Received Date : 25-Feb-2016

Revised Date : 09-Jun-2016

Accepted Date : 01-Aug-2016

Article type : Systematic Review

Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review

D. Heinl[1], C.A.C. Prinsen[2], T. Sach[3], A.M. Drucker[4], R. Ofenloch[5], C. Flohr[6], C. Apfelbacher[1,7§]

1 Medical Sociology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, Germany
2 VU University Medical Center, Department of Epidemiology and Biostatistics, EMGO+ Institute for Health and Care Research, Amsterdam, The Netherlands
3 Norwich Medical School, University of East Anglia, Norwich, United Kingdom
4 Department of Dermatology, The Warren Alpert Medical School of Brown University, Providence, RI, USA
5 Department of Clinical Social Medicine, University Hospital Heidelberg, Heidelberg, Germany
6 St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust and King's College London, London, United Kingdom
7 Division of Public Health and Primary Care, Brighton and Sussex Medical School, Falmer, United Kingdom

§ corresponding author

Address details of corresponding author:

Christian Apfelbacher
Medical Sociology, Institute of Epidemiology and Preventive Medicine
University of Regensburg
Dr.-Gessler-Str. 17
93051 Regensburg
Germany
Tel.: +49 941 944 5231
Fax: +49 941 944 5252
E-Mail: christian.apfelbacher@klinik.uni-regensburg.de

Running head: Eczema QoL measures for infants and young people: a systematic review

Conflicts of interest: All authors are ordinary members of the HOME initiative. Christian Apfelbacher is a member of the HOME Executive Committee. Carsten Flohr is a member of the Scientific Advisory Board of HOME. Aaron Drucker is involved with the development of a novel quality of life assessment instrument for atopic dermatitis that is as yet unpublished. The authors declare that they have no other competing interests.

Funding statement: The authors declare that they have not received any financial funding to conduct this study. Tracey Sach is funded by a Career Development Fellowship (CDF-2014-07-006) supported by the National Institute for Health Research. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. Carsten Flohr holds a UK National Institute for Health Research (NIHR) Career Development Fellowship (CDF-2014-07-037). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

What's already known about this topic?

- Most eczema trials include the Infants' Dermatitis Quality of Life Index (IDQoL) or the Children's Dermatology Life Quality Index (CDLQI) as quality of life (QoL) measurement instruments
- It is unclear which instruments are most appropriate to measure QoL in infants, children and adolescents with eczema

What does this study add?

- Most QoL instruments for infants, children and adolescents with eczema are poorly validated, indicating a clear need for further validation work

Summary

Background

Quality of life (QoL) is one of the core outcome domains identified by the Harmonising Outcome Measures for Eczema (HOME) initiative to be assessed in every eczema trial. There is uncertainty about the most appropriate QoL instrument to measure this domain in infants, children and adolescents.

Objectives

To systematically evaluate the measurement properties of existing measurement instruments developed and/or validated for the measurement of QoL in infants, children and adolescents with eczema.

Methods

A systematic literature search in PubMed and EMBASE, complemented by a thorough hand search of reference lists, retrieved studies on measurement properties of eczema QoL instruments for infants, children and adolescents. For all eligible studies, we judged the adequacy of the measurement properties and the methodological study quality with the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist. Results from different studies

were summarized in a best evidence synthesis and formed the basis to assign four degrees of recommendation.

Results

17 articles, 3 of which were found by hand search, were included. These 17 articles reported on 24 instruments. No instrument can be recommended for use in all eczema trials because none fulfilled all required adequacy criteria. With adequate internal consistency, reliability and hypothesis testing, the US version of the Childhood Atopic Dermatitis Impact Scale (CADIS), a proxy-reported instrument, has the potential to be recommended depending on the results of further validation studies. All other instruments, including all self-reported ones, lacked significant validation data.

Conclusions

Currently, no QoL instrument for infants, children and adolescents with eczema can be highly recommended. Future validation research should primarily focus on the CADIS, but also attempt to broaden the evidence base for the validity of self-reported instruments.

Systematic review registration: CRD42015023483

Keywords: Core outcome set; eczema; HOME initiative; measurement properties; quality of life

Introduction

Affecting more than 10% of infants and children, eczema (synonyms: 'atopic eczema', 'atopic dermatitis') is one of the most common chronic diseases in children in many countries.[1-3] A high eczema prevalence is also observed in adolescence,[2] with a substantial risk of the disease persisting into adulthood.[4] Despite a multitude of treatment options, evidence-based decision making based on systematic reviews and meta-analyses is hampered due to the heterogeneity of outcome measurement instruments used, particularly in randomized controlled trials.

Therefore, the Harmonising Outcome Measures for Eczema (HOME) initiative (www.homeforeczema.org) aims to develop a core outcome set (COS) for use in all future eczema trials. A COS is a minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population.[5] The core outcome domains suggested by the HOME initiative are clinical signs, symptoms, long-term control of flares and quality of life (QoL).[6-8]

Following the HOME roadmap,[9] we performed a systematic review of the measurement properties of all instruments that were developed and validated to measure QoL in infants, children and adolescents with eczema. For adults, this step has already been completed.[10]

Material and Methods

Protocol and registration

This systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] A completed PRISMA checklist is available as an online appendix to this publication. The study protocol was published[12] and registered in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015023483.

Literature search

A systematic literature search in PubMed and EMBASE was conducted on 18 June 2015. The entire search strategy is shown in detail in the study protocol.[12] Hand searching the PROQOLID database (http://www.proqolid.org) and reference lists of included studies and key articles on QoL in infants, children and adolescents with eczema complemented the systematic search.

Eligible studies

We applied the eligibility criteria presented in the protocol.[12] Briefly, the study population of eligible development and validation studies of dermatology- or eczema-specific QoL instruments had to consist of at least 50% eczema patients younger than 16 years of age, or studies had to present subgroup analyses for this patient group.

Content comparison

The content of the included instruments was compared at the content domain level based on information from the original development paper.

Assessment of the methodological quality of included studies

We used the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist to judge the methodological quality of the included studies (www.cosmin.nl).[13-16] This checklist consists of 5 to 18 items per measurement property covering methodological standards; the compliance with these standards is rated on a four-point rating scale (that is, 'poor,' 'fair,' 'good,' 'excellent'). The lowest rating for any item pertaining to a certain measurement property determines the overall rating for this measurement property.

Assessment of measurement properties and further characteristics of QoL instruments

With the exception of criterion validity, all measurement properties from the COSMIN checklist were evaluated in this systematic review. Where available, interpretability and feasibility data were collected. Because we view them as distinct instruments, different language versions of the same questionnaire were considered separately throughout this review except for content comparison and instrument characteristics.

Assessment of the adequacy of the measurement properties

To evaluate the adequacy of the investigated measurement properties, we applied the corresponding predefined criteria recommended by the COSMIN group in a slightly modified version (Table 1).[17] The specific changes we made to these criteria are explained in the protocol.[12] Where studies used item response theory (IRT) methods in the assessment of measurement properties instead of the development of measurement instruments, we assessed the adequacy and

methodological quality of internal consistency, construct validity, structural validity, and cross-cultural validity.

Best evidence synthesis

Findings on the same instrument from multiple studies were synthesized if the characteristics of the included studies were sufficiently similar, the results did not show considerably different or conflicting findings and the methodological quality of the included studies was adequate.[18] Criteria for best evidence synthesis are found in Table 2.

Generating recommendations for the use of QoL measurement instruments for eczema

Depending on the adequacy of each instrument and the methodological quality of the included studies, a standardized recommendation for usage and necessary future validation work was made for each investigated instrument.

Four categories of recommendation were made:[12]

A. QoL measurement instrument meets all requirements and is recommended for use.
B. QoL measure meets two or more adequacy criteria, but performance in all other required adequacy criteria is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies.
C. QoL measure has low adequacy in at least one required adequacy criterion (≥1 rating of 'minus') and therefore is not recommended to be used any more.
D. QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy criteria is unclear so that it is not recommended to be used until further validation studies clarify its adequacy.

Finally, we aimed to identify one best (currently available) instrument to assess QoL in infants, one best (currently available) instrument to assess QoL in children, and one best (currently available) instrument to assess QoL in adolescents with eczema.

Results

17 articles were included (Fig. 1).[19-35] One paper complying with the inclusion criteria presented only summary information, making analyses of the evaluated questionnaires and measurement properties impossible; the paper was consequently excluded.[36] Another paper containing data on the content validity of the Childhood Impact of Atopic Dermatitis (CIAD) did not formally meet inclusion criteria and was thus excluded.[37] However, read in conjunction with the eligible development article of the CIAD,[32] information on content validity could be extracted from that excluded paper and was therefore considered for this review.

Most included studies reported on the Children's Dermatology Life Quality Index (CDLQI, n=6)[20,27-29,31,34] and the Infants' Dermatitis Quality of Life Index (IDQoL, n=6).[19,22,23,27,30,35] Three studies evaluated the Childhood Atopic Dermatitis Impact Scale (CADIS)[24,25,33] and two studies assessed the DISABKIDS Atopic Dermatitis Module (DISABKIDS-ADM).[21,26] Information on the CIAD was available from two studies,[32,37] but only one of them met the inclusion criteria.[32]

A comparison of the content covered by these five instruments is presented in Table 3. The CDLQI and the IDQoL are the most similar in content out of the five instruments. Table 4 shows other general characteristics of the included instruments. The CADIS, CIAD and IDQoL are proxy-reported, whereas the CDLQI is completed by children themselves. The questionnaire DISABKIDS-ADM is available both in a self- and a proxy-reported version. Only the CDLQI is a dermatology-specific instrument, all others are eczema-specific. The lowest number of items in a questionnaire is 7, the highest 45. Four of the five questionnaires apply a 4- or 5-point Likert scale; only the CIAD uses a dichotomous response format.

Characteristics of the included studies

An overview of settings and study populations in the included studies is shown in Table 5. Most studies were conducted in secondary/tertiary care settings in Europe. Sample sizes ranged from 8 to 370 patients.

Validity of the instruments and recommendations

In total, we were able to rate the methodological quality of 84 measurement properties. Two measurement properties (2%) had good, 18 (21%) had fair and 64 (76%) had poor methodological quality. Detailed results for every instrument and study investigated in this systematic review can be found in the online appendix to this article (Tables S1-S80).

Proxy-reported instruments

Table 6 shows the number of studies assessing the different measurement properties of each included proxy-reported QoL instrument. The results of best evidence synthesis and the degree of recommendation for each proxy-reported instrument are found in Table 7. There was no instrument for which all relevant measurement properties have been investigated. Hence, there was also no instrument that fulfilled all pre-specified requirements of truth, discrimination and feasibility.

With Cronbach's α ranging from 0.76 to 0.93 for its subscales, internal consistency of the US version of the CADIS was found adequate.[24] Most language versions of the CIAD demonstrated also good internal consistency, with Cronbach's α values between 0.72 and 0.85.[32] For the other instruments, internal consistency assessment was either done methodologically poorly or was not done at all. Measurement error was not investigated for any of the proxy-reported instruments included. Good reliability was shown for the US version of the CADIS, with Intraclass Correlation Coefficients (ICC) of 0.89-0.95 for the domain scores and 0.96 for the total score between the two administrations.[25] An ICC of 0.89 was found for the Dutch IDQoL, proving this instrument adequately reliable.[35] While three language versions of the CIAD obtained an indeterminate rating for reliability, there was either no evidence or only evidence from methodologically poor studies for the other instruments.

Data on content validity could be extracted for the US version of the CADIS, the UK version of the IDQoL and all language versions of the CIAD. However, all content validity assessments were done methodologically poorly. No clear rating could be assigned for the IRT methods used to investigate structural validity of the US version of the CIAD.[32] Hypothesis testing was the measurement property most frequently evaluated, with information available for 14 of the 16 proxy-reported instruments. The two Italian CADIS versions correlated well with other QoL instruments; for instance, Spearman's correlation coefficients of 0.74 with the IDQoL and 0.68 with the Dermatitis Family Impact were found for the long Italian CADIS.[33] Discriminative validity of the US version of the CADIS was proven adequate since the instrument could differentiate patients according to severity as measured by

SCORing Atopic Dermatitis (SCORAD).[25] Convergent validity of the UK version of the IDQoL was assessed in a study of fair methodological quality, but resulted in an indeterminate adequacy rating as only correlations with unrelated constructs were determined.[30] Evidence on hypothesis testing for the remaining questionnaires was available from methodologically poor studies only.[19,22,26,27,32,35] Likewise, we could not draw a conclusion on cross-cultural validity, which was assessed for the long version of the Italian CADIS and four language versions of the CIAD, due to poor methodological study quality.[32,33]

Responsiveness in eczema patients was investigated for only three questionnaires, but these assessments were of poor methodological quality.[23,25,30,32]

Values for the minimal important change (MIC), the minimal important difference (MID) or validated banding systems are not available for the IDQoL.[38] Evidence from several included validation studies suggests that the IDQoL does not exhibit floor and ceiling effects (i.e. ≥15% of patients having the lowest/highest possible score).[22,27,30,35] We could not find information on the interpretability of the other proxy-reported questionnaires. Completion time of the CADIS amounted to approximately 6 minutes in one study.[24]

Self-reported instruments

Table 8 shows the number of studies assessing the different measurement properties of each included self-reported QoL instrument. The results of best evidence synthesis and the degree of recommendation for each self-reported instrument are found in Table 9. There was no instrument for which all relevant measurement properties have been investigated. Hence, there was also no instrument that fulfilled all pre-specified requirements of truth, discrimination and feasibility.

Internal consistency assessments were available for four included self-reported QoL instruments, but all were conducted methodologically poorly. Measurement error was not evaluated for any self-reported instrument included. Both the Malay and the Mexican Spanish CDLQI were assigned an indeterminate rating for reliability, whereas this measurement property was not investigated for any other included self-reported instrument.

Content validity was only investigated for the unknown language version of the DISABKIDS-ADM, but the methodological study quality was poor.[21] Information on structural validity of the included self-reported instruments was not available. Data on hypothesis testing was available for all instruments except the unknown language version of the DISABKIDS-ADM. We found an intermediate rating for discriminative validity of the Swedish CDLQI because the instrument was able to differentiate patients according to age, but could not distinguish patients with eczema only from patients with eczema and another allergic comorbidity.[27] The assessments of construct validity of all other questionnaires were of poor methodological quality. Cross-cultural validity was not assessed for any self-reported QoL instrument included.

An investigation of responsiveness was available for the Danish CDLQI only, but was done methodologically poorly.[28]

Little information on interpretability is available for the self-reported QoL instruments. No floor and ceiling effects were found for the CDLQI in an analysis of 50 Swedish children with eczema.[27] Similarly, the CDLQI showed no floor and ceiling effects in the 47 children participating in its

development study.[29] A recent meta-analysis provides an overview of CDLQI scores in different conditions, enabling comparisons of eczema patients' scores with those of patients suffering from other diseases and helping to interpret patients' CDLQI scores.[39] Values for the MIC/MID for the CDLQI in eczema patients, as well as interpretability data for the DISABKIDS-ADM, could not be found.

Discussion

This systematic review assessed the measurement properties of five different QoL instruments for use in infants, children and adolescents with eczema. None of these instruments complied with all pre-specified filter criteria of truth, discrimination and feasibility, clearly indicating that more validation work is required.

Strength and limitations of this review

Strengths of this systematic review include a registered and published protocol, the application of a validated, precise search filter[40] and of predefined eligibility criteria, and the use of the COSMIN checklist[13-16] to judge the methodological quality of included studies. Every step of the review process was carried out by at least two reviewers. Furthermore, one reviewer (DH) was involved in every step of the review to ensure consistency across the participating reviewers. Discrepancies were resolved by frequent discussions within the whole team.

A limitation of this review is the fact that only PubMed and EMBASE were searched. A thorough hand search of reference lists of included studies, important reviews and the PROQOLID database retrieved ten articles of interest not found in our initial systematic search, three of which were judged eligible and included. Another limitation may be that we could not consider responsiveness results of the CIAD obtained in the whole European sample because the paper provided no corresponding country-specific data. Also, information on discriminative validity of the CIAD could not be considered because the specific p values were not presented by McKenna *et al.*[32]

Discussion of the results in light of other research

Of all instruments reviewed, only the US version of the CADIS[24] reached category B, hence having the potential to be recommended in the future depending on the results of further validation studies. All other questionnaires were placed in category D; their future use cannot be endorsed until further validation data is available.

The CADIS, intended for use in eczema patients 0-6 years of age, is an internally consistent, reliable questionnaire with adequate construct validity. Its conceptual framework is based on a literature review and directed focus sessions with experts and parents. Compared to the other included instruments, the CADIS is unique in that it assesses both the QoL of the affected infant or child and the QoL of their parents. Although the instrument provides a total score, separate scores for the domains relating to the child's QoL can also be calculated. Results from both the infant- or child-related domains and the parent-related domains were considered for this systematic review. The 45-item questionnaire was quickly completed. A disadvantage of the CADIS is that only three validated language versions of the instrument are currently available, with a validation study of a Spanish version being prepared for publication.[41] The validation article of the Japanese CADIS version, still in press and recently published online,[42] was not investigated in this systematic review because it had not yet been available when our systematic review was conducted. It will be taken into account in

the first update to this systematic review. Measurement error and structural validity of the CADIS have not yet been investigated. Moreover, future studies of improved methodological quality should look at content validity, cross-cultural validity, responsiveness and interpretability of the CADIS.

The major finding of this systematic review is that nearly all existing QoL instruments for infants, children and adolescents with eczema are lacking significant validation data and were hence classified in category D. One reason for this is that 76% of the measurement properties were investigated in a methodologically poor manner, as compared to 25% in our preceding systematic review assessing the measurement properties of adult eczema QoL instruments.[10] Part of this difference can be attributed to a stricter approach in judging whether hypotheses were formulated *a priori* when assessing hypothesis testing and responsiveness (item 4 in COSMIN box F, item 8 in COSMIN box I) in this review compared to the afore-mentioned review of adult eczema QoL instruments. However, only 16 of the 32 COSMIN boxes of hypothesis testing and responsiveness rated as 'poor' in this systematic review would obtain a better COSMIN rating if a less strict approach concerning hypotheses formulation was applied, still leaving 57% methodologically poorly investigated measurement properties in total. This result suggests that the methodological study quality is indeed worse than in the previous review on adult eczema QoL instruments.

In addition to insufficient or methodologically poor validation of most instruments included, interpretability data is also lacking. A MID of 2.5 points on the CDLQI has been found in psoriasis patients,[43] but corresponding data for eczema patients do not exist. Similarly, a banding system to help interpreting CDLQI scores has been developed,[44] but the study did not meet our eligibility criteria because it reported on general dermatology patients in abstract form only. Interpretability in eczema patients is an important topic future validation studies should address.

Only two of the five included instruments are self-reported by the affected children. While proxy-reported measures, including the CADIS, may be particularly useful in infants and younger children, they are not suitable for older children and adolescents. As both the CDLQI and the DISABKIDS-ADM were placed in category D, there is currently no self-reported QoL instrument for paediatric eczema that can be recommended for use. CDLQI and DISABKIDS-ADM are also intended for use in adolescents. However, it has been argued that factors influencing adolescents' QoL are fundamentally different from those observed in children and adults, leading to the development of the adolescent-specific Skindex-Teen.[45] The development study of this questionnaire was not eligible for this review, though. Future validation studies of self-reported QoL instruments should therefore investigate whether they are suitable for adolescents with eczema as well, or if separate instruments for this age group are needed.

Recommendations to researchers, clinicians and decision makers

Currently only the CADIS has the potential to be recommended for use depending on the results of further validation studies. These validation studies should include all existing language versions of the CADIS and specifically examine measurement error, content validity, structural validity, cross-cultural validity, responsiveness and interpretability. If these studies find favourable measurement properties of the CADIS, it should be translated and validated in more languages to increase international applicability. As the IDQoL is the QoL instrument most often used in eczema trials involving infants,[46] it seems also advisable to undertake further validation work for this questionnaire. Additionally, future validation research should focus on self-reported QoL instruments for children and adolescents with eczema included in this review (CDLQI and DISABKIDS-ADM). For

the time being, since none of the investigated QoL instruments can be highly recommended, we suggest using the proxy-reported CADIS for infants and younger children with eczema, until formal consensus is reached by the HOME initiative. For older children and adolescents with eczema, there is currently no valid, reliable and feasible self-reported instrument. Trials in this age group should include the QoL instrument that in their authors' opinion is best suited for children and adolescents with eczema. In older adolescents, the two QoL instruments for adults with eczema placed in category B in a previous systematic review,[10] the Quality of Life Index for Atopic Dermatitis (QoLIAD)[47] and the Dermatology Life Quality Index (DLQI),[48] may be applicable.

Abbreviations

CADIS, Childhood Atopic Dermatitis Impact Scale; *CDLQI,* Children's Dermatology Life Quality Index; *CIAD,* Childhood Impact of Atopic Dermatitis; *COS,* core outcome set; *COSMIN,* COnsensus-based Standards for the selection of health Measurement INstruments; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *DLQI,* Dermatology Life Quality Index; *HOME,* Harmonising Outcome Measures for Eczema; *ICC,* Intraclass Correlation Coefficient; *IDQoL,* Infants' Dermatitis Quality of Life Index; *IRT,* item response theory; *MIC,* minimal important change; *MID,* minimal important difference; *PRISMA,* Preferred Reporting Items for Systematic Reviews and Meta-Analyses; *QoL,* quality of life; *QoLIAD,* Quality of Life Index for Atopic Dermatitis; *SCORAD,* SCORing Atopic Dermatitis; *UK,* United Kingdom; *US,* United States (of America);

Acknowledgments

We owe a great debt of gratitude to Rosemary Humphreys (Budleigh Salterton, United Kingdom) who commented on this manuscript and our research results from a patient's and a caregiver's view. We are very grateful to Joanne Chalmers (Nottingham, United Kingdom) and Helen Scott (Nottingham, United Kingdom) for assisting us in finding colleagues that could help with foreign language articles. We are indebted to Valeria Aoki (Sao Paulo, Brazil), Jonathan Batchelor (Nottingham, United Kingdom), Ievgen Kozin (Regensburg, Germany), Haibo Liu (Nanjing, China) and Luigi Naldi (Bergamo, Italy) for their help with foreign language articles.

Authors' contributions

DH conceptualized the research plan for the systematic review, screened search results, extracted data, assessed measurement properties, coordinated the work of the other reviewers, wrote the manuscript and reviewed it for important intellectual content. CP screened search results, assessed measurement properties, helped with methodological questions, wrote the manuscript and reviewed it for important intellectual content. TS performed the literature search, screened search results, extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. AD screened search results, extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. RO screened search results, assessed measurement properties and reviewed the manuscript for important intellectual content. RH contributed to the study design and reviewed the manuscript for important intellectual content. CF extracted data, assessed measurement properties and reviewed the manuscript for important intellectual content. CA conceptualized the research plan for the systematic review, screened search results, extracted data, assessed measurement properties, wrote the manuscript and reviewed it for important intellectual content.

Tables

Table 4: Characteristics of the different instruments.

Characteristic	CADIS	CDLQI	CIAD	DISABKIDS-ADM	IDQoL
Target population	Children with eczema aged 0-6 years (and their parents)	Children with skin disease aged 4-16 years	Children with eczema	Children and adolescents with eczema	Infants with eczema aged under 4 years
Mode of administration	Proxy-reported[a]	Self-reported[b]	Proxy-reported[a]	Self- or proxy-reported[b]	Proxy-reported[a]
Number of items	45/41/33*	10	9/7†	12	10
Number of subscales	5	6	ND	2	8
Number/type of response categories	5-point Likert scale	4-point Likert scale	Dichotomous (true/not true)	5-point Likert scale (and 'not applicable')	4-point Likert scale
Scoring algorithm	Calculation of domain scores by summing up item scores of all items in one domain; calculation of a total score by summing up scores of all items in the questionnaire	Calculation of a sum score, range 0-30	ND	Calculation of a mean standardized score for each dimension, range 0-100	Calculation of a sum score, range 0-30
Recall period in the items	4 weeks	1 week	None ('at the moment')	ND	1 week
Administration costs	No administration costs[41]	No charge for non-funded studies; $11.50 per patient for pharmaceutical companies[51]	ND	ND	No charge for use in non-funded studies and routine clinical practice; $11.50 per patient for pharmaceutical companies[52]
Available translations	English (US), Italian, Japanese[41]	More than 50[51]	Dutch, English (UK), English (US), French, German	Brazilian Portuguese, other languages‡	More than 20[52]

a 'Proxy-reported' means that the (primary) caregiver of an infant fills in a questionnaire that assesses the quality of life of the infant. Proxy-reported instruments are often used in infants and younger children because they cannot report on their quality of life themselves due to their inability to read and a lack of understanding.

b 'Self-reported' instruments are used in older children and adolescents. These questionnaires are filled in by the children/adolescents themselves, not by their caregiver.

*45 items in the original version, 41 items in the long Italian version, 33 items in the short Italian version (Italian versions include fewer items as some were found to misfit in factor analysis).

†9 items in the Dutch, English (UK), French and German version each; 7 items in the English (US) version. The European versions and the US questionnaire have 6 items in common (of these, 3 are used as link items).

‡Not described which language versions were tested in the European validation study.

Abbreviations: *CADIS,* Childhood Atopic Dermatitis Impact Scale; *CDLQI,* Children's Dermatology Life Quality Index; *CIAD,* Childhood Impact of Atopic Dermatitis; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *IDQoL,* Infants' Dermatitis Quality of Life Index; *ND,* not described; *UK,* United Kingdom; *US,* United States (of America).

Table 5: Important characteristics of the included development and validation studies.

		Study characteristics				
					Study population	
QoL instrument	**Number of studies**	**Geographic location(s)**	**Language(s)**	**Setting(s)**	**Number of participants per study**	**Age range**
English CADIS (US)	2[24,25]	United States of America	English (US)	Secondary/tertiary care	270	1.5-71.4 mos
Italian CADIS (long version)	1[33]	Italy	Italian	Secondary/tertiary care	135	2-72 mos
Italian CADIS (short version)	1[33]	Italy	Italian	Secondary/tertiary care	135	2-72 mos
Danish CDLQI	1[28]	Denmark	Danish	Secondary/tertiary care	35	ND
English CDLQI (UK)	1[29]	United Kingdom	English (UK)	Secondary/tertiary care	47	ND (mean±SD: 9.2±3.6 yrs)
Malay CDLQI	1[20]	Malaysia	Bahasa Malaysia	Secondary/tertiary care	33	ND (youngest: 7 yrs)
Serbian CDLQI	1[31]	Serbia	Serbian	Secondary/tertiary care	64	4-16 yrs
Spanish CDLQI (Mexico)	1[34]	Mexico	Mexican Spanish	Secondary/tertiary care	64	8-16 yrs
Swedish CDLQI	1[27]	Sweden	Swedish	Secondary/tertiary care	50	5-15 yrs
Dutch CIAD	1[32,37]*	Netherlands	Dutch	Secondary/tertiary care and community[37]	15 (item generation)[37]	ND[37]
					20 (field testing)[37]	ND[37]
				Clinical trial[32]†	48[32]	ND[32]
English CIAD (UK)	1[32,37]*	United Kingdom	English (UK)	Secondary/tertiary care and community[37]	35 (item generation)[37]	ND[37]
					20 (field testing)[37]	ND[37]
				Clinical trial[32]†	21[32]	ND[32]
English CIAD (US)	1[32,37]*	United States of America	English (US)	Secondary/tertiary care and community[37]	20[37]	ND[37]
				Clinical trial[32]†	243[32]	ND (mean±SD: 48±21.6 mos)[32]
French CIAD	1[32,37]*	France	French	Secondary/tertiary care and community[37]	19[37]	ND[37]
				Clinical trial[32]†	52[32]	ND[32]
German CIAD	1[32,37]*	Germany	German	Secondary/tertiary care and community[37]	19[37]	ND[37]
				Clinical trial[32]†	87[32]	ND[32]

Italian CIAD	1[37]*	Italy	Italian	Secondary/tertiary care and community	15 (item generation)	ND
					8 (field testing)	ND
Spanish CIAD	1[37]*	Spain	Spanish	Secondary/tertiary care and community	20	ND
DISABKIDS-ADM (unknown language)	1[21]	ND (2 European countries)	ND	ND	29	ND
Portuguese DISABKIDS-ADM (Brazil, proxy-reported version)	1[26]	Brazil	Brazilian Portuguese	Secondary/tertiary care	52	8-18 yrs
Portuguese DISABKIDS-ADM (Brazil, self-reported version)	1[26]	Brazil	Brazilian Portuguese	Secondary/tertiary care	52	8-18 yrs
Arabic IDQoL	1[19]	Saudi Arabia	Arabic	Secondary/tertiary care	370	ND (mean±SD: 8.8±9.9 mos)
Dutch IDQoL	1[35]	Netherlands	Dutch	Primary care	66	0.5-83.5 mos
English IDQoL (UK)	2[23,30]	United Kingdom	English (UK)	Secondary/tertiary care[23]	203[23]	1-53 mos[23]
				Secondary/tertiary care and community[30]	89 (validation)[30]	ND (mean: 20.16 mos)[30]
				Secondary/tertiary care[30]	92 (development)[30]	ND[30]
Italian IDQoL	1[22]	Italy	Italian	Secondary/tertiary care	21	12-48 mos
Swedish IDQoL	1[27]	Sweden	Swedish	Secondary/tertiary care	28	24-48 mos

Abbreviations: *CADIS,* Childhood Atopic Dermatitis Impact Scale; *CDLQI,* Children's Dermatology Life Quality Index; *CIAD,* Childhood Impact of Atopic Dermatitis; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *IDQoL,* Infants' Dermatitis Quality of Life Index; *mos,* months; *ND,* not described; *QoL,* quality of life; *SD,* standard deviation; *UK,* United Kingdom; *US,* United States (of America); *yrs,* years.

*The study by McKenna *et al.* from 2005 did not formally meet the inclusion criteria. However, read in conjunction with the eligible 2007 CIAD development article by McKenna *et al.,* information on content validity of the CIAD could be extracted from the 2005 article. As a result, only the article by McKenna *et al.* from 2007 was formally included, but information from the 2005 article was also taken in consideration for content validity assessment.

†These studies were conducted in the context of a clinical trial. No further information on the participating health service providers was presented, which is why it was not possible to group these study populations in one of the three categories community, primary care, or secondary/tertiary care.

Table 7: Summary of measurement properties of proxy-reported QoL instruments for infants, children and adolescents with eczema.

Measurement property	English CADIS (US)	Italian CADIS (long version)	Italian CADIS (short version)	Dutch CIAD	English CIAD (UK)	English CIAD (US)	French CIAD	German CIAD	Italian CIAD	Spanish CIAD	Portuguese DISABKIDS-ADM (Brazil, proxy-reported version)	Arabic IDQoL	Dutch ID QoL	English IDQoL (UK)	Italian IDQoL	Swedish IDQoL
Internal consistency	+	Weak	Weak	+	Weak	+	+	+	/	/	Weak	Weak	/	/	Weak	/
Measurement error	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Reliability	+	Weak	Weak	Weak	Weak	? (limited)	? (limited)	? (limited)	/	/	/	/	+	Weak	Weak	/
Content validity	Weak	/	/	Weak	Weak	Weak	Weak	Weak	Weak	Weak	/	/	/	Weak	/	/
Structural validity	/	Weak	/	/	/	? (limited)	/	/	/	/	/	/	/	/	/	/
Hypothesis testing	+	+	+	Weak	Weak	Weak	Weak	Weak	/	/	Weak	Weak	Weak	? (limited)	Weak	Weak
Cross-cultural validity	/	Weak	/	Weak	Weak	/	Weak	Weak	/	/	/	/	/	/	/	/
Responsiveness	Weak	/	/	/	/	Weak	/	/	/	/	/	/	/	Weak	/	/
Recommendation	**B**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**

Abbreviations: *CADIS,* Childhood Atopic Dermatitis Impact Scale; *CIAD,* Childhood Impact of Atopic Dermatitis; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *IDQoL,* Infants' Dermatitis Quality of Life Index; *QoL,* quality of life; *UK,* United Kingdom; *US,* United States (of America).

Recommendations are defined as follows: *A,* QoL measurement instrument meets all requirements and is recommended for use; *B,* QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies; *C,* QoL measure has low adequacy in at least one required adequacy criterion (≥1 rating of 'minus') and therefore is not recommended to be used any more; *D,* QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy.

+, positive rating indicating adequate measurement property; *? (limited),* intermediate rating indicating intermediate measurement property; *Weak,* measurement property was assessed only in studies of poor methodological quality (please refer to Table 2 for further details); */* = not assessed.

Table 9: Summary of measurement properties of self-reported QoL instruments for infants, children and adolescents with eczema.

Measurement property	Danish CDLQI	English CDLQI (UK)	Malay CDLQI	Serbian CDLQI	Spanish CDLQI (Mexico)	Swedish CDLQI	DISABKIDS-ADM (unknown language)	Portuguese DISABKIDS-ADM (Brazil, self-reported version)
Internal consistency	/	/	Weak	Weak	Weak	/	/	Weak
Measurement error	/	/	/	/	/	/	/	/
Reliability	/	/	? (limited)	/	? (limited)	/	/	/
Content validity	/	/	/	/	/	/	Weak	/
Structural validity	/	/	/	/	/	/	/	/
Hypothesis testing	Weak	Weak	Weak	Weak	Weak	? (limited)	/	Weak
Cross-cultural validity	/	/	/	/	/	/	/	/
Responsiveness	Weak	/	/	/	/	/	/	/
Recommendation	**D**	**D**	**D**	**D**	**D**	**D**	**D**	**D**

Abbreviations: *CDLQI,* Children's Dermatology Life Quality Index; *DISABKIDS-ADM,* DISABKIDS Atopic Dermatitis Module; *QoL,* quality of life; *UK,* United Kingdom; *US,* United States (of America).

Recommendations are defined as follows: *A,* QoL measurement instrument meets all requirements and is recommended for use; *B,* QoL measure meets two or more adequacy items, but performance in all other required adequacy items is unclear, so that the outcome measure has the potential to be recommended in the future depending on the results of further validation studies; *C,* QoL measure has low adequacy in at least one required adequacy criterion (≥1 rating of 'minus') and therefore is not recommended to be used any more; *D,* QoL measure has (almost) not been validated. Its performance in all or most relevant adequacy items is unclear so that it is not recommended to be used until further validation studies clarify its adequacy.

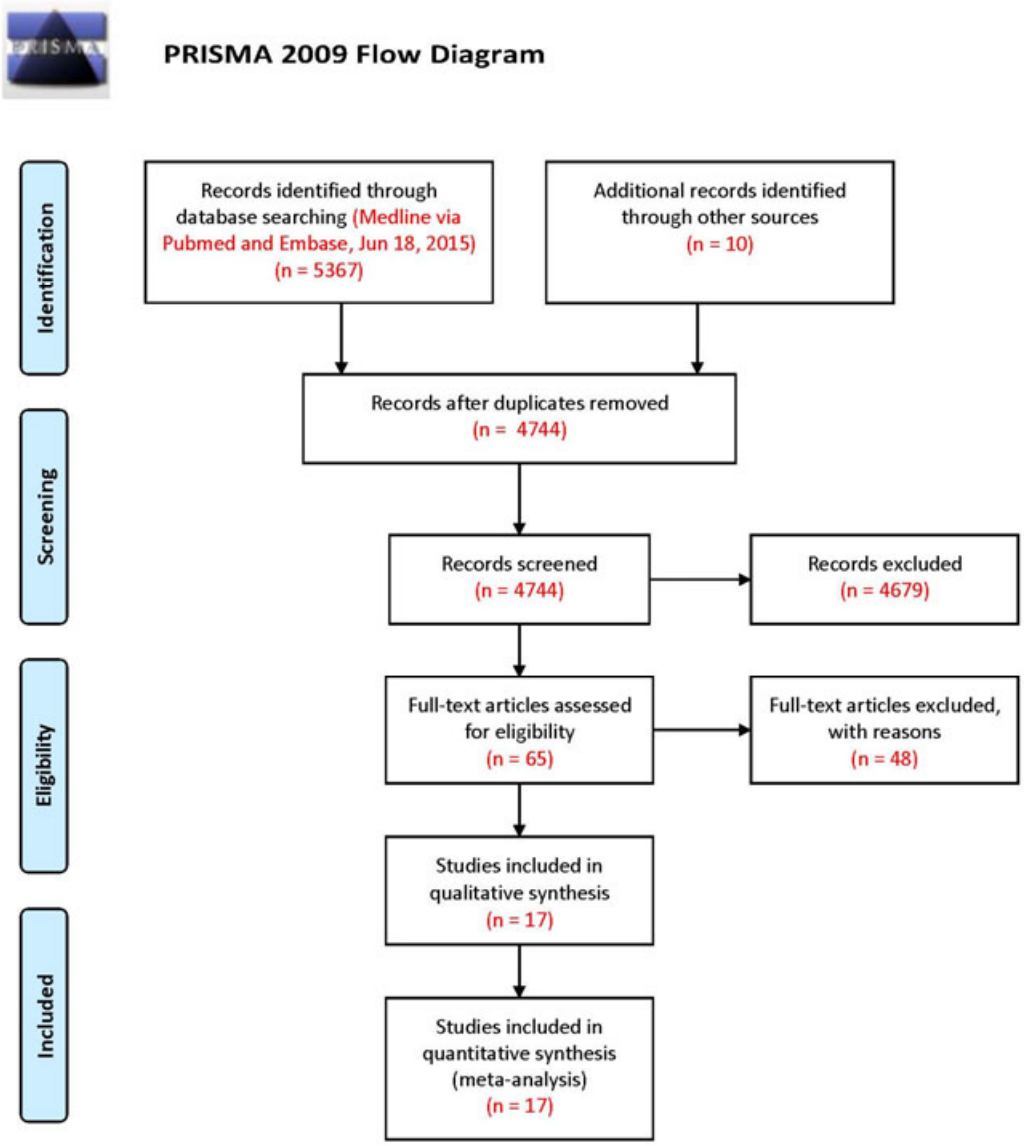
? (limited), intermediate rating indicating intermediate measurement property; *+/-,* conflicting findings; *Weak,* measurement property was assessed only in studies of poor methodological quality (please refer to Table 2 for further details); */* = not assessed.

References

1. Apfelbacher CJ, Diepgen TL, Schmitt J. Determinants of eczema: population-based cross-sectional study in Germany. *Allergy* 2011; **66**: 206-13.
2. Henriksen L, Simonsen J, Haerskjold A *et al.* Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol* 2015; **136**: 360-6 e2.
3. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis* 2014; **25**: 107-14.
4. Mortz CG, Andersen KE, Dellgren C *et al.* Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy* 2015; **70**: 836-45.
5. Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials* 2007; **8**: 39.
6. 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**: 623-30.
7. 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* 2012; **67**: 1111-7.
8. Schmitt J, Williams H, Group HD. Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010, Munich, Germany. *Br J Dermatol* 2010; **163**: 1166-8.
9. Schmitt J, Apfelbacher C, Spuls PI *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**: 24-30.
10. Heinl D, Prinsen CA, Deckert S *et al.* Measurement properties of adult quality-of-life measurement instruments for eczema: a systematic review. *Allergy* 2016; **71**: 358-70.
11. Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
12. Heinl D, Prinsen CA, Drucker AM *et al.* Measurement properties of quality of life measurement instruments for infants, children and adolescents with eczema: protocol for a systematic review. *Syst Rev* 2016; **5**: 25.

13. Mokkink LB, Terwee CB, Knol DL *et al.* The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. *BMC Med Res Methodol* 2010; **10**: 22.
14. Mokkink LB, Terwee CB, Patrick DL *et al.* The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010; **63**: 737-45.
15. 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. *Qual Life Res* 2010; **19**: 539-49.
16. Terwee CB, Mokkink LB, Knol DL *et al.* 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.
17. Terwee CB, Bot SD, de Boer MR *et al.* Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007; **60**: 34-42.
18. Furlan AD, Pennick V, Bombardier C *et al.* 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; **34**: 1929-41.
19. Alzolibani AA. Cultural adaptation of the Arabic version of the Infants` Dermatitis Quality of Life Index. *Saudi Med J* 2013; **34**: 518-24.
20. Aziah MS, Rosnah T, Mardziah A *et al.* Childhood atopic dermatitis: a measurement of quality of life and family impact. *Med J Malaysia* 2002; **57**: 329-39.
21. Baars RM, Atherton CI, Koopman HM *et al.* The European DISABKIDS project: development of seven condition-specific modules to measure health related quality of life in children and adolescents. *Health Qual Life Outcomes* 2005; **3**: 70.
22. Baranzoni N, Scalone L, Mantovani L *et al.* Validation of the Italian version of the Infants' Dermatitis Quality of Life and Family Dermatitis indexes. *G Ital Dermatol Venereol* 2007; **142**: 423-32.
23. 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.
24. Chamlin SL, Cella D, Frieden IJ *et al.* Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol* 2005; **125**: 1106-11.
25. Chamlin SL, Lai JS, Cella D *et al.* Childhood Atopic Dermatitis Impact Scale: reliability, discriminative and concurrent validity, and responsiveness. *Arch Dermatol* 2007; **143**: 768-72.
26. Deon KC, Santos DM, Bullinger M *et al.* Preliminary psycometric assessment of the Brazilian version of the DISABKIDS Atopic Dermatitis Module. *Rev Saude Publica* 2011; **45**: 1072-8.
27. Ganemo A, Svensson A, Lindberg M *et al.* Quality of life in Swedish children with eczema. *Acta Derm Venereol* 2007; **87**: 345-9.
28. Holm EA, Wulf HC, Stegmann H *et al.* Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; **154**: 719-25.
29. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995; **132**: 942-9.
30. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. *Br J Dermatol* 2001; **144**: 104-10.
31. Maksimovic N, Jankovic S, Marinkovic J *et al.* Health-related quality of life in patients with atopic dermatitis. *J Dermatol* 2012; **39**: 42-7.
32. McKenna SP, Doward LC, Meads DM *et al.* Quality of life in infants and children with atopic dermatitis: addressing issues of differential item functioning across countries in multinational clinical trials. *Health Qual Life Outcomes* 2007; **5**: 45.
33. Neri E, Agostini F, Gremigni P *et al.* Italian validation of the Childhood Atopic Dermatitis Impact Scale: a contribution to its clinical application. *J Invest Dermatol* 2012; **132**: 2534-43.

34. Ramirez-Anaya M, Macias ME, Velazquez-Gonzalez E. Validation of a Mexican Spanish version of the Children's Dermatology Life Quality Index. *Pediatr Dermatol* 2010; **27**: 143-7.
35. van Valburg RW, Willemsen MG, Dirven-Meijer PC *et al.* Quality of life measurement and its relationship to disease severity in children with atopic dermatitis in general practice. *Acta Derm Venereol* 2011; **91**: 147-51.
36. Chernyshov PV. [Creation and cross-cultural adaptation of ukrainian versions of questionnaires for assessment of quality of life of children with atopic dermatitis and their families]. *Lik Sprava* 2008: 124-8.
37. McKenna SP, Whalley D, Dewar AL *et al.* International development of the Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD). *Qual Life Res* 2005; **14**: 231-41.
38. Basra MK, Gada V, Ungaro S *et al.* Infants' Dermatitis Quality of Life Index: a decade of experience of validation and clinical application. *Br J Dermatol* 2013; **169**: 760-8.
39. Olsen JR, Gallacher J, Finlay AY *et al.* Quality of life impact of childhood skin conditions measured using the Children's Dermatology Life Quality Index (CDLQI): a meta-analysis. *Br J Dermatol* 2016; **174**: 853-61.
40. Terwee CB, Jansma EP, Riphagen, II *et al.* Development of a methodological PubMed search filter for finding studies on measurement properties of measurement instruments. *Qual Life Res* 2009; **18**: 1115-23.
41. Personal Communication: Administration costs and available validated language versions of CADIS. Inquiry about administration costs and available validated language versions of CADIS by e-mail. [12/12/2015]
42. Yamaguchi C, Futamura M, Chamlin SL *et al.* Development of a Japanese Culturally Modified Version of the Childhood Atopic Dermatitis Impact Scale (JCMV-CADIS). *Allergol Int* 2016.
43. Langley RG, Paller AS, Hebert AA *et al.* Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. *J Am Acad Dermatol* 2011; **64**: 64-70.
44. Waters A, Sandhu D, Beattie PE *et al.* Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. *Br J Dermatol* 2010; **163**: 121.
45. Smidt AC, Lai JS, Cella D *et al.* Development and validation of Skindex-Teen, a quality-of-life instrument for adolescents with skin disease. *Arch Dermatol* 2010; **146**: 865-9.
46. Heinl D, Chalmers J, Nankervis H *et al.* Eczema Trials: Quality of Life Instruments Used and Their Relation to Patient-reported Outcomes. A Systematic Review. *Acta Derm Venereol* 2016; **96**: 596-601.
47. Whalley D, McKenna SP, Dewar AL *et al.* A new instrument for assessing quality of life in atopic dermatitis: international development of the Quality of Life Index for Atopic Dermatitis (QoLIAD). *Br J Dermatol* 2004; **150**: 274-83.
48. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210-6.
49. PROMIS Methodology. Patient Reported Outcomes Measurement Information System (PROMIS) Standards 2015. Available at: http://www.nihpromis.org/science/methodology (last accessed 14/07/2015)
50. Schellingerhout JM, Verhagen AP, Heymans MW *et al.* Measurement properties of disease-specific questionnaires in patients with neck pain: a systematic review. *Qual Life Res* 2012; **21**: 659-70.
51. Children's Dermatology Life Quality Index (CDLQI): Department of Dermatology, University of Cardiff. Available at: http://sites.cardiff.ac.uk/dermatology/quality-of-life/childrens-dermatology-life-quality-index-cdlqi/ (last accessed 12/12/2015)
52. The Infants' Dermatitis Quality of Life Index (IDQoL): Department of Dermatology, University of Cardiff. Available at: http://sites.cardiff.ac.uk/dermatology/quality-of-life/the-infants-dermatitis-quality-of-life-index-idqol/ (last accessed 12/12/2015)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.