

Measuring long-term disease control in atopic dermatitis: a validation study of well controlled weeks

Sinéad M Langan PhD¹, Beth Stuart PhD², Lucy Bradshaw MSc³, Jochen Schmitt MPH^{4,5}, Hywel C. Williams PhD⁴, Kim S Thomas PhD⁴

¹ Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine

² Faculty of Medicine, University of Southampton, Southampton, United Kingdom

³ Nottingham Clinical Trials Unit, University of Nottingham. ⁴ Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, United Kingdom

⁵ Centre for Evidence-based Healthcare, Medical Faculty Carl Gustav Carus, TU Dresden, Germany

Corresponding author: Dr Sinéad M Langan, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, WC1E 7HT. Tel +44 2079272680. Email: sinead.langan@lshtm.ac.uk

Funding sources: This work was supported by an NIHR Clinician Scientist Fellowship (to SML, grant number: NIHR/CS/010/014). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the UK Department of Health. This article presents independent research funded in part by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the Department of Health.

Abstract (250 w)

Background

Because atopic dermatitis (AD) is a relapsing, remitting disease, assessing long-term control is important. Well controlled weeks (WCWs) have been used to assess asthma long-term control, but never validated for AD.

Objectives

To assess feasibility, validity and interpretability of WCWs in AD patients.

Methods

Three studies of patients with moderate-to-severe AD including 4-6 months of daily/weekly symptom and treatment use data were evaluated (Study A: n=336; Study B: n=60; Study C: n=224). WCWs were defined by worsening symptoms and increased medication use. Feasibility, construct validity and interpretability of WCWs were determined by assessing missing data, association with validated AD outcomes, and floor/ceiling effects. Analysis used linear and logistic regression.

Results

WCWs were feasible to collect - 95.2% (study A) and 94.7% (study B) contributed data for at least half of the weekly data-points, and 93.2% and 88.7% contributed to all data-points up to 4 months. WCWs were significantly associated with validated AD severity instruments including patient-reported (POEM) and objective signs (EASI, TIS and SASSAD). The odds of experiencing a WCW if AD severity was clear/mild was 5.8 (95% confidence interval (CI) 3.5 to 9.7), 1.9 (95%CI 0.8 to 4.4) and 8.1 (95%CI 4.5 to 14.6) in Studies A, B and C, respectively. WCWs were associated with ceiling effects- 31.6% (study A) and 37.5% (study B) of participants had no WCWs for >90% of the time.

Conclusions

WCWs are valid and feasible for measuring long-term control in AD trials. However, ceiling effects and burden of data collection may limit use.

Key messages

- Well Controlled Weeks (WCWs) are a composite measure of treatment use and symptoms that have been proposed as a measure of long-term AD control.
- WCWs appear to be closely related to other measures of AD severity indicating construct validity.
- Capturing data for WCWs can be time consuming, but the limited missing data supports acceptability to patients.
- Ceiling effects may be problematic in moderate to severe patients and might limit the ability to detect change if participants experience few WCWs during follow-up.

Capsule summary (35 words)

WCWs were feasible to collect and demonstrated construct validity (closely related to other measurements of AD severity); however, ceiling effects may be problematic in patients with moderate to severe disease.

Key words: AD, long-term control, outcome measures

Abbreviations:

Atopic dermatitis (AD)

Harmonising Outcome Measures in Eczema (HOME)

Well Controlled Weeks (WCW)

Softened Water Eczema Trial (SWET)

Clothing for the relief of Eczema Symptoms (CLOTHES)

Patient orientated eczema measure (POEM)

Three item severity score (TIS)

Eczema area and severity Index (EASI)

Six Signs, Six Areas Atopic Dermatitis scale (SASSAD)

Patient Reported Outcome Measures (PROMs)

Outcome Measures in Rheumatology (OMERACT) filter

Topical corticosteroids (TCS)

Minimum Clinically Important Difference (MCID)

Introduction

Atopic dermatitis (AD, also known as atopic eczema or eczema) is the most common inflammatory disease of childhood, affecting 20% of children at some point in their lives and approximately 3% of adults.^{1,2} It is characterised by a chronic relapsing, remitting disease course. Flares are a major component of the morbidity of the disease, with major impacts on sufferers and their families.³ Capturing chronicity of disease and measures of longer-term disease control is an important clinical outcome and is becoming increasingly important with the drive for more pragmatic, longer-term comparative effectiveness trials.⁴

Research in AD has been hampered by the use of a vast array of outcome measures, the majority of which have not been adequately validated.⁵ The Harmonising Outcome Measures in Eczema (HOME) initiative (www.homeforeczema.org) is an international collaborative effort comprising international stakeholders, who are working together to establish consensus over a core outcome set for AD research. Measuring long-term control has been identified as a core outcome domain for clinical trials in AD, but at present, there is no established and validated measure to do this.^{4,6}

To address the lack of an accepted and validated way of measuring long-term control in AD, our group previously proposed a definition for Well Controlled Weeks (WCW) based on the literature in the field of asthma.⁷ The proposed definition for WCW is based on having two days or fewer with i) symptoms above a pre-specified level and ii) escalation of treatment required. Hence, WCWs reflect a behavioural response to the worsening of AD. WCWs are distinct from Totally Controlled Weeks (TCWs) where no symptoms are observed during a week. Thus, a WCW is based on the concept that if the chronic disease is only associated with increased symptoms for two or less days that week, it is relatively well controlled. Hence, if a study participant has fewer WCWs, they have worse disease control, whereas those with many WCWs have well controlled disease. This definition of WCWs has not previously been validated or evaluated in an AD research setting.^{7,8} There is little clarity on how

WCWs should be measured or interpreted; and how they relate to other validated outcome measures for AD. This paper reports our experiences of using WCW in three clinical studies (two randomised controlled trials (RCTs) and one observational study): the Softened Water Eczema Trial (SWET), an observational study of environmental triggers of disease flares in childhood AD, and the Clothing for the relief of Eczema Symptoms (CLOTHES) trial).⁹⁻¹¹ Study objectives were:

1. To assess the feasibility of WCWs as measure of long-term AD control.
2. To explore the association between WCWs and other validated AD outcome severity instruments (patient-reported severity and objective severity scales).
3. To evaluate the interpretability of WCWs by examining floor and ceiling effect, and the relationship between WCWs and eczema severity.

Floor and ceiling effects occur when a high proportion of study participants experience the “best” or “worst” outcome for the majority of the study period respectively. In this study, floor effects occurred if a substantial proportion experienced a state of well controlled weeks for the majority of the study period. Conversely, ceiling effects occurred when a substantial proportion of individuals failed to achieve a well controlled week for the majority of the study period. Both floor and ceiling effects are problematic as they hamper the ability to distinguish at extremes of disease severity.

Methods:

Ethics approval was not required for this study as it represents a secondary analysis of existing datasets from previously conducted and ethically approved studies.

Data Sources

Data from three UK-based studies (two funded by the National Institute for Health Research, and one by the BUPA foundation) have been used to inform these analyses. The datasets include children with moderate to severe AD, who were recruited in both primary and secondary care settings.

Study A: Softened Water Eczema Trial (SWET) :¹²

The SWET trial was a randomised controlled trial of four months' duration involving 336 children with moderate to severe AD aged between six months and 16 years recruited between 2007 and 2009. Children were recruited from 8 UK secondary care centres. Participants received normal care plus an ion-exchange water softener, or normal care alone. Participants had clinic visits at baseline, 4, 12 and 16 weeks. Data to define WCWs were collected daily using paper diaries. Validated AD severity scales (Patient orientated Eczema measure (POEM), Six Signs, Six Areas Atopic Dermatitis scale (SASSAD) and Three item severity score (TIS)) were completed during the clinic visits.¹³⁻¹⁵

Study B: Observational study to identify flare triggers:⁹

This study was a six-month prospective cohort study involving 60 children with moderate to severe AD assessing the associations between environmental exposures and disease flares in AD between 2006-2007. Participants were aged up to 15 years and were recruited from a single UK centre. Participants had clinic visits at baseline, and monthly for six months. Data to define WCWs were collected using daily electronic diaries. Validated AD severity scales (POEM and TIS) were completed during the clinic visits.

Study C:¹¹

The CLOTHES trial was a randomised controlled trial of six months' duration involving 300 children with moderate to severe AD aged 1-15 years recruited from 5 secondary care centres in the UK between 2013-2015. Participants received standard care plus silk therapeutic clothing, or standard care alone. Participants had clinic visits at baseline, 8, 16 and 24 weeks, and completed weekly on-line questionnaires. WCWs were not a specified outcome for the CLOTHES trial, however, data necessary to define WCWs were available from weekly on-line questionnaires and from clinic visits, making it possible for inclusion in this validation study. Validated AD severity scales (POEM, AD area and severity Index (Eczema Area and Severity Index (EASI) and TIS) were completed during the clinic visits.

Defining WCWs

We previously suggested that a well-controlled week should be defined whereby treatment escalation (stepping up of treatment) was only used for 2 or less days for that week AND where symptoms were increased above a pre-specified level for two or less days during that week⁸. Valid symptom assessment tools could include either a patient global assessment, or a self-reported bother/itch/scratch score. The pre-specified symptom level was proposed as being greater than 1 on a five point Likert scale (0-4), or greater than 4 on an eleven-point visual analogue scale (0-10).

We defined escalation of treatment as any additional treatment that had been specified in the study protocol to deal with disease deterioration. In some study designs, study treatment is used as an "as required" treatment in response to disease worsening, and therefore study treatment could be considered as treatment escalation. If a treatment was used for less than two days per week as proactive therapy for the prevention of flares, this was not considered to be escalation of treatment.¹⁶ In those using low potency steroids, escalation could include increasing the steroid

potency to moderate or potent topical steroids. In those using potent steroids, stepping up to super-potent topical steroids, or using wet-wraps, could constitute an escalation.

Table 1 provides a summary of how WCWs were defined in each of the included studies. For Studies A and B, escalation of treatment was defined on an individual basis for each child by parents in conjunction with study investigators at the start of the study. For study C, number of days of topical corticosteroids each week was used to define treatment escalation.

WCW data were collected daily for studies A and B, and weekly for Study C. For Study C, data on the number of days that topical corticosteroids were used was collected weekly, and global bother over the last week was collected every two months. As such, WCWs in Study C could only be calculated at 8, 16 and 24 weeks, despite the availability of weekly treatment use data.

Details of other outcomes related to eczema severity collected in the included studies are outlined in Table 1.

Evaluation of WCWs and hypotheses tested

Feasibility of collecting WCWs in clinical studies

- Assessed based on the amount of missing data for each of the included datasets
- WCWs were judged to be feasible to collect if more than 50% of participants completed at least half of the daily/weekly questionnaires, and if more than 80% of participants were eligible for inclusion in the repeated measures analysis of WCWs (Studies A and B only).

Association between WCWs and other commonly used AD outcome scales (construct validity)

- The degree to which WCWs relate to other validated outcome scales (POEM, EASI, TIS and SASSAD).
- We hypothesised that participants reporting a WCW would have lower severity scores for AD symptoms (POEM) and AD signs (EASI, TIS and SASSAD) for that week.

Interpretability of WCWs

- Assessed by examining the distribution of WCWs to look for floor and ceiling effect, and by assessing the odds of experiencing a WCW according to eczema severity (using previously validated POEM bandings for mild, moderate and severe disease).¹⁷
- WCWs were assumed to have problematic ceiling effects if more than 15% of participants experienced no WCWs for more than 90% of the time or floor effects if more than 15% of participants experienced a WCW for more than 90% of the time.¹⁸

Statistical methods

Data management

The three datasets were analyzed individually to explore the consistency and replication of our findings across different datasets. Analysis of dataset A was considered exploratory and analysis of datasets B and C confirmatory.

For Study C we included participants who had completed weekly questionnaires (providing data on topical corticosteroid use and POEM scores) up to three days prior to a clinic visit, or one day following the clinic visit, to ensure that data were reported in the same time period as the disease severity measures (EASI and TIS) and bother scores, which were captured during the 2-monthly clinic visits. This meant that 224 of the 300 trial participants (75%) contributed to this validation study. As a result, Study C was excluded from the analysis of missing data (as all had available data to be included in the study) and floor & ceiling effects (as only 3 data-points were available).

Feasibility - missing data

The quantity of missing data was determined for WCWs in Studies A and B. The following rules were developed to handle missing data:

- If there were three days or more with either a bother score greater than 4 or where “stepping up” was required, then the week was not defined as a WCW.
- If only one day had a bother score >4 and there is only one missing day, then the week was classed as a WCW; the same rules apply for treatment escalation (stepping-up of treatment).

Construct validity - association between WCWs and validated scales

The strength and direction of the association between WCW and other measures of disease severity (POEM, TIS, SASSAD and EASI scores) was assessed for weeks 4, 12 and 16 in study A; weeks 4, 8, 12, 16, 20 and 24 in study B, and weeks 8,16 and 24 in study C.

As the data were captured at different time points in the three studies (Table 1), the primary analysis (Table 3) included participants with data for at least two of the time points.

Given the repeated measures nature of the study, data were analysed using mixed linear models in Stata version 14. This allows participants who have missing data to contribute information for any periods for which they have data at the same time point for both WCW and the validated severity instrument; no assumptions were made about missing values.

Interpretability

In order to explore whether WCWs were subject to floor and ceiling effects, the proportion of the study period spent with a WCW was calculated for all participants who contributed data for at least 50% of the study period (Studies A and B only).

To evaluate clinical interpretability, pre-defined categorical bands for POEM scores were used: clear/mild (0-7); moderate (8-16); severe/very severe (17 – 28) AD¹⁷. In order to contribute to the analysis, participants needed to have data on WCWs and POEM for at least one time point after baseline. The relationship between POEM severity and WCWs was determined using mixed logistic regression; with the moderate severity group as the reference group.

Power

No formal sample size estimation was conducted, as the sample size for this study was pragmatic based on data availability. A sample size of >100 participants per analysis has been recommended as sufficient for validation studies.²¹

Results

Overall, 608 participants contributed to the analyses (Study A: n=325; Study B: n=59; Study C: n=224). Baseline characteristics of included participants are summarized and demonstrate similar baseline characteristics, although Study B is significantly smaller than studies A and C (**Table 2**).

Objective 1. Feasibility of WCWs as a measure of long-term control

Testing the hypothesis that more than 50% of participants would complete at least half of the daily/weekly questionnaires during the study period, we found high completion rates for WCWs. In Study A, 320/336 (95.2%) participants contributed WCW data for more than half of the 16 week study period and 325/336 (97%) had at least one WCW after baseline. In Study B, 56/59 (94.7%) contributed WCW data for more than half of the 24 week study period. In Study A, sufficient data was available to calculate a WCW 94.5% of the time at 3 months and 93.2% of the time at 4 months. For Study B, the data was available 91.9% of the time at 3 months and 88.7% of the time at 4 months.

Testing the hypothesis that at least 80% of participants would be eligible for inclusion in a repeated measures analysis (assuming that participants could be included if they contributed at least one data-point for WCWs after baseline), most participants were able to be included (97% in Study A and 100% in Study B).

Objective 2. Association between WCWs and other commonly used AD outcome scales

The hypothesis that participants reporting a WCW would have lower AD severity scores for the corresponding week was supported. For all three studies, POEM and TIS scores were lower in individuals with a WCW compared to those who did not have a WCW ($p < 0.05$ for study B and < 0.01 for study A and B) (Table 3). In Studies A and C, where data for SASSAD and EASI were available, a similar pattern was observed (Table 3).

Objective 3: Interpretability of WCWs by examining floor and ceiling effect, and the relationship between WCWs and eczema severity.

The proportion of time spent with a WCW during the study period is shown (Figure 1), and suggests potentially problematic ceiling effects, in that more than 15% of the participants spent more than 90% of the time without a WCW (Figure 1); hence a substantial proportion of individuals had poor control of their eczema throughout the study period.

In Study A, 32 participants (10%) spent more than 90% of the study with a WCW and 101 (31.6%) spent more than 90% of the study period without a WCW. In Study B, 2 participants (3.4%) spent more than 90% of the study period with a WCW and 21 participants (37.5%) spent more than 90% of the study period without a WCW.

The association between WCW scores and AD severity (based on validated POEM bandings) suggest that WCWs are a useful reflection of AD severity. Compared to those with moderate POEM scores, those with mild or clear AD were more likely to have a WCW, whilst those with severe or very severe AD were much less likely to have had a WCW (**Table 4**). For Studies A and C, these differences were statistically significant whilst for Study B, the relationship was in the same direction but not statistically significant, though this may reflect the smaller sample size of this study.

Discussion

Main findings

In this study we have shown that WCWs as defined in the three included datasets show good feasibility and construct validity, but may be limited by ceiling effects in patients with moderate to severe disease. WCWs appear to correlate well with other measures of AD severity, including both patient reported outcomes (POEM) and objective outcome instruments capturing AD signs (TIS, EASI and SASSAD).

Assessment of feasibility is particularly important, as measures that are unduly time consuming to collect and analyse, or are prone to missing values, are unlikely to be recommended for a core outcome instrument.²² Measuring long-term control on a daily or weekly basis to define WCWs (using a combination of symptoms and the need to use AD medications), is a novel approach to determining disease control, but is potentially burdensome to both patients and researchers. However, the high completion rates in the included studies would suggest acceptability to patients. It is possible that with increasing use of on-line tools and mobile phone 'apps', the technological difficulties of collecting daily or weekly data may be overcome.

Responsiveness is an important criterion for quality assessment of outcome instruments, which has not yet been evaluated. As a binary measure, it may be difficult for a WCW to adequately capture change over time, and the observed ceiling effects, could make it difficult to demonstrate meaningful change.¹⁸ Further work to evaluate responsiveness of WCWs is required.

Relevance to other studies

It is not yet clear what measure to use and how frequently AD should be assessed in order to estimate longterm control within the context of a randomised controlled trial – a topic that has been identified as a key priority for future research by a multidisciplinary stakeholder group²³. The majority of previous studies have used either patient reported or objective severity scores assessed

1 to 2 months apart; usually during clinic visits.^{5, 24} The optimum frequency of data collection to capture the chronic relapsing nature of AD is not yet known, although it has been reported that assessment of AD severity twice a week provides additional information compared to AD severity collected at 2 months.²⁵ The concept of WCWs has been developed specifically to assess the nature of long-term control of eczema. It is a complex measure capturing both the impact of eczema symptoms and the need for treatment escalation. Although capturing the multiple dimensions of eczema control is attractive, using WCWs increases the questionnaire burden on participants and investigators.

Previous work looking at the validation of flare outcomes has suggested that use of topical corticosteroids and/or calcineurin inhibitors is as sensitive for capturing AD flares as the concept of treatment escalation.²⁶ The current study supports this finding as WCWs defined by use of topical corticosteroids/calcineurin inhibitors (in Study C) demonstrated similar levels of association with validated scales as those seen in the two studies that used escalation of treatment in defining WCWs.

Strengths and limitations

This study used existing datasets that had been originally collected for another purpose. As a result, some of the analyses were limited by the available data. In the case of Study C, the definition of WCWs was *post-hoc* and may have influenced the analyses. Nevertheless, we explored the performance of WCWs in the three datasets separately and tested pre-defined hypotheses. We were able to replicate findings in the separate datasets, lending support to the validity of these findings. It is possible that there may have been some overlap of study populations between the included studies as all three recruited in Nottingham, and there was some additional overlap between studies A and C in the recruiting sites. However, the studies were conducted at different periods from 2006 to 2015, so any overlap is likely to be small.

It is currently unclear what proportion of time in a WCW would represent 'good control' (which might vary by disease severity), and further work is required to determine whether definitions used to define WCWs can be consistently applied to different studies and populations. Our findings were remarkably consistent across the three included studies, but these studies were all conducted in children with moderate to severe disease, and with participants who were predominantly recruited in secondary care.

Clinical and research implications

Understanding how to characterise and measure long-term control is a key research priority for the Harmonizing Outcome Measures for Eczema (HOME) initiative⁶, and consensus discussions will be taking place at the next HOME meeting in June 2017 (www.homeforeczema.org). WCWs appear to fulfil many of the criteria for consideration as an instrument for measuring long-term control, but it has limitations that require further assessment.

References

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; 124:1251-8.e23.
2. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113:832-6.
3. Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families: further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. *Br J Dermatol* 2006; 155:1249-55.
4. Schmitt J, Langan S, Stamm T, Williams HC, panel HOMiEHD. Core outcome domains for controlled trials and clinical recordkeeping in eczema: international multiperspective Delphi consensus process. *J Invest Dermatol* 2011; 131:623-30.
5. Schmitt J, Langan S, Williams HC, Network ED-E. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007; 120:1389-98.
6. Chalmers JR, Simpson E, Apfelbacher CJ, Thomas KS, von Kobyletzki L, Schmitt J, et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *Br J Dermatol* 2016.
7. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004; 170:836-44.
8. Langan SM, Thomas KS, Williams HC. What is meant by a "flare" in atopic dermatitis? A systematic review and proposal. *Arch Dermatol* 2006; 142:1190-6.
9. Langan SM, Silcocks P, Williams HC. What causes flares of eczema in children? *Br J Dermatol* 2009; 161:640-6.
10. Thomas KS, Koller K, Dean T, O'Leary CJ, Sach TH, Frost A, et al. A multicentre randomised controlled trial and economic evaluation of ion-exchange water softeners for the treatment of eczema in children: the Softened Water Eczema Trial (SWET). *Health technology assessment* 2011; 15:1-156.
11. Harrison EF, Haines RH, Cowdell F, Sach TH, Dean T, Pollock I, et al. A multi-centre, parallel group superiority trial of silk therapeutic clothing compared to standard care for the management of eczema in children (CLOTHES Trial): study protocol for a randomised controlled trial. *Trials* 2015; 16:390.
12. Thomas KS, Dean T, O'Leary C, Sach TH, Koller K, Frost A, et al. A randomised controlled trial of ion-exchange water softeners for the treatment of eczema in children. *PLoS Medicine* 2011; 8.
13. 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; 140:1513-9.
14. Berth-Jones J. Six area, six sign atopic dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br J Dermatol* 1996; 135 Suppl 48:25-30.
15. Oranje AP, Glazenburg EJ, Wolkerstorfer A, De Waard-Van Der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: The SCORAD index, objective SCORAD and the three-item severity score. *British Journal of Dermatology* 2007; 157:645-8.
16. Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol* 2011; 164:415-28.

17. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol* 2013; 169:1326-32.
18. De Vet H, Terwee, CB, Mokkink L, Knol D. Measurement in Medicine: a practical guide: Cambridge University Press; 2011.
19. Thomas KS, Sach TH. A multicentre randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children: protocol for the Softened Water Eczema Trial (SWET) (ISRCTN: 71423189). *Br J Dermatol* 2008; 159:561-6.
20. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol* 2015; 172:1353-7.
21. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Qual Life Res* 2012; 21:651-7.
22. Barbarot S, Rogers NK, Abuabara K, Aubert H, Chalmers J, Flohr C, et al. Strategies used for measuring long-term control in atopic dermatitis trials: A systematic review. *J Am Acad Dermatol* 2016; 75:1038-44.
23. Schmitt J, Spuls P, Boers M, Thomas K, Chalmers J, Roekvisch E, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. *Allergy* 2012; 67:1111-7.
24. Barbarot SR, Natasha K. Abuabara, Katrina Aubert, Helene Chalmers, Joanne Flohr, Carsten Hanifin, Jon Naldi, Luigi Margolis, David J. Paul, Carle Ridd, Matthew J. Schuttelaar, Marie-Louise Anna Simpson, Eric Tauber, Marie Volke, Annika Weidinger, Stephan Wilkes, Sally R. Wollenberg, Andreas Thomas, Kim S. Strategies used for measuring long-term control in atopic dermatitis trials: A systematic review. *Journal of the American Academy of Dermatology* 2016; In press.
25. Barbarot S, Aubert H, Stadler J-F. How patient-reported outcomes can be important in routine practice in children with atopic dermatitis. *International Society for Atopic Dermatitis*. Sao Paulo, Brazil, 2016.
26. Thomas KS, Stuart B, O'Leary CJ, Schmitt J, Paul C, Williams HC, et al. Validation of treatment escalation as a definition of atopic eczema flares. *PLoS One* 2015; 10:e0124770.

