in previous trials, to group them in domains, and to identify their measurement instruments. We conducted a systematic review of

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controlled and randomized controlled hand eczema trials published since 2000. Sixty-one eligible studies were identified. Each assessed one or more out of 47 outcomes in the “skin” domain. Eighteen trials (30%) additionally focused on preventive behaviour in risk occupations. Quality of life was measured in 13 studies (21%). Thirty-two distinct named instruments were applied, but 223 measurements (62%) were conducted with unnamed instruments. Only 32 studies (52%) defined a primary outcome. Twenty-nine trials (48%) provided some information on adverse events but none gave any references concerning relevant methods. Our review confirms the need to harmonize outcome measurements in hand eczema trials. The findings are the basis for a consensus process to generate a core outcome set to improve the explanatory power and comparability of future hand eczema studies.

Keywords: Core Outcome Set, CSG-COUSIN, Hand Dermatitis, Outcome Measurement Instruments

1. Introduction

Hand eczema is a complex, multifactorial and impairing skin disease. With a one-year prevalence of nearly 10% it is common in the general population (1). Moreover, occupational hand eczema is one of the most common occupational diseases and constitutes 40% of all occupational diseases in industrialized nations causing substantial psychological and economic burden for affected individuals and society (2,3,4,5).

Considerable research efforts are therefore undertaken in order to develop and evaluate interventions aiming to prevent the development, recurrence or worsening of hand eczema, or to ease its burden. However, trials studying these interventions use a variety of outcomes to determine their success. The problems arising from such heterogeneity have been explained in detail by the Core Outcome Measures in Effectiveness Trials (COMET) initiative (6). In short, heterogeneity considerably limits the comparability and overall confidence in the study results, and thereby the strength of recommendations for clinical practice (7). To help overcome these problems, the Hand Eczema Core Outcome Set (HECOS) initiative was formed. This international working group of dermatologists and researchers experienced in hand eczema trials aims to develop a core outcome set for standardized evaluation of therapeutic and preventive interventions in future hand eczema trials and reviews. This core outcome set will define the minimum that should be measured and reported in interventional trials of hand eczema (8). Apart from enhancing the methodological quality, comparability, and usefulness of hand eczema trials for clinical decision-making, the COS will also considerably reduce the effort of planning, conducting, and reporting individual hand eczema studies as well as reviews and meta-analyses. The methodology of HECOS will

follow the guidance provided by the Cochrane Skin Group Core Outcomes Set Initiative (CS-COUSIN) (9,10).

As an early step in the core outcome set development, we systematically reviewed controlled or randomized controlled hand eczema trials published since 2000, covering all types of participants, interventions, and comparisons. We aimed to identify the outcomes they measured (e.g. “itch”), to group relatively similar outcomes in domains (e.g. “skin”), and to specify the instruments that were applied to measure them (e.g. “visual analogue scale”). This overview will facilitate the HECOS consensus process by providing an overview of relevant outcomes and instruments to be considered for the core outcome set.

2. Methods

The review was conducted according to an unpublished protocol.

2.1 Explanation of terms

No distinction was made between efficacy and effectiveness outcomes. We distinguished between outcomes, outcome domains, outcome measurement instruments, and measurements. Outcomes specify what is measured: hand eczema trials report, for instance, the presence of hand eczema, or the extent of skin dryness or erythema. Outcome domains are categories of outcomes that are similar in content, e.g. the categories “skin” or “social functioning”. Outcome measurement instruments on the other hand specify *how* an outcome is measured: The presence of hand eczema, for example, may be measured by applying diagnostic criteria developed by the study researchers or by pre-existing instruments such as certain items of the Nordic Occupational Skin Questionnaire (11). The number of measurements, in our context, means how often outcomes were measured across trials. If, for instance, 10 trials

measure transepidermal water loss (TEWL) (12), this adds up to 10 measurements of one outcome. This distinction is important for this review because relevant properties (like who assesses the outcome) apply to measurement instead of outcome level.

2.2 Search methods

In May 2017, we performed a systematic literature search in Ovid Medline and Embase. Additionally, references of overview articles that were identified during this process as well as hand-eczema-related systematic reviews published in the Cochrane library were searched. We further looked for protocols of eligible ongoing hand eczema trials in relevant clinical trials registries. The search terms are given in Supplemental Table 1.

We included controlled and randomized controlled clinical hand eczema trials published in English or German since January 1, 2000, covering all types of participants, interventions (including preventive interventions), and comparisons. Retrospective or observational studies without intervention, laboratory experiments, and conference abstracts were excluded. Study eligibility was assessed independently by two investigators per record based on titles and abstracts. When this was not possible, full texts were obtained and evaluated. All differences were dissolved by discussion, involving a third investigator when needed.

2.3 Data extraction

Full texts were obtained for all eligible studies. A data extraction template (including guidance for its use) was developed and pretested. All relevant information was extracted independently by two researchers for each trial: Study details, data on efficacy / effectiveness outcomes, data on safety outcomes, and baseline characteristics. Discrepancies were resolved by discussion and in case of conflict a third investigator was involved.

Reported outcomes that were not specified in the article's methods section were included as well. All efficacy and safety outcomes were extracted, even when considered unrelated to hand eczema. Control variables / factors were not extracted. The identified efficacy outcomes were mapped according to the taxonomy developed by the Core Outcome Measures in Effectiveness Trials (COMET) initiative (13). In accordance with this taxonomy, clinical signs as well as symptoms were classified within the "physiological or clinical" core area. Composite outcomes addressing several domains were classified within each of the covered domains.

3. Results

3.1 Included studies

Figure 1: PRISMA flow diagram adapted from Moher et al (14)

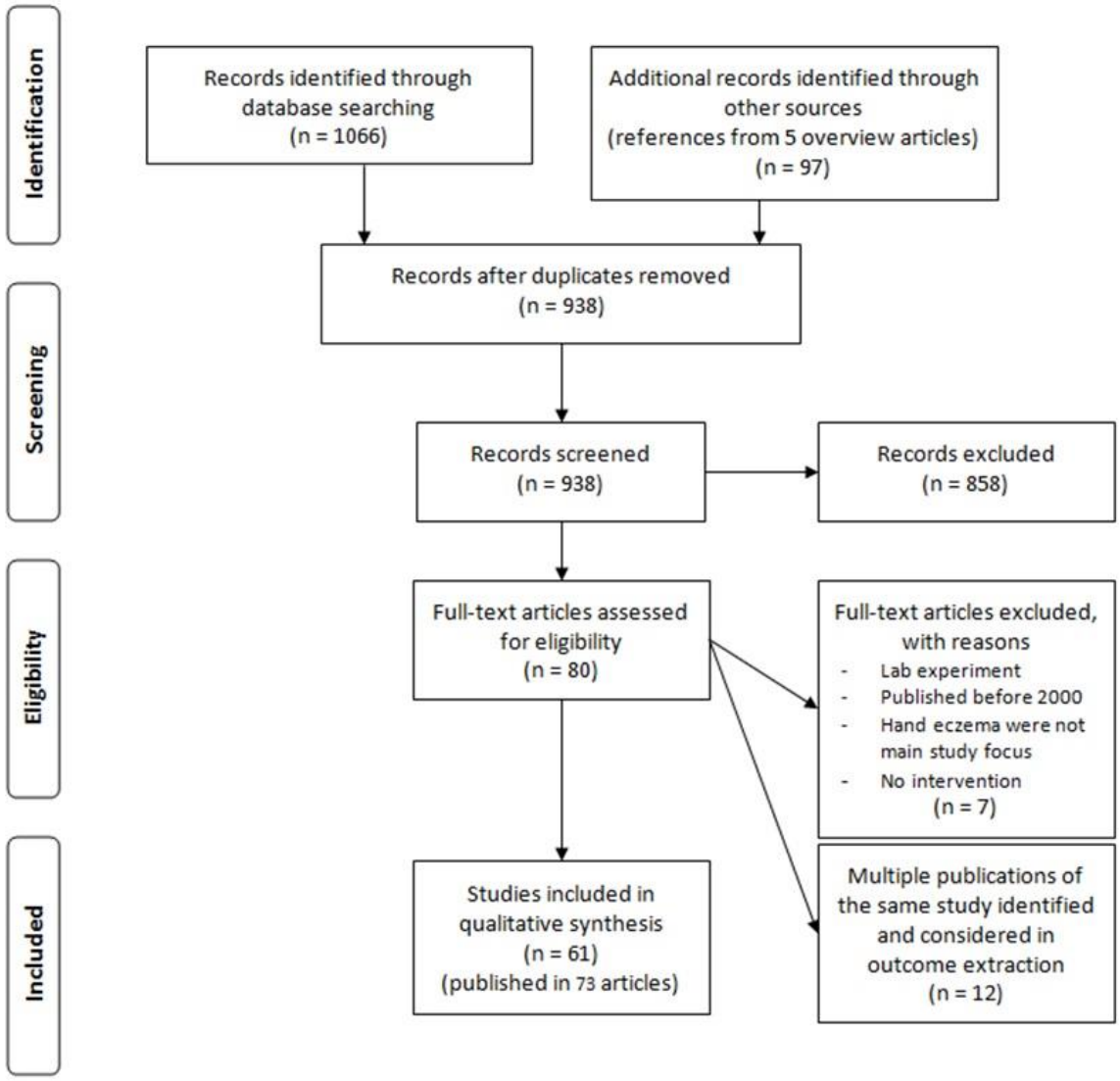


Figure 1: PRISMA flow diagram adapted from Moher et al. (15)

After removing duplicates, we identified and screened 938 potentially eligible records (Fig. 1). Twenty-four of these articles were written in languages other than English or German and were therefore excluded. Two of them (1 Turkish and 1 Polish) were potentially eligible (apart from the language criterion), judging from their abstracts. Most studies were conducted in Europe (Table 1). Finally, 16 non-randomized, 41 randomized, and 4 ongoing randomized studies were included (Supplemental Table 2).

Fifty-nine per cent of the trials investigated therapeutic interventions while 38% assessed preventive interventions. Two studies (3%) provided no clear indication whether their intervention was therapeutic or preventive. The severity of the study populations' hand condition varied considerably, ranging from participants with healthy skin (in prevention studies) to patients with severe chronic hand eczema.

Several studies evaluated complex interventions (e.g. recommendations to apply various protective measures). It was therefore impossible to derive actual counts from our database. However, more than half of the trials investigated topical treatments and about one third evaluated skin protection education, training or counselling. Around 10% investigated oral treatments or phototherapy, respectively. Hand cleansing and glove use were specifically investigated in one trial each and were part of an unknown number of complex interventions. One trial investigated the effects of a nickel-reduced diet in nickel-sensitive hand eczema patients.

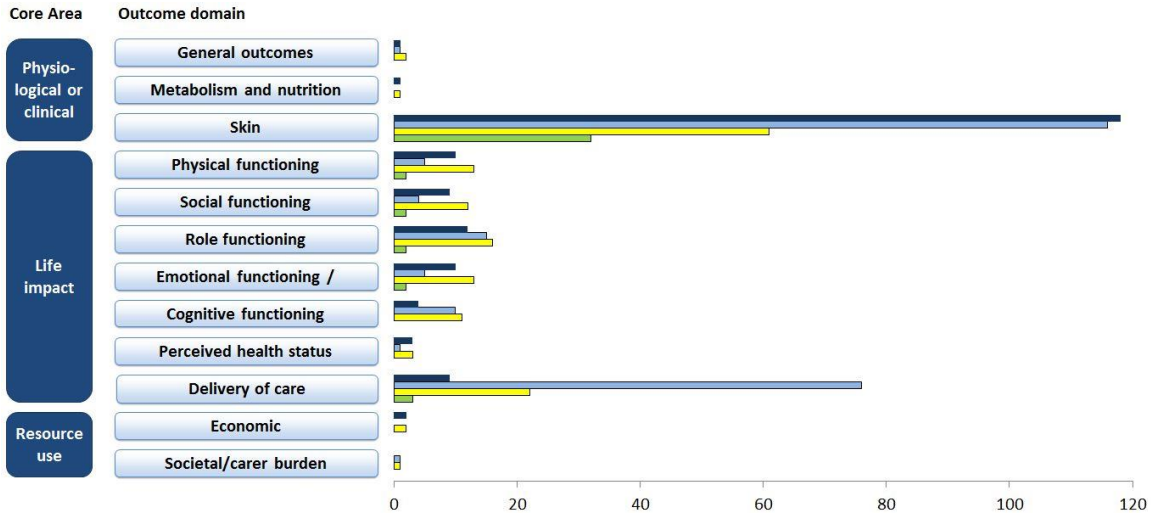
The following study characteristics apply to the studies for which they were reported: A total of 12620 participants were recruited, ranging from 8 to 1649 per study. The average participants' age per study ranged from 17 to 55 years. More women than men were included (62% female, unweighted mean).

3.2 Efficacy / effectiveness outcomes and outcome measurement instruments

Thirty-two studies defined a primary outcome (25% of CCTs and 62% of RCTs); 26 of them defined one and the remaining trials up to 5 primary outcomes. More recent trials were more likely to define a primary outcome: From 2009 to 2016, 70% of the trials defined a primary outcome as compared to 42% of the trials published from 2000 to 2008 (Fisher's Exact test: $P = 0.06$). Each study conducted between 1 and 28 measurements (mean = 3.8 in therapeutic and 9.7 in prevention trials), amounting to a

total of 360 measurements. Two hundred twenty-three measurements applied unnamed instruments (54% in therapeutic and 67% in prevention trials). The remaining 137 measurements were conducted with 32 distinct instruments (25 in therapeutic and 17 in prevention trials).

Figure 2: Outcome domains of efficacy outcomes categorized according to Dodd et al. (13)
▪ number of measurements in therapeutic trials; ▪ number of measurements in prevention trials; ▪ number of trials; ▪ number of trials with this primary outcome
Empty domains are not displayed.



3.3 "Skin" domain

Most outcomes, by far, were measured in the "skin" domain (all 61 trials, see Fig. 2). In accordance with the taxonomy, this domain covers physiological / clinical skin outcomes including physiological function, signs, and symptoms. Forty-seven skin outcomes were assessed in hand eczema trials (Table 2).

The most often applied outcome measurement instrument in the skin domain was an item of the Dermatology Quality of Life Index (DLQI; "Over the last week, how itchy, sore, painful or stinging has your skin been?"; 10 trials) but this was not reported as a separate outcome. The Hand Eczema Severity Index (HECSI) was applied in 6 and

Tewameter measurements in 8 trials. Other outcomes were assessed in less than 10% of the trials (Supplemental Table 3).

3.4 "Delivery of care" domain

The second largest domain was "delivery of care", in particular the sub-domain "adherence / compliance". This sub-domain was important in prevention trials in occupations with particular risk of developing hand eczema. There, it referred to skin protective behaviour of the employees (18 trials) and preventive measures provided by the employer (5 trials). A list of all 72 non-skin outcomes is provided in Supplemental Table 4.

3.5 "Functioning" and other domains

The domains "physical functioning" (13 trials), "social functioning" (12 trials), and "emotional functioning / wellbeing" (13 trials) addressed e.g. fatigue, affectedness of physical or social activities, or embarrassment and were measured only as part of a health-related quality of life (HRQOL) questionnaire. "Cognitive functioning" (11 trials) was either measured as part of a health-related quality of life (HR-QoL) questionnaire (e.g. worries about hand eczema) or referred to preventive knowledge. The domain "role functioning" was evaluated in 16 trials. It always referred to the participant's ability to work or study and was assessed as part of a HR-QoL questionnaire (7 trials), as an outcome of its own (3 trials), or both (6 trials). All other domains were covered by few studies (Fig. 2).

3.6 Properties of the outcome measurements

Out of the total of 360 measurements, a vast majority of 195 were patient-reported (33% of the measurements conducted in therapeutic trials and 69% of the measurements in

prevention trials). Sixty-two measurements were performed by physicians, 8 by other study personnel, and 19 were patient-reported as well as assessed by a physician or other personnel. Two laboratory measurements, 24 skin-physiological measurements (e.g. skin hydration), and 6 other measurements with technical devices (e.g. L-a-b histogram, skin contrast) were performed. For 46 measurements, the information was lacking in the study reports. The proportion of studies that included at least one (partly) patient-reported outcome was 74%. It varied from year to year without a clear tendency (71% from 2000 to 2008; 78% from 2009 to 2016; Fisher's Exact test: $P = 0.76$). Overall, some reference was provided for 161 of the 360 measurements, implying that the instruments had been used before. However, only 102 referred to development or validation studies or to guidelines for the use of the instruments.

3.7 Safety outcomes

Thirteen trials reported their methods to detect adverse events. Six of these methods were unspecified (e.g. stating that adverse events were recorded). Another 16 trials reported adverse events without mentioning their methods to detect them. None of the studies gave any references concerning methods of registering adverse events.

4. Discussion

To our knowledge, this is the first systematic review that summarizes the use of outcomes and outcome measurement instruments in hand eczema trials. It is part of the HECOS initiative and will be the basis for developing a core outcome set for future hand eczema trials. Sixty-one eligible studies were identified.

4.1 Outcomes in the "Skin" and other domains

Not surprisingly, the majority of all measurements were conducted within the "skin" domain. However, 47 distinct skin outcomes were measured, encompassing various symptoms such as itch or pain, clinical signs like vesicles or scaling, overall ratings of hand eczema severity or extent, and parameters with unclear relevance for hand eczema like skin surface pH or skin contrast. The complete list of these outcomes will be used in a Delphi survey to determine which are considered crucial by patients, clinicians, investigators, and other stakeholders. Other domains were investigated mainly to evaluate the participants' HRQOL, their ability to work, and outcomes related to the prevention of occupational hand eczema. The outcomes will be considered in the Delphi survey.

4.2 Differences between therapeutic and prevention trials

In the "skin" domain, half of the outcomes were measured in therapeutic as well as in prevention trials. For the remaining outcomes (with the exception of "ever had hand eczema"), no reason was apparent why these outcomes should not be eligible for both types of study. Prevention trials conducted more than twice as many measurements per trial and the proportion of patient-reported outcomes was twice as high compared to therapeutic trials. Prevention trials also applied more unnamed instruments.

Most of the additional outcomes belonged to the domain "delivery of care", in particular the uptake of protective behaviour and the status of skin protection at the workplace. These intermediate outcomes do not directly benefit the patient. Instead, it is expected that they are associated with physiological outcomes. Since 38% of the trials addressed prevention strategies, an extended core outcome set will probably be

necessary for prevention trials, which will be considered in the consensus process to identify core outcomes.

4.3 Outcome measurement instruments

Each of the 32 named outcome measurement instruments was applied in only a minority of studies. The most frequent were the DLQI in 16%, Tewameter measurements in 13%, and the HECSI in 10% of the trials. In addition, the majority of outcomes were measured without referring to any development or validation studies of the respective instruments. Beyond that, however, we did not yet explore to which extent the instruments were validated. This will be the next step of HECOS and topic of a separate publication. Apart from the validity of the instruments, it remains unclear how far they may be comparable to each other. This concerns in particular the assessment of skin impairment, for which a large number of instruments were applied. Across other domains as well, unnamed instruments, predominantly questionnaires, were applied more than twice as often as named instruments.

4.4 Safety outcomes

While an in-depth analysis of the applied safety outcomes will be covered in another publication, it is already apparent that none of the included studies provided any references concerning safety outcomes. The Patient-Reported Outcomes Safety Event Reporting (PROSPER) Consortium Guidance provides insight on how to gather such outcomes (15). This process involves validating the instruments that measure safety outcomes, which so far has not been reported for any of the included hand eczema trials. Complementary, more specific guidance on clinician-reported safety outcomes is needed for hand eczema studies. The US National Institutes of Health Ongoing Trials Register offers detailed advice on how to report safety outcomes (16). HECOS will

provide guidance on how to collect such data with validated instruments in hand eczema trials.

4.5 Outcome taxonomy

A recent review by Dodd et al (13) revealed that despite availability of a variety of outcome taxonomies, none of them was sufficient for categorizing the outcomes of all clinical trials. They developed a new taxonomy, which proved to be very suitable for categorizing the outcomes identified in our review. It is structured by 5 core areas and domains within these areas and also provides a comprehensive guidance on how to map outcomes accordingly. Most outcomes that were identified by our review could be fitted into exactly one of the domains. Only HR-QoL outcomes were difficult to map because the taxonomy requires categorizing composite outcomes within each domain covered by their components and some individual questionnaire items did not fit the domains well. In the DLQI (17), for example, the first question ("Over the last week, how itchy, sore, painful or stinging has your skin been?") was considered as an item that addresses skin symptoms and was therefore classified in the "skin" domain. If the item had a slightly different wording (like "How much did you suffer from itchy, sore, painful or stinging skin?"), it would cover the "emotional functioning/well-being" category instead. For another DLQI question ("Over the last week, how much has your skin influenced the clothes you wear?"), no category was completely appropriate – the question may refer to social or emotional functioning, or neither. While we agree with Dodd et al that it is important to identify the content of score components for some purposes, this may not be necessary for many other objectives. Composite scores are designed to measure constructs (like HR-QoL) as a whole and we therefore consider that it would be appropriate to categorize them at construct level. Also, the categorization process would

be simpler and would result in less variability between raters. In this review, however, composite outcomes were categorized at component level as proposed by the taxonomy developers. This approach was accompanied by the uncertainties described above for HR-QoL scores, but other composite outcomes were not affected because all of their components fell into the “skin” domain.

4.6 Strengths and limitations

Our review has some limitations. Firstly, it was restricted to articles published since 2000 in English or German language. Thus, outcomes and measurement instruments that were exclusively published in older articles or other languages were not considered. However, only two additional articles would have been eligible without the language restriction. Secondly, we were unable to assess how many of the unnamed instruments were actually identical. The photographic guide developed by Coenraads et al (18), for instance, was used in several studies, but from the data gathered it was impossible to determine the exact number. Other outcomes, like various 3-point scales of skin impairment, appeared similar but also lacked a name to clarify if they were identical or not. A strength of this review was that the databases were searched intensely for all eligible trials and all data were extracted in duplicate with a pretested template so that we are confident that all contemporary hand eczema outcomes and outcome measurement instruments were covered in this review insofar they were applied in controlled trials.

5. Conclusion

This review provides an overview of efficacy / effectiveness outcomes that have been applied in interventional hand eczema trials since 2000. Our findings confirm the need

for harmonizing outcome measurement instruments and for promoting the usage of validated instruments.

The results of the review are the basis for a consensus process to generate a core outcome set. In the course of the project, the core outcome set is going to be completed by determining appropriate, validated measurement instruments for each relevant domain. This systematic review ensures that all previously applied outcomes will be considered in this process. As a result of this harmonization, the explanatory power and comparability of future hand eczema trials will be improved considerably.

Researchers who are planning new hand eczema trials are invited to visit the HECOS website for updates. Scientists, clinicians, and patients who wish to participate in HECOS are encouraged to contact us.

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Tables

Table 1: Geographic setting of the studies

	Therapeutic trials		Prevention trials	
	Number of trials	Percent	Number of trials	Percent
Germany	6	10%	11	18%
USA	6	10%	2	3%
Denmark	3	5%	5	8%
The Netherlands	5	8%	0	0%
UK	0	0%	2	3%
Iran	3	5%	0	0%
India	3	5%	0	0%
other*	10	16%	3	5%

* Belgium, Canada, Estonia, Finland, France, Greece, Hungary, Israel, Italy, Norway, Poland, Switzerland, Turkey

Table 2: Skin outcomes identified in therapeutic and preventive hand eczema trials

Outcome	therapeutic trials	prevention trials
aching, pain, sore skin, tenderness	x	x
breaks in the skin, fissures, fissuring, cracking, cracks, rhagades, splits, cuts	x	x
burning	x	x
coarseness, roughness	x	x
crusting, crusts, serum crusting	x	x
desquamation, scaling, flaking, squamation	x	x
dryness, dry skin	x	x
dyshidrosis, vesicles, vesiculation, tiny water blisters	x	x
erythema, reddening, redness	x	x
ever had hand eczema	x	x
general change of hand eczema	x	x
general hand eczema severity	x	x
general improvement of hand condition	x	x
infiltration	x	x
irritated skin	x	x
itch, itching, pruritus	x	x
lichenification, thickened skin	x	x
number of eruptions during past 3 months	x	x
oedema, edema, swelling	x	x
papulation, papules, red papules	x	x
skin capacitance, moisture, skin hydration	x	x
time to relapse	x	x
trans-epidermal water loss (TEWL), barrier function	x	x
area affected, general extent of hand eczema	x	
furrowing, lined skin	x	
hyperkeratosis, hyperkeratoses	x	
impairment of mobility	x	
induration	x	
inflammation	x	
oxidative stress	x	
prurigo nodules	x	
scratching	x	
sensitive skin	x	
bleeding		x
erosions, abrasions, excoriation, excoriations		x
ever had eczema on wrists or forearms		x
last episode of hand eczema		x
last episode of wrist / forearm eczema		x
oozing, weeping		x
prickling, stinging		x
rapidly appearing itchy wheals / welts (urticaria)		x
skin contrast		x
skin surface pH		x
skin tightness (symptom), tight skin		x
suppurating skin		x
sweating		x
thin skin		x