Core Outcome Domains for Controlled Trials and Clinical Recordkeeping in Eczema: International Multiperspective Delphi Consensus Process

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There is wide variation in the use of outcome measures for eczema. We performed a three-stage web-based international Delphi exercise to develop consensus-based sets of core outcome domains for eczema for "controlled trials" and "clinical recordkeeping". A total of 57 individuals from four stakeholder groups (consumers, clinical experts, regulatory agency representatives, and journal editors) representing 13 countries were asked to rate the importance of 19 outcome domains for eczema and to choose which domains should be included in two core sets of outcomes. Forty-six individuals (81%) participated. Participants received standardized feedback, including the group median, interquartile range, and previous responses, and the assessment was repeated in two subsequent rounds. We defined consensus *a priori* if at least 60% of the members of at least three stakeholder groups, including consumers, recommended domain inclusion in the core set. Consensus was achieved for inclusion of symptoms, physician-assessed clinical signs, and a measurement for long-term control of flares in the core set of outcome domains for eczema trials. We recommend including these three core outcomes in future eczema trials in order to enhance clinical interpretability and to enable meta-analyses across different studies. For recordkeeping, consensus was reached to regularly monitor eczema symptoms in clinical practice. Future work is needed to select which existing or new scales should be used to measure the domains identified as relevant for the core set.

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INTRODUCTION

Eczema (synonymous with atopic dermatitis and atopic eczema) is a common chronic relapsing inflammatory skin disorder that affects up to 20% of children and 3–5% of adults (Williams *et al.*, 1999; Williams, 2005; Schmitt *et al.*, 2009c). Because population-based studies have shown that ''atopy'' (defined as the presence of circulating allergen-specific IgE antibodies) is inconsistently associated with the clinical phenotype of eczema (Flohr *et al.*, 2008), we simply use the term ''eczema'' throughout this article, as recommended by the World Allergy Organization (Johansson *et al.*, 2004). Intractable itching associated with poor sleep and the visible stigmata on visible areas of the skin can lead to psychological and psychiatric comorbidities (Carroll *et al.*, 2005; Schmitt *et al.*, 2009a, b). Eczema imposes a high economic burden and is the most common cause of occupational skin disease (Kemp, 1999; Dickel *et al.*, 2003). Despite the public health relevance of eczema, it is unclear which aspects of eczema are most relevant for assessment in randomized controlled trials and in daily clinical practice.

One systematic review of 93 randomized controlled trials of therapeutic interventions for eczema found that only 27% of the investigators who incorporated an objective assessment of clinical severity applied a severity scale that had been published before (Charman *et al.*, 2003). In another systematic review, we found that only 3 out of 20 named outcome measurements for eczema have been tested sufficiently and performed adequately in terms of validity, reliability, and ease of use (Schmitt *et al.*, 2007). Because every investigator may select from a plethora of different objective and subjective, physician- and patient-assessed outcome domains, therapies evaluated in studies are simply not comparable. The failure of the scientific community to restrict themselves to a defined set of relevant and validated outcome domains in eczema trials is a significant barrier hindering progress in comparative effectiveness research for eczema. Core sets of appropriate standard

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outcome domains are useful for increasing clinical interpretability, preventing selective reporting outcome bias, limiting statistical errors by reducing the number of variables to be analyzed, and enabling valid pooling of results across different studies. Such core sets are available for a variety of musculoskeletal diseases (Tugwell and Boers, 1993; Bellamy *et al*., 1997; van der *et al*., 1997; Taylor, 2005; Tugwell *et al*., 2007), but are still missing for eczema.

Ideally, similar outcome domains should be assessed in eczema trials and in daily recordkeeping to enable the translation of trial evidence into clinical practice. However, it is unclear which eczema outcome domains are important for regular documentation in clinical practice.

To achieve better standardization in the outcomes applied in clinical research and practice, we performed and moderated an international multiperspective Delphi consensus project to develop core sets of outcome domains for eczema for controlled trials and for recordkeeping in clinical practice.

RESULTS

A total of 46 individuals from 11 countries participated in the first round (response rate 81%). Of those, 100% ($n=46$) and 93% ($n=43$) participated in the second and third rounds. Participants' characteristics and responses by stakeholder group and country are summarized in Table 1. Response rates were 100% for consumers and 78% for clinical experts. Seven out of eight journal editors (88%) participated (all except the representative of *Acta Dermato-Venereologica*) and completed all three rounds. Unfortunately, the Food and Drug Administration representative (Lead Medical Officer, Division of Dermatology and Dental Products) declined participation ''*due to workload/resource priorities*''; therefore, only one regulatory agency was represented (Table 1).

In addition to the 16 domains addressed in round one, participants suggested including overall extent of disease, involvement of high expression areas, and treatment utilization as additional domains of potential relevance to be

Table 1. Participants' characteristics and responses by stakeholder group

	No. of participants invited	No. participated in round 1; response rate (%)	No. participated in round 2; response rate (%)	No. participated in round 3; response rate (%)
Stakeholders				
Consumers	6	6 (100)	6 (100)	6 (100)
Clinical experts	41	32 (78)	32 (100)	29 (91)
Regulatory agency representatives	2	1 (50)	1 (100)	1 (100)
Journal editors	8	7 (88)	7 (100)	7 (100)
Country				
Australia	2	1 (50)	1 (100)	1 (100)
Brazil	3	2 (67)	2 (100)	2 (100)
Denmark	2	1 (50)	1 (100)	0 (0)
France	2	2 (100)	2 (100)	2 (100)
Germany	11	11 (100)	11 (100)	9 (82)
Italy	2	2 (100)	2 (100)	2 (100)
Korea	1	0 (0)		
Netherlands	2	2 (100)	2 (100)	2 (100)
Sweden	3	2 (67)	2 (100)	2 (100)
Scotland	1	0 (0)		
Switzerland	1	1 (100)	1 (100)	1 (100)
United Kingdom	7	6 (86)	6 (100)	6 (100)
United States	15	11 (73)	11 (100)	11 (100)
Sex				
Female	18	14 (78)	14 (100)	14 (100)
Male	39	32 (82)	32 (100)	29 (91)
Total	57	46 (81)	46 (100)	43 (93)

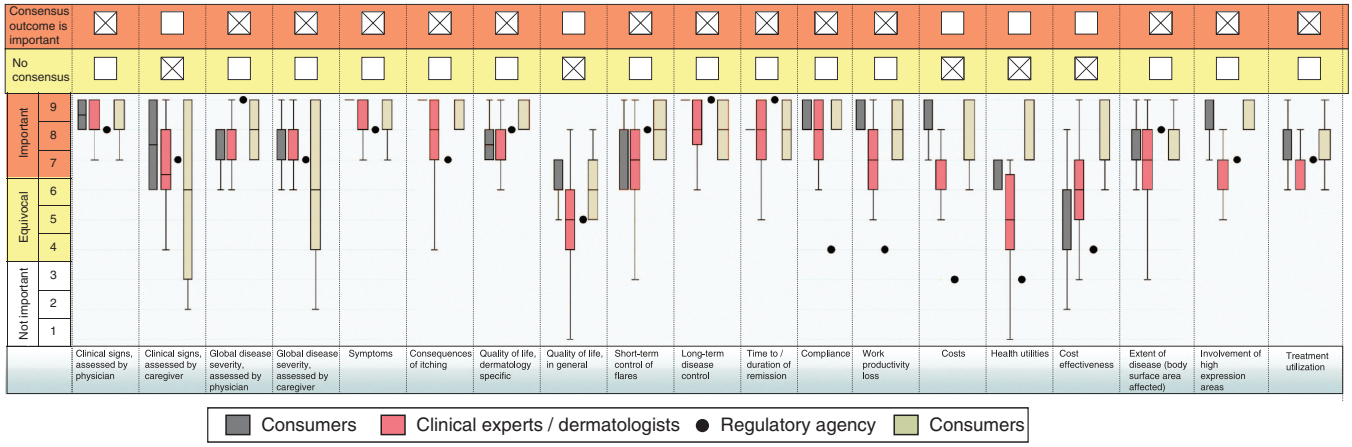

Figure 1. Rating of importance of outcome domains in the context of randomized controlled trials to measure the efficacy of interventions for eczema by the Delphi panel, stratified by stakeholder group.

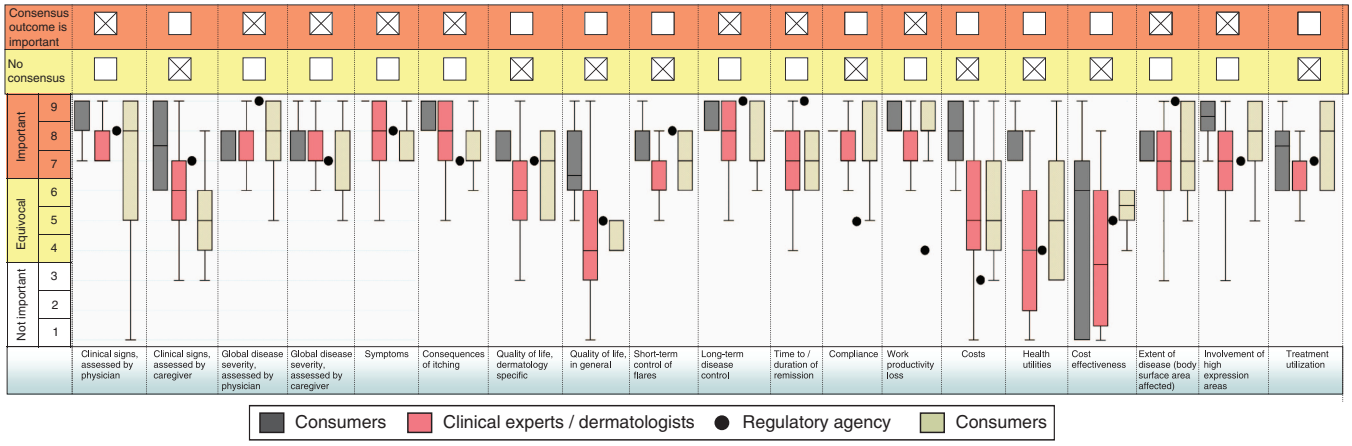

Figure 2. Rating of importance of outcome domains for eczema in the context of clinical recordkeeping by Delphi panel, stratified by stakeholder group.

included into the core set. The main effect of the feedback process was to reduce variability in scores assigned to each domain, but with little change in the median score of each domain (Data not shown). Figures 1 and 2 summarize the results of the rating of importance of the 19 different outcome domains in the context of clinical trials and recordkeeping, respectively. The panel reached consensus that 14 out of 19 domains are important in the context of clinical trials for eczema (Figure 1) and that 10 domains are important in the context of recordkeeping in daily clinical practice (Figure 2).

Although the panel considered a broad set of different outcome domains as important, the panel indicated that only three different domains should be included in the core set (median rating by the whole panel). Tables 2 and 3 summarize the panel's third and final round responses as to which domains should be included in the core set for both contexts.

Respondents agreed that symptoms of eczema, clinical signs assessed by a physician, and a measurement for long-term control of flares should be included in the core set of outcomes for eczema trials. In contrast to clinical experts, journal editors, and the European Medicines Agency representatives, who advocated including dermatology-specific health-related quality of life into the core set, the majority of consumers (67%) indicated that quality of life should not be assessed in every eczema trial. No other domains were recommended for inclusion into the core set for clinical trials by any stakeholder group (Table 2).

There was panel consensus that assessment of eczema symptoms should be in the core set of outcomes for recordkeeping. No consensus was reached concerning assessment of the following domains in clinical practice: clinical signs, global disease severity, consequences of itching, and measurement for long-term control of flares (Table 3).

DISCUSSION

Statement of principal findings

Using structured consensus methods and taking into account the perspectives of consumers, clinical experts, journal editors, and regulatory agencies, this study recommends assessing symptoms, clinical signs, and long-term control of flares in eczema trials, and regularly monitoring symptoms in

Table 2. Core set of outcomes for clinical trials to measure the efficacy of interventions for eczema, as determined by Delphi consensus panel involving consumers, clinical experts, regulatory agencies, and journal editors

	Proportion recommending inclusion of outcome domain into the core set of outcomes for eczema that should be routinely assessed in every clinical trial on eczema				Consensus criteria[1] met to include outcome in core set for clinical trials		
Outcome domain	**Consumers (*n*=6)**	**Experts (*n*=29)**	**Regulatory agencies (*n*=1)**	**Journal editors (*n*=7)**	**To be included into core set**	**No consensus**	**Not to be included into core set**
Clinical signs assessed by physician using a score	6/6 (100%)	29/29 (100%)	1/1 (100%)	7/7 (100%)	●		
Clinical signs assessed by patient using a score	1/6 (17%)	6/29 (21%)	0/1 (0%)	0/7 (0%)			●
Investigator global assessment of disease severity based on clinical signs	2/6 (33%)	17/29 (59%)	0/1 (0%)	4/7 (57%)			●
Patient global assessment of disease severity based on clinical signs	1/6 (17%)	10/29 (34%)	0/1 (0%)	2/7 (29%)			●
Symptoms	5/6 (83%)	22/29 (76%)	0/1 (0%)	4/7 (57%)	●		
Quality of life (dermatology specific)	2/6 (33%)	21/29 (72%)	1/1 (100%)	6/7 (86%)		●	
Quality of life (in general)	1/6 (17%)	1/29 (3%)	0/1 (0%)	0/7 (0%)			●
Short-term control of flares	2/6 (33%)	2/29 (7%)	0/1 (0%)	0/7 (0%)			●
Long-term control of flares	4/6 (67%)	18/29 (62%)	1/1 (100%)	3/7 (43%)	●		
Cost	1/6 (17%)	1/29 (3%)	0/1 (0%)	0/7 (0%)			●
Overall extent of disease	1/6 (17%)	6/29 (21%)	0/1 (0%)	1/7 (14%)			●
Involvement of high expression areas	1/6 (17%)	2/29 (7%)	0/1 (0%)	1/7 (14%)			●
Treatment utilization	1/6 (17%)	9/29 (31%)	0/1 (0%)	1/7 (14%)			●

[1]*Consensus criteria to include outcome domain in core set*: at least 60% of all members of at least three stakeholder groups including consumers recommended including a domain in the core set of outcomes. *Consensus criteria not to include outcome domain in core set*: <60% of all members of at least three stakeholder groups including consumers recommended including a domain in the core set of outcomes.

daily clinical care of patients with eczema. The core outcome domains were identified with a high degree of consensus among the different stakeholder groups and, therefore, have the potential to establish an international standard. The core sets identified are meant to define the minimum set of domains to be assessed. Other variables needed to answer specific research questions can be added to the core set variables in a particular study.

Our study extends a previous research on eczema, as it not only defines a core set of outcomes but also considered different contexts in the field of eczema outcomes research, that is, clinical trials and recordkeeping in clinical practice. Use of different assessments for disease severity/treatment response in randomized controlled trials and clinical practice will result in problems of translating external evidence to individual patients; hence, it is reassuring that our study has identified disease symptoms as a core domain for both clinical trials and daily practice.

Strengths and weaknesses of the study

The Delphi process is a useful consensus method to define core sets of outcome domains, as it aims to maximize the benefits from expert panels while minimizing some of the disadvantages associated with collective decision making, for example, domination by individual interests (Pill, 1971; Jones and Hunter, 1995). We aimed to select panel members without an interest in a specific outcome measurement. To minimize the domination of one or two domains, we also excluded researchers with strong ties to the pharmaceutical industry that had developed and used the same outcome measures.

During this Delphi consensus project, the issue of medical outcome research has gained momentum. One group that aims to collate relevant resources on defining core sets of outcomes for different conditions is the COMET (Core Outcome MEasures in Trials) initiative (Williamson *et al.*, 2010). In a systematic review determining which outcomes should be included in clinical trials in children, members of the COMET initiative concluded that only very few studies involved parents or children in selecting outcomes that should be measured, and none directly involved children (Sinha *et al.*, 2008). Our Delphi consensus study is therefore unique, in that we included six individuals from eczema self-help groups from four different continents and we directly

Table 3. Core set of outcome domains to monitor patients with eczema in the context of clinical recordkeeping, as determined by Delphi consensus panel

	Proportion recommending inclusion of outcome domain into the core set of outcomes for eczema that should be routinely assessed in daily practice, that is, to be used at every physician visit				Consensus[1] regarding the inclusion of domain in core set for clinical recordkeeping		
Outcome domain	**Consumers (*n*=6)**	**Experts (*n*=29)**	**Regulatory agency (*n*=1)**	**Journal editors (*n*=7)**	**To be included into core set**	**No consensus**	**Not to be included into core set**
Clinical signs assessed by physician using a score	5/6 (83%)	10/29 (34%)	0/1 (0%)	3/7 (43%)		●	
Clinical signs assessed by patient using a score	2/6 (33%)	4/29 (14%)	0/1 (0%)	0/7 (0%)			●
Investigator global assessment of disease severity based on clinical signs	1/6 (17%)	19/29 (66%)	1/1 (100%)	5/7 (71%)		●	
Patient global assessment of disease severity based on clinical signs	3/6 (50%)	8/29 (28%)	0/1 (0%)	3/7 (43%)		●	
Symptoms	6/6 (100%)	24/29 (83%)	0/1 (0%)	6/7 (86%)	●		
Consequences of itching	4/6 (67%)	5/29 (17%)	0/1 (0%)	0/7 (0%)		●	
Quality of life (dermatology specific)	1/6 (17%)	3/29 (10%)	0/1 (0%)	0/7 (0%)			●
Quality of life (in general)	0/6 (0%)	2/29 (7%)	0/1 (0%)	0/7 (0%)			●
Short-term control of flares	2/6 (33%)	4/29 (14%)	1/1 (100%)	0/7 (0%)			●
Long-term control of flares	4/6 (67%)	12/29 (41%)	1/1 (100%)	2/7 (29%)		●	
Compliance	2/6 (33%)	9/29 (31%)	0/1 (0%)	0/7 (0%)			●
Work/school limitations	1/6 (17%)	4/29 (14%)	0/1 (0%)	0/7 (0%)			●
Overall extent of disease	1/6 (17%)	6/29 (21%)	0/1 (0%)	2/7 (29%)			●
Involvement of high expression areas	1/6 (17%)	5/29 (17%)	0/1 (0%)	1/7 (14%)			●
Treatment utilization	0/6 (0%)	10/29 (34%)	1/1 (100%)	1/7 (14%)			●

[1]*Consensus criteria to include outcome domain in core set*: at least 60% of all members of at least three stakeholder groups including consumers recommended including a domain in the core set of outcomes. *Consensus criteria not to include outcome domain in core set*: <60% of all members of at least three stakeholder groups including consumers recommended including a domain in the core set of outcomes.

included children and adolescents in the assessment of content validity of the outcome domains included in existing outcome measurements.

Another strength of this study is the high response rate and the high proportion of participants who completed all three rounds of the Delphi exercise. Other studies have found that investigators who are willing to participate in consensus panels are generally representative of their colleagues (McKee *et al.*, 1991). It is possible that the predominance of academic experts in our study could limit generalizability to non-academic settings. Another important caveat is that the consensus achieved by this study does not mean that the core set of outcomes is necessarily correct or even ideal. We would like to emphasize that the consensus achieved has to be considered as preliminary. Future research may lead to a refinement of the core set identified in this paper (Pill, 1971; Jones and Hunter, 1995; Alahlafi and Burge, 2005; Taylor, 2005).

Meaning of the study: possible explanations and implications for clinicians, researchers, and policymakers

An efficient system of research should use outcomes considered important by patients and clinicians. We encourage clinicians to record symptoms for clinical recordkeeping and researchers to record symptoms, signs, and long-term course in clinical trials in order to facilitate meta-analyses

performed within systematic review such as those developed by the Cochrane Collaboration. The core set of domains identified in this study provides a good starting point to recommend which of the 20 or so published outcome measures for eczema should be used in terms of matching the domains closely, as well as completeness and performance according to psychometric properties. As defined by Boers *et al.* (1998) outcome measures should adequately meet the criteria of truth (that is, validity; measure what they intend to measure), discrimination (that is, reliability and sensitivity to change; discriminate between situations), and feasibility (that is, be applied and interpreted easily) in order to be recommended.

According to our systematic review (Schmitt *et al.*, 2007), the Severity Scoring of Atopic Dermatitis index (SCORAD, 1993) and the Eczema Area and Severity Index (Tofte *et al.*, 1998) were identified as valid and reliable instruments to measure clinical signs of eczema. The Patient-Oriented Eczema Measure (Charman *et al.*, 2004) has adequate psychometric properties to be recommended to measure eczema symptoms. The standardized use of the defined core set of outcomes will simplify the design of new trials and eventually help to reduce the risk of bias from selective reporting of outcomes (Kirkham *et al.*, 2010).

Unanswered questions for future research

As exemplified by the OMERACT initiative for joint diseases (Tugwell *et al.*, 2007), future research and international consensus informed by evidence is now needed to identify which valid and reliable measure should be adopted for each domain identified as relevant for the core eczema set. This Delphi exercise also revealed areas of disagreement between stakeholder groups, indicating opportunities for further research. Interestingly, consumers were the only stakeholder group that did not recommend including a measurement of health-related quality of life into the core set of outcomes for clinical trials. Qualitative research is necessary to better understand why patients with eczema, at least those participating in this panel, are less interested in the concept of quality of life, as assumed by clinicians, journal editors, and regulatory agencies.

Our previous systematic review failed to identify validated measures for capturing long-term control of eczema (Schmitt *et al.*, 2007). Some workers have suggested measuring the number of well-controlled weeks analogous to asthma studies (Langan *et al.*, 2006). Long-term control of eczema is clearly an important future research priority.

MATERIALS AND METHODS

Study type

We conducted a three-stage, web-based international Delphi consensus exercise between June 2008 and March 2010. The Delphi process is a consensus method that takes its name from the Delphic oracle's skills of foresight and interpretation. The Delphi method uses a structured iterative process: after a first assessment of the problem/question of interest, each participant receives standardized feedback on his own previous response relative to the group's previous response and is allowed to modify his assessment in subsequent rounds of the Delphi exercise (Jones and Hunter, 1995; Hasson *et al.*, 2000).

Participants

To allow multiprofessional collaboration and to include the views of different stakeholder groups, we invited a total of 57 consumers, clinical experts, representatives of regulatory agencies, and journal editors representing 13 countries to participate in the Delphi consensus study. Consumer representatives included six individuals from different eczema self-help groups including Australia, Brazil, Germany, the United Kingdom, and the United States. Clinical experts ($n = 41$) were selected on the basis of a major interest in eczema, and included members of the organization committee and/or scientific advisory board of the 5th International Society for Atopic Dermatitis conference, Kyoto 2008; members of the scientific committee for the International Dermato-Epidemiology Association congress in Nottingham, 2008; and other individual clinical experts nominated by the senior author (HW). Individuals who were involved in the development of any named outcome measurement for eczema and clinical experts strongly affiliated with pharmaceutical industry were not included. Journal editors included the editors in chief (or a designated co-editor) of four European and four US journals with a broad readership and a high interest in eczema, as shown in the in the panel membership list; one employee of the US Food and Drug Administration and one representative from the European Medicines Agency with expertise in eczema were asked to participate.

Study procedures

To provide an evidence base for the consensus, we systematically collected, summarized, and critically appraised all named eczema

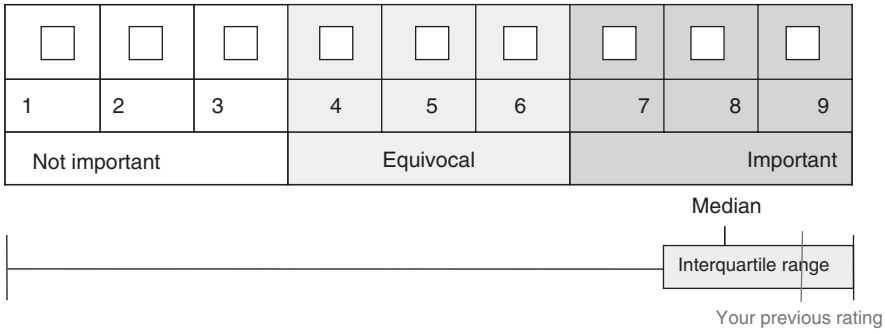

Figure 3. Example of second round question. How important do you consider the assessment of clinical signs of atopic eczema (for example, erythema, infiltration, scaling), when assessed by a physician?

outcome scales in the run-up to the Delphi project (Schmitt *et al.*, 2007). This review identified 20 named outcome measurements for eczema that covered the domains of clinical signs, disease extent, symptoms, involvement of visible areas such as the face, course of disease, global disease severity, and epidermal function. Assessment of content validity by 12 consumers (four patients with eczema, aged ⩾18 years; four affected children/adolescents, aged 8–14 years; four caregivers of affected children aged 1–7 years) and six dermatology experts who were not involved in scale development indicated that all of these domains except epidermal function are important from the patients' and clinical experts' perspectives (Schmitt *et al.*, 2007). Additional domains considered as potentially relevant for the core set were general and dermatology-specific quality of life, control of disease flares, health utilities, work/school limitations, consequences of pruritus, cost effectiveness, direct/indirect cost, and compliance.

The study protocol was finalized in April 2008, and nominated panel members were contacted through email and invited to participate in June 2008. Background information, study aims, explanations on how to participate, and a questionnaire asking them to rate the importance of 16 outcome domains for eczema on a nine-point Likert scale in the context of (a) clinical trials and (b) recordkeeping in daily practice were sent to each nominated panel member.

It was specified that scores of 1–3 represent a region where participants believe the domain is not important; 4–6 a region of equivocal value; and 7–9 a region where they feel the domain is important (Jones and Hunter, 1995). In the first round of the Delphi exercise, participants were asked to list additional outcome domains they considered as potentially relevant. Additionally, they were asked in the first round to indicate how many domains should be included in the final core set of outcome domains for each context. In subsequent rounds, participants received feedback on their own response along with the group opinion for each domain (median and interquartile range, calculated using Stata 10, Stata, College Station, TX) from the previous round. (Figure 3) Respondents could submit new scores or leave their scores unchanged. Three rounds were conducted by electronic mail or facsimile.

In the final round, instead of ranking the importance of the individual domains on a Likert scale, participants were asked explicitly which domains they recommend incorporating into the core set. It was specified that outcomes included in the core set for eczema trials ''*should be assessed routinely in every clinical trial, but not necessarily as a primary outcome*'' and that those outcomes included into the core set for clinical recordkeeping ''*should be assessed routinely at every patient visit in routine practice*''.

Definition of consensus

A priori consensus was defined as being achieved if at least 60% of all members of at least three stakeholder groups including consumers recommended including a domain in the core set of outcomes. Consensus that an outcome is important for eczema was defined as a score of 7 or more (as described above, a score of 7–9 indicated that the participating experts felt that a certain domain was important to include) by at least 60% of all members of at least three stakeholder groups including consumers (Loughlin and Moore, 1979; Hasson *et al.*, 2000).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Author contributions: All authors planned the study. Statistical analysis was conducted by JS. All authors discussed and interpreted the results. JS drafted the manuscript. All authors contributed to the final manuscript. All the Delphi panel members had an opportunity to read, review, and approve the final paper.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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