POEM a core instrument to measure symptoms in clinical trials: a HOME statement

Ph.I. Spuls, MD, PhD,[1] L.A.A. Gerbens, MD,[1] E. Simpson, MD,[2] C.J. Apfelbacher, PhD,[3] J.R. Chalmers, PhD,[4] K.S. Thomas, PhD,[4] C.A.C. Prinsen, PhD,[5] L.B. von Kobyletzki, MD, PhD,[6] J.A. Singh, MD, MPH,[7] H.C. Williams, FRCP, DSc,[4] and J. Schmitt, MD, MPH,[8] on behalf of the HOME initiative collaborators*

[1] Department of Dermatology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
[2] Department of Dermatology, Oregon Health & Sciences University, Portland, Oregon, USA
[3] Medical Sociology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany
[4] Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[5] Department of Epidemiology and Biostatistics, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands
[6] Institution for Clinical Science, Dep. of Dermatology, Lund University, Malmö, Sweden
[7] Department of Rheumatology and Division of Epidemiology, University of Alabama Birmingham, & and Veterans Affairs Medical Center, Birmingham, Alabama, USA; & Mayo Clinic College of Medicine, Rochester, Minnesota, USA
[8] Centre for Evidence-based Healthcare, University Hospital Carl Gustav Carus, TU Dresden, Germany
*Participants Malmo meeting

Correspondence:
Phyllis I. Spuls
Department of Dermatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
Tel.: +31 20 5664763
Fax: +31 20 5669152
E-mail: ph.i.spuls@amc.uva.nl

Funding sources: For the consensus meeting funding was received from the Swedish asthma and allergy association, LEO foundation, and region of Skåne (county), Sweden.

Conflict of interest: Hywel Williams was involved with the development and validation of the POEM. Christian Apfelbacher, Eric Simpson, Phyllis Spuls, Kim Thomas, Jochen Schmitt, and Hywel Williams are members of the executive committee of the HOME initiative. All other authors, except Jasvinder Singh, are members of the HOME initiative. Jasvinder Singh is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies. The authors state there are no other conflicts of interest for this study.

Word count text: 1827

Word count abstract: 174

Manuscript table count: 2

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

- There is insufficient high quality evidence for many of the treatments of atopic eczema (AE), which is partly due to the heterogeneity in outcomes used in clinical trials.
- The Harmonising Outcome Measures for Eczema (HOME) initiative defined "symptoms" as one of the core outcome domains that should be measured in AE clinical trials.

WHAT DOES THIS STUDY ADD?

- Consensus was reached on the Patient-Oriented Eczema Measure (POEM) as the core instrument to measure symptoms.
- This statement should promote awareness amongst all stakeholders.

SUMMARY

Background: The Harmonising Outcome Measures for Eczema (HOME) initiative has defined four core outcome domains for a core outcome set (COS) to be measured in all atopic eczema (AE) trials to ensure cross-trial comparison: clinical signs, symptoms, quality of life and long-term control.

Objectives: The aim of this paper is to report on the consensus process that was used to select the core instrument to consistently assess symptoms in all future AE trials.

Methods: Following the HOME roadmap, two systematic reviews were performed which identified three instruments that had sufficient evidence of validity, reliability, and feasibility to be considered for the final COS.

Results: At the 4th international HOME meeting there was broad consensus among all stakeholders that the Patient-Oriented Eczema Measure (POEM) should be used as the core instrument (87.5% agreed, 9.4% unsure, 3.1% disagreed).

Conclusions: All relevant stakeholders are encouraged to use POEM as the chosen instrument to measure the core domain of symptoms in all future AE clinical trials. Other instruments of interest can be used in addition to POEM.

INTRODUCTION

There is insufficient high quality evidence for many of the treatments of atopic eczema (AE) (synonym atopic dermatitis), which is partly due to the high clinical and methodological heterogeneity in AE studies[1]. Results cannot be compared and pooled properly in systematic reviews (SRs) due to heterogeneity in outcomes used, hampering evidence-based clinical decision making. The international Harmonising Outcome Measures for Eczema (HOME) initiative, founded in 2010, standardizes outcome measurement in AE clinical trials by developing a core outcome set (COS) for AE clinical trials.[2-5] A COS is defined as an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials of a specific disease or trial population.[6] The use of a COS does not preclude the use of additional outcome measurement instruments (further referred to as 'instruments') of interest for a particular trial nor does a COS specify which instrument should be used as a primary outcome.

To guide the development of a COS, HOME has developed a roadmap,[7] which includes the Outcome Measures in Rheumatology (OMERACT) filter of Truth, Discrimination, and Feasibility in order to recommend core instruments [8] and the methodology of the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist (cosmin.nl). It was agreed within HOME that there should be an instrument per domain, rather than a composite instrument covering more than one domain.

Previously, HOME defined physician-assessed clinical signs, patient-reported symptoms, health-related quality of life, and long-term control as core outcome domains for AE clinical trials (HOME II meeting Amsterdam 2011).[4] During the HOME III meeting (San Diego, 2013), consensus was reached that the Eczema Area and Severity Index (EASI) should be used as the core instrument to measure clinical signs.[5, 9, 10]

The objective of the current consensus study (HOME IV, Malmö, April 2015) was to establish an agreement statement on the core instrument to measure the domain of patient-reported symptoms in AE clinical trials.

HOME ROADMAP STEPS AND RESULTS OF THE HOME IV MEETING

To identify and recommend an adequate instrument to measure symptoms of AE in clinical trials, a pre-defined process was followed as detailed in the HOME roadmap.[7]

To adequately assess symptoms of AE, the following definition of AE symptoms was employed[11]: "a departure from normal function, appearance or feeling which is noticed by a patient, indicating the presence of disease or abnormality". A symptom is subjective and can only be measured by patients themselves.

Stage 1: Identify instruments used to measure symptoms in AE treatment trials

A systematic review of all AE trials published since 2000 showed that most (78%, 295/378) randomised controlled trials (RCTs) of AE treatments reported symptoms of AE with itch and sleep-loss the most frequently measured.[12] However, symptoms were assessed by only 37% of RCTs by a stand-alone symptom measurement (visual analogue scale or numeric rating scale). Sixty-three percent reported symptoms as part of a composite measure (such as the SCORing Atopic Dermatitis (SCORAD) index, a composite instrument of clinician-rated signs and patient-reported symptoms) rather than a stand-alone outcome. A total of 30 composite instruments that included symptoms were identified, of which SCORAD was the most commonly used. Only 23% of RCTs reported the SCORAD symptom score separately.

Stage 2: Establish the extent and quality of testing of the identified instruments

A subsequent systematic review of published validation studies of instruments to measure symptoms of AE was performed according to COSMIN methodology.[13] This review provided evidence of how well the instruments performed for measuring the symptoms of AE and the methodological quality of the validation studies. The methods and detailed results of this SR are published separately.[14, 15]

Preliminary results included 26 eligible papers evaluating 15 different instruments for assessing symptoms of AE with varying degrees of validation (Table 1).

Only three instruments had the potential to be recommended for the COS based on validation studies: the Itch Severity Scale (ISS), Patient-Oriented Eczema Measure (POEM) and Self-Administered EASI (SA-EASI). The most extensively validated instrument was the POEM with adequate internal consistency,[16] construct validity,[16, 17] responsiveness[16-18] and content validity.[16] Performance of test-retest reliability[16] and measurement error[16, 18] remain unknown due to poor methodological study quality or limited evidence. Interpretation was assessed and demonstrated a minimal clinically important difference (MCID) of 3.4 points,[18] five bands of severity (i.e. clear, mild, moderate, severe, very severe),[19] and a mean absolute change in score from baseline of 7.9 (standard deviation (SD) 6.0).[17]

Stage 3 to 5: Recommendation of a core outcome instrument for the domain symptoms

A two day consensus meeting involving 70 stakeholders (HOME IV: Malmö, Sweden, April 23-24, 2015) was held to determine which instrument(s) could be recommended for the COS for the domain of symptoms.[15] All conflicts of interest were disclosed to the meeting prior to discussions and voting. In line with previous HOME consensus meetings,[4, 5] consensus was achieved if less than 30% of the voters disagreed. Full details of the meeting and attendees can be found in the published meeting report.[15]

The consensus process began by agreeing which patient-reported symptoms were considered essential. The long-list of symptoms and discussions that led to this consensus were based on previously published studies,[14, 20] the results of a large international survey of patients[21] and input from patients discussions at the pre-meeting patient session and the main meeting. It was agreed that itch, sleep loss, dryness, red skin and irritation should be ideally included in the core instrument (Table 2).

The results of the systematic reviews (Stage 1 and 2) were then considered alongside this agreed short-list of essential symptoms to determine which instruments were of sufficient quality and relevance to be considered further (Table 1). Despite performing well in validation studies, the Itch Severity Scale (ISS) was excluded because it only measures itch and itch-related aspects and therefore does not reflect the multiplicity of symptoms associated with AE. The Nottingham Eczema Severity Score (NESS) was also excluded as it is primarily an epidemiological tool. Atopic Dermatitis Quickscore (ADQ), web-based Characteristics of Itch Questionnaire (CoIQ), method 4 and Skin Detective Questionnaire (SDQ) lack sufficient validation studies to enable any meaningful assessment to be made. Instruments that demonstrated low quality in at least one criterion in validation studies were not considered further.

The POEM, Patient-Oriented SCORAD (PO-SCORAD) and Self-administered EASI (SA-EASI) were considered in detail for their suitability. PO-SCORAD was included in these further discussions and voting despite a lack of validation studies because it was felt important by some participants. After lengthy small and large group discussions, a vote was held to establish whether any of the instruments that had been considered in detail could be recommended as the core outcome instrument.

After lengthy discussions and consideration of the evidence presented, consensus was achieved (87.5% agreed, 9.4% unsure) in the voting that the POEM is the most appropriate instrument

to measure symptoms and was therefore recommended for inclusion in the COS to measure AE symptoms in clinical trials.

The PO-SCORAD and SA-EASI were not favoured, largely because it was argued that these instruments ask patients to perform an assessment of clinical signs ratings rather than being a true measurement of patient-reported symptoms.

The POEM (http://nottingham.ac.uk/research/groups/cebd/resources/poem.aspx) is free to use and typically takes less than two minutes to complete. It asks about the frequency of seven symptoms (itch, sleep disturbance, dryness, flaking, weeping or oozing, bleeding and cracking) in the past seven days. However, the agreed essential symptom of redness is not included in POEM. In the development of this instrument, redness was deliberately excluded because of the difficulties in detect it in people with darker skin types [16]. Additionally, POEM only captures the frequency of symptoms but does not measure the intensity; the relative importance of intensity of symptoms requires further investigation.

The POEM generally meets the OMERACT filter of truth, discrimination and feasibility, but some validation gaps remain including structural validity and cross-cultural validity which is particularly important for global use of the instrument. These validation gaps will be addressed as per the HOME roadmap (Stage 4). If POEM does not perform well in these additional validation studies, its inclusion in the core set will be reassessed. All core outcome sets should evolve over time in response to new data. These validation studies are now ongoing and the results will be discussed at a future HOME consensus meeting.

CONSENSUS RECOMMENDATION

POEM is recommended as the core outcome instrument to measure symptoms of AE in all future clinical trials. We encourage all stakeholders, including clinicians, researchers, pharmaceutical industries, regulatory agencies, journal editors and insurance companies to acknowledge this recommendation and include POEM in all future trials in AE.

STRENGTHS AND LIMITATIONS

The inclusion of core outcome instruments in all future trials will reduce selective outcome reporting bias and facilitate comparison and pooling of study data allowing clinicians and patients to make better evidence-based decisions in clinical practice.

The HOME consensus process is an evidence-based approach with participants from several continents providing an international perspective at the meeting and in the wider HOME initiative. The inclusion of different stakeholder groups, all of whom participate on a voluntary basis, ensures that recommendations are widely applicable and support widespread dissemination and implementation. The systematic reviews investigating which instruments were used and the quality of these instruments provided a good evidence base and allowed the discussions to focus on the instruments with good measurement properties.

The inclusion of patients is a key element of the HOME consensus process. Patients' views are actively sought and have equal weight. The international survey by von Kobyletzki provided the opinion of a large number of patients with different skin types and ethnicities from several continents regarding what symptoms are important.[21] Also, POEM was explicitly developed with patients using focus groups.[16] Taken together with discussions from the pre-meeting patient session and active participation of patients during the main meeting, we hope the results of this consensus process are a good reflection of what is important to patients with regards to the symptoms of AE.

Although the interdisciplinary, multi-stakeholder HOME group agreed a list of essential symptoms, it was clear that there is no available instrument that measures all of these. The most relevant stakeholders such as patient representatives, clinicians, and researchers and industry representatives planning, performing, and interpreting AE trials agreed to use the POEM as the core instrument to assess AE symptoms. However, there were no representatives from regulatory agencies or government funders of research at the HOME IV meeting, so greater efforts to engage with these stakeholder groups is required to ensure awareness and support for this core outcome instrument recommendation.

FUTURE RESEARCH RECOMMENDATIONS

Future research concerning instruments for AE symptoms should prioritise the investigation of the structural and cross-cultural validity of the POEM, and investigate the importance of intensity of symptoms in addition to the frequency of symptoms as captured using POEM. Work is also required to establish the role of pain/soreness in AE. Further efforts are required to ensure dissemination and uptake of this recommendation, and the wider HOME membership will be important facilitators in this regard.

Anyone who is interested in contributing to HOME should contact the HOME project manager (HOME@nottingham.ac.uk).

REFERENCES

1. Roekevisch E, Spuls P, Kuester D, et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review. J Allergy Clin Immunol. 2014;133(2):429-38.
2. Schmitt J, Williams H, Home Development Group. Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010, Munich, Germany. The British journal of dermatology. 2010;163(6):1166-8.
3. Schmitt J, Langan S, Stamm T, et al. Core outcome domains for controlled trials and clinical recordkeeping in eczema: International Multiperspective Delphi Consensus Process. J Invest Dermatol. 2011;131(3):623-30.
4. Schmitt J, Spuls P, Boers M, et al. Towards global consensus on outcome measures for atopic eczema research: Results of the HOME II meeting. Allergy Eur J Allergy Clin Immunol. 2012;67(9):1111-7.
5. Chalmers J, Schmitt J, Apfelbacher C, et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). Br J Dermatol. 2014;171(6):1318-25.
6. Williamson P, Altman D, Blazeby J, et al. Developing core outcome sets for clinical trials: Issues to consider. Trials. 2012;13.
7. Schmitt J, Apfelbacher C, Spuls P, et al. The Harmonizing Outcome Measures for Eczema (HOME) Roadmap: A Methodological Framework to Develop Core Sets of Outcome Measurements in Dermatology. J Invest Dermatol. 2015;135(1):24-30.
8. Boers M, Brooks P, Strand C, et al. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol. 1998;25(2):198-9.
9. Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. The Journal of allergy and clinical immunology. 2013;132(6):1337-47.
10. Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. The Journal of allergy and clinical immunology. 2014;134(4):800-7.
11. De Vet H, Terwee C, Mokkink L, et al. Measurement in Medicine, 1st edn. Cambridge, UK: University Press, 2011; 11.
12. Gerbens LA, Chalmers JR, Rogers NK, et al. Reporting of symptoms in randomised controlled trials of atopic eczema treatments: a systematic review 2016; doi:10.1111/bjd.14588 (accessed 25 March 2016) [e-pub ahead of print].
13. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2010;19(4):539-49.
14. Gerbens LA, Prinsen CA, Chalmers JR, et al. Evaluation of the measurement properties of symptom measurement instruments for atopic eczema: a systematic review. Allergy. 2016; doi:10.1111/all.12959 (accessed 20 June 2016) [e-pub ahead of print].
15. Chalmers JR, Simpson E, Apfelbacher CJ, et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). The British journal of dermatology. 2016;175(1):69-79.
16. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004;140(12):1513-9.

17. Coutanceau C, Stalder JF. Analysis of correlations between patient-oriented SCORAD (PO-SCORAD) and other assessment scores of atopic dermatitis severity and quality of life. Dermatology. 2014;229(3):248-55.
18. Schram ME, Spuls PI, Leeflang MM, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99-106.
19. Charman CR, Venn AJ, Ravenscroft JC, et al. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. The British journal of dermatology. 2013;169(6):1326-32.
20. Charman C, Chambers C, Williams H. Measuring atopic dermatitis severity in randomized controlled clinical trials: what exactly are we measuring? J Invest Dermatol. 2003;120(6):932-41.
21. von Kobyletzki LB, Thomas KS, Schmitt J, et al. What is important to patients when assessing treatment response: an international cross-sectional survey. Acta Derm Venereol. 2016; doi:10.2340/00015555-2480 (accessed 22 July 2016) [e-pub ahead of print].

Tables

Table 1. Recommendations of identified symptom instruments[1]

Rating	Instrument	Recommendation
A	-	Instrument meets all required quality items and is recommended for use.
B	ISS, POEM, SA-EASI	Instrument meets two or more required quality items, but performance in all other required quality items is unclear, so it has the potential to be recommended in the future depending on the results of further validation studies.
C	ADAM, EIQ, LIS, subjective SCORAD, ZRADSQ	Instrument has low quality in at least one required quality criteria and is not recommended for use.
D	ADQ, CoIQ, mEASI, method 4, NESS, PO-SCORAD, SDQ	Instrument has almost not been validated or the performance in all or most relevant quality items is unclear, so that it is not recommended to be used until further validation studies clarify its quality.

Abbreviations: *ADAM*, Atopic Dermatitis Assessment Measure; *ADQ*, Atopic Dermatitis Quickscore; *CoIQ*, Web-based Characteristics of itch questionnaire; *EIQ*, Eppendorf Itch Questionnaire; *ISS*, Itch Severity Scale; *LIS*, Leuven Itch Scale; *mEASI*, modified Eczema Area and Severity Index; *NESS*, Nottingham Eczema Severity Score; *POEM*, Patient-Oriented Eczema Measure; *PO-SCORAD*, Patient-Oriented SCORing Atopic Dermatitis index; *SA-EASI*, Self-administered Eczema Area and Severity Index; *SCORAD*, SCORing Atopic Dermatitis index; *SDQ*, Skin Detective Questionnaire; *ZRADSQ*, Zheng-related atopic dermatitis symptom questionnaire.

[1] An update of this SR, performed after the consensus meeting, evaluated 3 additional instruments for assessing symptoms of AE, but these were not discussed at the consensus meeting.[14]

Table 2. Symptoms of importance to patients

Symptoms important to patients	Considered essential?
Amount of body affected	
Bleeding	
Burning	
Cracking	
Discoloration	
Dry, flaky skin	Yes
Fatigue	
General symptoms	
Hypersensitivity	
Involvement of "visible" or "sensitive" body sites	
Irritation	Yes
Itch	Yes
Lichenification	
Pain / soreness	
Rash	
Redness	Yes
Scratch marks	
Skin feels hot or inflamed	
Sleep loss	Yes
Tightness	
Weeping / oozing	