



# What Factors are Important to Patients when Assessing Treatment Response: An International Cross-sectional Survey

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**This study investigated the perspective of international patients on individual symptoms of atopic dermatitis (eczema) in determining treatment response. A questionnaire was developed to evaluate the importance of symptoms from the patient's perspective. Patients were asked: "How important are these features in deciding whether or not a treatment is working?", and rated symptoms on a 5-point Likert scale. Patients were approached via Harmonising Outcome Measures for Eczema (HOME) collaborators and self-selected to take part in the on-line survey. Patients from 34 countries (n = 1,111) completed the survey; of these, 423 (38.3%) were parents of children with eczema. Ten items were rated as being "quite important" or "very important" by more than 80% of the respondents: itch, pain/soreness, skin feels hot or inflamed, bleeding, involvement of visible or sensitive body sites, cracks, sleep difficulties, amount of body affected, and weeping/oozing. These results may be of use in determining the face validity of scales from a cross-cultural patients' perspective.**

*Key words:* eczema; dermatitis, atopic; outcome assessment.

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Atopic dermatitis (AD) is a common disease in both childhood and adulthood; affecting 15–20% of preschool children (1, 2) and approximately 5% of adults (3–5). AD has a high impact on the wellbeing of patients, their families and society (6, 7). It is a chronic disease that comes and goes (7), and a large number of different treatments and interventions are available (3–10).

In order to compare the results of different clinical studies, standardized outcome measures are required (11), and it is important that the measures include items that are relevant to patients.

The international, multi-disciplinary Harmonizing Outcome Measures for Eczema (HOME) initiative aims to standardize outcome measurements for AD within 4 different domains (11–13): (i) clinical signs measured

with a physician-assessed instrument; (ii) symptoms measured with a patient-assessed instrument; (iii) health-related quality of life; and (iv) long-term control.

Although itch is the most commonly reported symptom of AD, little is known about the relative importance of other symptoms from the patients' perspective (14–16). International studies on the importance of symptoms are lacking, although this information is required for assessment of face validity of symptom measures.

The aim of this study was to establish an international perspective on which symptoms were most important to patients in determining response to AD treatments.

## METHODS

### *Study design*

This was an international, cross-sectional survey involving patients with AD, or parents of children with AD in 34 countries.

### *Questionnaire development*

A list of symptoms of AD was identified from previous studies of symptoms of importance to patients (14–16) and items used in existing scales.

A draft questionnaire was developed, evaluating the importance of these symptoms from the patient's perspective in relation to "response to treatment" for AD. The questionnaire was sent to all HOME collaborators, modified and finalized by consensus discussion of the participating HOME collaborators in the UK, the Netherlands, Sweden, France, Italy, Spain, Germany, Japan, China, Taiwan, Tanzania, Australia and the USA. The collaborators were clinicians (n = 14), methodologists (n = 5) and patients with AD (n = 2). For symptoms with more than one descriptor, the most appropriate wording was chosen through consensus amongst the collaborators. All collaborators could make suggestions, as did the authors; consensus was defined as all collaborators agreed or did not actively disagree. The final questionnaire included 18 items: itch, tightness of the skin, skin feels hot or inflamed, soreness or pain, sleep difficulties, scratch marks on the skin, weeping/oozing, bleeding, blisters, amount of body affected by eczema, thickening of the skin (feels like leather), crusts covering eczema lesions, dry flaky skin, swelling, cracks in the skin, redness of the skin (or darkening of coloured skin), involvement of sensitive body sites (e.g. the face), and involvement of visible body sites (e.g. the hands and face).

Patients were asked "How important are these features in deciding whether or not a treatment is working?" Response items were rated by importance on a 5-point Likert scale, ranging from "very important" to "not relevant to me".

Demographic information was recorded regarding the age and sex of the person with AD, whether the questionnaire was completed by the patient or the parent of a child with AD, age at onset of AD, and patient global assessment of severity (How severe has your/your child's eczema been during the last week? No eczema, mild eczema, moderate eczema, severe eczema). In order to inform future decisions on the frequency of data collection when assessing long-term control, participants were also asked "How often do you think this information should be recorded in order to capture how well controlled the eczema is? and "... in a research study lasting more than 6 months, how often would you be willing to complete it (a research diary)?" with "daily", "weekly", "monthly", or "every few months" as possible answers (see Appendix S1<sup>1</sup>).

#### Translation of questionnaire

The questionnaire was translated from English into Swedish, German and Portuguese and then back-translated according to a standardized protocol (17). Two bilingual translators translated the questionnaire independently. The 2 translators and, if needed, an observer (LK) synthesized the translation. The questionnaire was then back-translated into English by 2 other bilingual translators. The content of the questionnaire in the translated language and the original English questionnaire were compared and discrepancies were resolved. The translated questionnaire was then tested in a small group of Swedish, German and Portuguese patients for comprehensibility, with special attention to whether or not items had been interpreted correctly.

The finalized online questionnaire was checked by the translation team to confirm that the text and its placing were correct. The countries with mother-tongue other than English who did not translate the questionnaire used the English version.

The final questionnaires were created online using Survey Monkey software (18).

#### Participants and data collection

All centres asked adult patients age 16 years and older and/or parents of children with AD to complete the survey. Patients and parents of children with AD were identified via social media or from existing mailing lists of patients interested in eczema research in the UK, patient groups in the USA and Sweden, and clinics in all countries apart from Sweden; and informed via collaborators of the HOME initiative. Patients were self-selected, and completion of the survey was assumed to indicate consent to use the data.

Links to the online survey were sent by e-mail and tweet to patients if contact details were available; otherwise the survey was accessed through a web-link. Paper questionnaires were provided on request.

#### Analyses

It was decided *a priori* that an item would only be considered important for inclusion in a core outcome measurement instrument of symptoms if at least 80% of the responders rated the item as either "quite important" or "very important". The list of items was then ranked according to the % of respondents who assessed the item as "very important" or "quite important". Differences between children (0–15 years) and adults (16 years or older), across sex, continent/region of residence, skin colour, participants answering in mother tongue and language other than mother tongue regarding the importance of symptoms were assessed using a  $\chi^2$  test with a significance level of  $p=0.05$ . Patients completing

questionnaires not containing data on the main question were excluded from the analysis.

#### Sample size

Sample size was not defined in advance; however, we aimed to include patients with different skin phototypes. Purposive sampling was used to include sufficient numbers of participants with both lighter and darker skin types and different ethnic groups.

## RESULTS

#### Questionnaire completion

Data collection took place from March 2013 to November 2014. A total of 34 different countries took part, from 7 regions of the world (Table S1<sup>1</sup>). Most participants completed the survey in <5 min (958/1062, 90.2%).

In total, 1,111 questionnaires were completed; 1,104 questionnaires contained complete data regarding the main questions from the following parts of the world: Europe ( $n=801$ ), Africa ( $n=21$ ), Middle East ( $n=15$ ), Asia ( $n=21$ ), Australia ( $n=9$ ), South America ( $n=67$ ), and North America ( $n=170$ ) (Table S1<sup>1</sup>). However, not all participants answered all the remaining questions.

A total of 692 (65.5%) responses were from females (Table I). Just over half of respondents were adult patients aged 16 years or older (668, 58.4%) and 423 (38.3%) were parents of children with eczema. Skin colour ranged from light 693 (65.3%), slightly coloured 265 (24.7%), dark 96 (8.7%), to very dark 27 (1.4%).

**Table I. Description of 1,104 patients with atopic dermatitis (AD) who participated in the Harmonising Outcome Measures for Eczema (HOME) survey in 2013 to 2014 and had complete data on the main questions**

Variable	Total <i>n</i> (%)	≥ 16 years <i>n</i> (%)	Children <sup>a</sup> <i>n</i> (%)
Sex			
Female	692 (65.5)	499 (75.15)	193 (49.23)
Male	364 (34.5)	165 (24.85)	199 (50.77)
Age category			
< 5 years	187 (17.6)		
6–15 years	207 (19.5)		
16–25 years	189 (17.8)		
26–45 years	265 (25.0)		
46–65 years	163 (15.4)		
> 66 years	51 (4.8)		
Skin colour			
Light	693 (65.3)	402 (60.27)	288 (73.47)
Slightly coloured	265 (24.7)	192 (24.74)	70 (17.86)
Dark	96 (8.7)	65 (8.69)	27 (6.89)
Very dark	27 (1.4)	8 (1.42)	7 (1.79)
Severity of AD			
No AD at the moment	52 (4.9)	32 (4.81)	20 (5.09)
Mild AD	296 (28.0)	182 (27.37)	114 (29.01)
Moderate AD	410 (38.8)	264 (39.70)	146 (37.15)
Severe AD	300 (28.4)	187 (28.12)	113 (28.75)
Onset of AD			
0–2 years	726 (68.3)	368 (55.76)	358 (90.86)
3–6 years	121 (11.4)	87 (13.18)	31 (7.87)
7–15 years	71 (6.7)	65 (9.85)	4 (1.02)
> 16 years	145 (13.6)	140 (21.21)	1 (0.25)

<sup>a</sup>Parents answered the HOME survey on behalf of their child. Although the participants answered the main question regarding the importance of items, some participants did not answer all subquestions.

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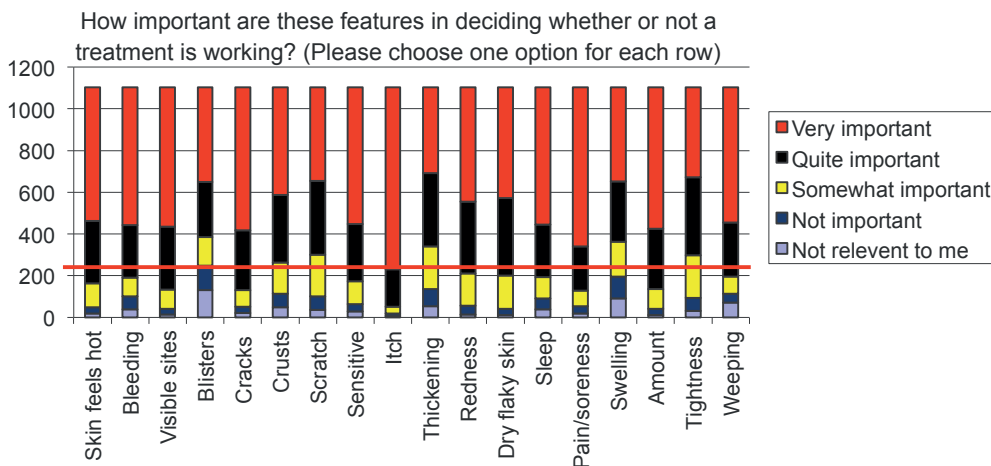


Fig. 1. Content validity of items assessing severity of atopic dermatitis (AD) from the international patients' perspective.

Severity of patient-reported AD ranged from “no AD at the moment” 52 (4.9%) to “severe AD” 300 (28.4%). Most patients (726; 68.3%) developed eczema in the age range 0–2 years; 121 (11.4%) in the age range 3–6 years, 71 (6.7%) in the age range 7–15 years, and 145 (13.6%) at age 16+ years. Detail of these variables split by children (<16 years of age) and adults aged (16 or over) can be found in Table I.

Main results

Ten items were identified as being “quite important” or “very important” by 80% or more of participants; itch, pain/soreness, skin feels hot or inflamed, bleeding, involvement of visible or sensitive body sites, redness, cracks in the skin, sleep difficulties, amount of body affected, and weeping/oozing (Fig. 1 and Table SII<sup>1</sup>). Of these, itch and pain/soreness were the most important items to patients when judging treatment response. These items were assessed as being quite important or very important by 1,053 (95.4%) and 976 (88.4%) participants, respectively.

There were some differences in the responses between adult patients and parents of children with eczema (Fig. S1<sup>1</sup> and Table SIII<sup>1</sup>). Significantly more parents of children with eczema rated bleeding, scratch marks, itch, sleeping difficulties and soreness/pain than did adult patients. Conversely, more adult patients reported dry flaky skin as being important compared with parents of children with AD. Significantly more adult women regarded

eczema at visible body sites as being important than did adult men (90.2% versus 85.5% respectively,  $p < 0.001$ , Table II), but otherwise the results did not differ by sex. Skin colour or severity of AD had no significant effect on the findings.

Differences between geographical regions

Significantly fewer people living in central Asia, Africa and South America ( $n=42$ , 37.8%) regarded pain/soreness as being important or highly important compared with people living in Europe, Australia, US and Canada and the Middle East ( $n=910$ , 91.6%;  $p < 0.001$ ). Bleeding was not considered so important by respondents in central Asia, and Central America ( $n=44$  (50.6%);  $p < 0.001$ ), and sleep difficulties were not so important in South America ( $n=44$  (66.6%);  $p < 0.001$ ).

Other results

When asked about frequency of data collection in order to capture how well controlled eczema is, 602 (54.3%) patients responded that daily information is needed to reflect the disease. A total of 553 (48.0%) respondents reported that they would be willing to complete a daily eczema diary. Sub-analyses comparing the importance of items between people answering the survey in their mother tongue and using an English version with a mother-tongue other than English did not find any significant differences between the 2 groups (e.g. for itch  $p=0.115$ ).

Table II. Importance of symptoms by sex

Eczema at visible body sites	Quite important and very important		Somewhat important, not important or not relevant		$\chi^2$ test $p$ -value
	Female $n$ (%)	Male $n$ (%)	Female $n$ (%)	Male $n$ (%)	
Total	615 (88.9)	313 (86.0)	77 (11.1)	51 (14.0)	0.006
≥ 16 years	450 (90.18)	141 (85.5)	49 (9.8)	24 (12.5)	< 0.001
Children	165 (85.49)	172 (86.4)	28 (14.5)	27 (13.6)	0.529

DISCUSSION

Main findings

This is the first international study of patients' assessment of the relative importance of different symptoms when assessing response to treatment in AD and, to our knowledge, the first providing results both for children and adults. This was a very large survey, including

participants from all over the world. Having a broad, international perspective is important when evaluating the content validity of potential measurement instruments for inclusion in international core outcome sets.

Itch and pain/soreness were consistently identified as being the most important items for assessing whether a treatment is working. However, pain/soreness is not commonly recorded in eczema clinical trials. In addition to itch and pain/soreness, several other items were found to be important to patients, and further work is required to establish which, if any, of the 9 items are independently associated with disease burden and treatment response.

Overall, the findings were similar across sub-groups of patients (age, sex, skin colour) suggesting good external validity. Parents of children regarded bleeding, itch, and sleep difficulties as being more important than did adult patients; possibly because itch and sleep difficulties in a child can affect the quality of life of all family members (6, 7), and parents may worry about visible symptoms, such as bleeding in the child. Adult patients regarded dry flaky skin as more important than did parents of children with eczema; possibly because dry skin is more common in older patients and might therefore be more relevant to this age group (19).

Certain symptoms, such as pain/soreness, were considered more important in some regions of the world, but these differences were not explained by skin colour. Possible reasons for these differences could be climate or lifestyle (20), but further research is required to establish the reasons.

The results of the current study are in line with the results of studies of content validity performed in the UK and Germany (14–16), which found that patients assessed symptoms, intensity of lesions and extent of disease, course of disease, cracking/fissuring, vesicles, bleeding, and erosions as important. The UK study used to inform development of the Patient Oriented Eczema Measure (POEM) (15), identified pain/soreness and redness as being important to patients, but these items were not included in the POEM scale due to concern that pain/soreness would be difficult to assess in young children, and because redness can be difficult to assess in dark skin.

### *Strengths and weaknesses*

The main strength of this study was that it represented a collaborative effort across 34 countries and recruited more than 1,000 participants of varied eczema severities, skin types, ethnic groups and ages. As a result, the external validity of our findings is high. Standardized techniques were used to translate the questionnaires and back translation ensured that the intended meaning was not altered through the translation process.

The cut-off used to judge whether items were important based on 80% of participants feeling that an item was “very important” or “important”, is consistent with

the literature and was defined *a priori*. However, it is possible that such an approach failed to identify symptoms that were generally less important, but nevertheless frequently occurring.

It was not possible to provide the questionnaire in a variety of languages; and it was reassuring that sensitivity analysis did not show differences in results for those answering in mother tongue and those answering in English with a mother tongue other than English. The participating countries contributed with different numbers. Whilst high numbers of participants were obtained from Europe and America, notably Brazil, UK, Sweden and the USA, the response rates for other regions, such as Africa and Asia, were much lower, making it unclear whether the observed differences in symptoms of importance was a result of chance, or whether they represented real differences in how patients experience AD.

### *Implications*

Currently, investigators can select from numerous different measurement instruments of disease severity. The Eczema Area and Severity Index (EASI), and SCORing Atopic Dermatitis (SCORAD) scales have been validated as suitable outcome instruments for the assessment of clinician-rated signs; and the HOME initiative recommended the application of at least EASI as scale for the domain clinical signs (21). However, few patient-reported outcome scales exist. The POEM (14, 15) remains the only patient-reported severity scale that has been adequately validated (16) and all 7 items included in the POEM scale are items found to be of importance to patients in the current study.

The results of this study can be useful in determining the face validity of outcome measurement instruments used to assess the core outcome domains of symptoms from a cross-cultural patients' perspective.

In the HOME initiative this information has been used to inform consensus discussions over the best outcome measurement instrument to use for the domain of symptoms (22).

### *Future research*

This study has identified several aspects of AD that are important to patients when judging treatment response. Further research is needed to establish how these items are correlated, and which items are likely to represent the minimum set for establishing the face validity of patient-reported outcomes in AD.

No patient-reported outcome instruments currently include pain or soreness, and the importance of this item (and the ability to record it accurately in all age groups) requires further investigation. Similarly, this study did not distinguish between the “intensity” of an AD symptom and the “frequency” with which it occurs, and so it remains unclear how best to measure individual symptoms.

## Conclusion

We identified symptoms that are relevant to patients for assessing whether a treatment is working.

Itch and pain/soreness are the most important items for assessing whether a treatment is working, skin feels hot or inflamed, bleeding, involvement of visible or sensitive body sites, cracks, sleep difficulties, amount of body affected and weeping/oozing were also important. These items should be included in scales measuring treatment outcome.

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