



Patient-reported outcomes and quality of life measures in atopic dermatitis

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Abstract Atopic dermatitis (AD) is a complex and heterogeneous disorder with a profound symptom burden and harmful impact on multiple domains of quality of life (QOL). Many different patient-reported outcome (PRO) measures exist to assess clinical manifestations and QOL impairment in AD, but none comprehensively assess all aspects of the disease. This review addresses the PRO and QOL measures currently used in AD and their properties, strengths, weaknesses, and feasibility for assessing AD in randomized controlled trials and clinical practice. Currently, the patient-oriented eczema measure (POEM) has emerged as a preferred PRO for AD clinical manifestations, though no single instrument has developed as a preferred QOL measure. Validated PRO and QOL measures should be incorporated in all clinical trials of AD and in clinical practice where feasible.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 15%–20% of children and 1%–10% of adults worldwide.^{1–3} AD is a heterogeneous disorder with a wide spectrum of clinical manifestations, signs, severity, and clinical course. Consequently, there is no single tool that comprehensively assesses all aspects of the disease. There are many different scales used to assess the signs, clinical manifestations, and quality of life (QOL) disturbance of AD.^{4–11} (See Table 1.)

There are currently no biomarkers that accurately reflect the severity of AD or its clinical manifestations; moreover, the large symptom burden of AD, including the sequelae of itch, pain, sleep, and mental health disturbance, may not be accurately depicted by objective measures of disease severity.¹² These clinical manifestations are likely better reflected by validated patient-reported outcomes (PRO) aimed at standardizing these subjective clinical manifestations. The profoundly negative impact of AD on QOL, such as physical and psychosocial well-being, warrants disease assessments that characterize patients' QOL.^{13–15}

There is an increasing trend toward including PROs and QOL measures in clinical studies, particularly for disorders with low mortality and high disability. Clinician assessments

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Table 1 Instruments assessing patient-reported outcomes and quality of life measures

Instrument	Instrument type	Target population	Number of items	Domains covered	Scoring	Respondent burden
SF-36	General health	General population	36	Physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions	● 0-100 *	5-10 minutes
PROMIS® Global Health	General health	General population	10	Physical health, pain, fatigue, mental health, social health, and overall health	● Two four-item scales: Raw score 4-20 * each, translated into T scores	2 minutes
NHP	General health	General population	Part 1:38 Part 2:7	Part 1: Energy levels, pain, emotional reactions, sleep, social isolation, and physical abilities Part 2: Paid employment, home duties, social life, home life/relationships, sex life, interests and hobbies, and vacations	● 0-100 *	5-10 minutes
EQ-5 D	General health	General population	5 and 1 VAS	Mobility, daily activities, self-care, psychological functioning, social and role performance, and pain or other health problems	● Index value from 0 to 100	1 minute
Skindex-29	Dermatology specific	Patients with dermatologic disorder	30	Symptoms, emotions, function	● 0-100 * ● Interpretation: Nijsten et al. ⁷⁴ : <5 = very little, 6-15 = mild, 18-36 = moderate, and >37 = severe Prinsen et al. ⁷⁵⁻⁷⁷ : 0-24 = none, 25-31 = mild, 32-43 = moderate, and >44 = severe	5-10 minutes
DLQI	Dermatology specific	Adults >18 years old with dermatologic disorder	10	Skin symptoms, feelings of embarrassment, day-to-day activities, working, and social life	● 0-30 * ● Interpretation: 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect	1-3 minutes
CDLQI	Dermatology specific	Children 4-16 years old with dermatologic disorder	10	Physical symptoms (itching, sleep loss) and psychosocial questions (friendships, bullying, school	● MCID: 4 points ● 0-30 * ● Interpretation: 0-1 = no effect on child's life, 2-6 = small effect,	1-2 minutes

(continued on next page)

Table 1 (*continued*)

Instrument	Instrument type	Target population	Number of items	Domains covered	Scoring	Respondent burden
VAS-pruritus	Pruritus specific	Patients with pruritus	1 VAS	performance, sports participation, enjoyment of vacation) Pruritus ranging from 0 (“no itch”) to 10 (“worst imaginable itch”)	7-12 = moderate effect, 13-18 = very large effect, and 19-30 = extremely large effect ● MCID: 4 points ● 0 (no itch) to 10 * (worst imaginable itch) ● Interpretation: Reich et al. ¹¹⁴ : 0 = no pruritus, 1-3 = mild pruritus, 4-6 = moderate pruritus, 7-8 = severe pruritus, and ≥9 points = very severe pruritus Kido-Nakahara et al. ¹²¹ : 0 = no pruritus, 1-2 = mild pruritus, 3-6 = moderate pruritus, 7-8 = severe pruritus, and ≥9 = very severe pruritus ● MCID = 2-3 points ● 0 (no itch) to 10 * (worst imaginable itch) ● MCID = 2-3 points ● Interpretation: 4-point scale: None, mild, moderate and severe pruritus 5-point scale: None, mild, moderate, severe and very severe pruritus ● Average score interpretation: 1-5 * ● Cumulative score interpretation: Love et al. ¹²⁴ : 0-30 = little, 31-50 = mild, 51-80 = moderate, and 81-110 = severe Vakharia et al. ⁹³ : 0-36 = mild, 37-54 = moderate, and 55-110 = severe ● Interpretation: Lai et al. ¹²⁵ : ≤8 = NRS score of 0, 9-11 = mild pruritus, 12-17 = moderate pruritus, 18-21 = severe pruritus, and ≥22 = very severe pruritus	<1 minute
NRS-pruritus	Pruritus specific	Patients with pruritus	1 NRS	Pruritus	● MCID = 2-3 points ● 0 (no itch) to 10 * (worst imaginable itch)	<1 minute
VRS-pruritus	Pruritus specific	Patients with pruritus	1 VRS	Pruritus	● MCID = 2-3 points ● Interpretation: 4-point scale: None, mild, moderate and severe pruritus 5-point scale: None, mild, moderate, severe and very severe pruritus	<1 minute
ItchyQoL	Pruritus specific	Patients with pruritus	22	Symptoms, functional limitations, and emotions	● Average score interpretation: 1-5 * ● Cumulative score interpretation: Love et al. ¹²⁴ : 0-30 = little, 31-50 = mild, 51-80 = moderate, and 81-110 = severe Vakharia et al. ⁹³ : 0-36 = mild, 37-54 = moderate, and 55-110 = severe	5-10 minutes
5-D Itch Scale	Pruritus specific	Patients with pruritus	5	Duration, degree, direction (of symptom change), disability, and distribution (areas involved)	● Interpretation: Lai et al. ¹²⁵ : ≤8 = NRS score of 0, 9-11 = mild pruritus, 12-17 = moderate pruritus, 18-21 = severe pruritus, and ≥22 = very severe pruritus	<5 minutes

ISS	Pruritus specific	Patients with pruritus	7	Pruritus	Vakharia et al. ⁹³ : 0-11 = mild, 12-17 = moderate, and 18-25 = severe ● 0-21 * ● MCID = 2 points ● n/a	1-2 minutes
DFI	AD specific	Caregiver/parent of child with AD	10	Housework, food preparation and feeding, sleep, family leisure activity, shopping, expenditure, fatigue, emotional distress, and relationships		2 minutes
IDQoL	AD specific	Infants <4 years old with AD	10	Symptoms and difficulties with mood, sleep, bathing, dressing, play, mealtimes, other family activities, and treatment	● 0-30 *	2 minutes
CADIS	AD specific	Children <6 years old with AD and parents	45	Child symptoms, child activity limitations and behavior, family and social function, parent sleep, and parent emotions	● 0-180 *	6 minutes
QoLIAD	AD specific	Adults with AD	25	Needs of individual	● 0-25 *	<5 minutes
PIQoL-AD	AD specific	Caregiver/parent of child ≤8 years old with AD	28	Needs of individual	● 0-28 * ● MCID = 2-3 points	4-5 minutes
POEM	AD specific	Patients with AD	7	Patient-reported frequency of symptoms	● 0-28 * ● Interpretation: 0-2 = clear/almost clear; 3-7 = mild, 8-16 = moderate, 17-24 = severe, and 25-28 = very severe ● MCID = 3.4; 3 in young children	1-2 minutes
SA-EASI	AD specific	Caregiver or parent of child with AD	BSA, 5 VAS	BSA involved, redness, thickness, dryness, number of scratches, and itchiness of the child's average AD lesion	● Calculated acute and chronic SA-EASI scores (Housman et al. ¹⁵⁰)	n/a
PO-SCORAD	AD specific	Patients with AD	6 items, BSA, 2 VAS	BSA affected, intensity of AD symptoms (dryness, redness, swelling, oozing/scabs, scratch marks, thickness of skin), itching, and trouble sleeping	● Calculated score (Vourc'h-Jourdain et al. ¹⁵¹)	n/a

AD, atopic dermatitis; BSA, body surface area; CADIS, Childhood Atopic Dermatitis Impact Scale; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatitis Family Index; DLQI, Dermatology Life Quality Index; EQ-5 D, EuroQol Five Dimensions; IDQoL, Infant's Dermatitis Quality of Life Index; ISS, itch severity scale; MCID, minimal clinically important difference; n/a, not available; NHP, Nottingham Health Profile; NRS, Numerical Response Scale; PIQoL-AD, Parents Index of Quality of Life in Atopic Dermatitis; PO-SCORAD, Patient-Oriented Scoring of Atopic Dermatitis; POEM, Patient-Oriented Eczema Measure; PROMIS®, Patient-Reported Outcomes Measurement Information System®; QoLIAD, Quality of Life Index for Atopic Dermatitis; SA-EASI, Self-Administered Eczema Area and Severity Index; SF-36, Medical Outcomes Study Short Form-36 Health Survey; VAS, Visual Analog Scale; VRS, Visual Response Scale.

* Indicates worse state of disease.

of disease severity do not necessarily align with patient-reported assessments.¹⁶ This was recently highlighted in a systematic review of QOL impairment in pruritus,¹⁷ the hallmark symptom of AD. There was only partial concordance with respect to how frequently different aspects of QOL and disease manifestations were reported in qualitative studies of patients' concerns from pruritus compared with clinical review publications. Physical manifestations of itch were the most frequently reported concern in the clinical literature, but only the fifth most important concern to patients. Functional limitations and relationship/social effects related to itch were the second and third most commonly reported concerns by patients and only the sixth and eighth most commonly reported concerns in the clinical literature. Assessing changes in these PRO and QOL measures may actually be better indicators of the patient burden of AD and itch in general, and treatment response. Unfortunately, research on PRO and QOL measures in AD is still lacking.^{18,19}

There is currently a lack of standardization in outcome measures used in clinical trials and practice for AD. This variability limits interpretability and comparability of clinical trial results, impairing evidence-based practice, which ultimately affects patient outcomes. As a result, the Harmonizing Outcome Measures for Eczema (HOME) international consensus group was developed to define a core outcome set that should be implemented in all future AD trials.^{11,20} At the HOME II meeting, the group determined that four domains should be measured in every AD trial: Clinical signs, patient-reported clinical manifestations, long-term control, and QOL.²¹ The addition and recognition of PRO and QOL assessments signifies the recognized importance of these measures in assessing the burden of AD. At the HOME III meeting, the HOME group defined a "symptom" as "any feature that is observed by the patient," thus broadening the outcomes that need to be captured.⁴ The HOME group set out to make this task feasible by working to recommend core instruments that can be used to assess PRO and QOL.

Because there are a variety of instruments that cover a broad spectrum of domains, our objective is the review of the instruments that can be used to assess PRO and QOL, including those that are general health related, dermatology specific, pruritus specific, and AD specific.

General health-related instruments

Short Form-36 Health Survey (SF-36)

The SF-36 was first developed in 1992, with the revised version created in 2000. The SF-36 was designed to assess patient-reported health-related quality of life (HRQOL) and can be used in general and clinical populations, thus allowing health comparability between disease states and populations.^{22,23} One review study in 2000 found it to be the global HRQOL instrument of choice. The SF-36 is a 36-item questionnaire covering 8

domains: 1, physical functioning; 2, role limitations due to physical problems; 3, social functioning; 4, bodily pain; 5, general mental health; 6, role limitations due to emotional problems; 7, vitality; 8, general health perceptions.

Total score ranges from 0 (worst) to 100 (best), broken into Physical Component Score (PCS) and Mental Component Score (MCS). The SF-36 has been well validated and shown to have high internal validity, construct validity, content validity, and convergent validity.^{24–28} More than 50 versions of the SF-36 exist in various languages; however, the questionnaire has questionable test-retest reliability, responsiveness, and discriminant validity.^{24,29} Additionally, some patients have had difficulty with question interpretation.^{30,31} The questionnaire takes approximately 5–10 minutes to complete, although shorter versions exist.^{32–34} The great, international efforts that went into the testing and validation of the SF-36 survey have led to its widespread use in health-related research. Additionally, the SF-36 has been a widely used instrument in AD research as a generic QOL measurement.^{14,35–38}

Patient-Reported Outcomes Measurement Information System® (PROMIS®) Global Health Scale

The PROMIS® initiative was developed by the National Institutes of Health (NIH) in 2004³⁹ to reliably measure PRO via valid HRQOL instruments. The PROMIS instruments have undergone significant qualitative and quantitative evaluation. The PROMIS Global Health Scale⁴⁰ is a 10-item questionnaire covering the following domains: Physical health, pain, fatigue, mental health, social health, general perception of health, physical function, quality of life, and emotional distress.

Of the 10 items, 8 questions are scored via 2 four-item scales, a global mental health (GMH) scale and a global physical health (GPH) scale. The GMH and GPH scales can each achieve a raw score ranging from 4 (best) to 20 (worst), which are translated into T scores that are evaluated on a global T score distribution.⁴¹

The PROMIS Global Health scale has shown internal consistency and sensitivity to change, performing well in both healthy and ill patient and has been shown not to have differential reporting by age or sex.⁴² Danish, Dutch, English, French, German, Italian, Portuguese, Mandarin, and Spanish translations exist as well. Due to its recent introduction, its use and validation in dermatology and AD is still ongoing.

Nottingham Health Profile (NHP)

The NHP,^{43–45} developed in the 1970s, is a generic health status questionnaire that assesses the impact of illness and health status change over time. The NHP comprises two parts: Part 1, which assess the individual's health status; part 2, which assesses the impact of ill health. Part 1 consists of 38 items covering the following domains: Energy levels, pain, emotional reactions, sleep, social isolation, and physical abilities.

Part 2 consists of 7 items covering the following domains: Paid employment, home duties, social life, home life/relationships, sex life, interests and hobbies, and vacations.

Although parts 1 and 2 can be used in conjunction or separately, it is recommended that part 1 be used alone.^{46,47} Responses are measured on a yes/no scale, and a calculated score ranges from 0 (best) to 100 (worst). The NHP has been shown to have internal consistency, internal validity, content validity, convergent validity, and discriminant validity^{44,45,48,49}; however, the questionnaire takes approximately 5–10 minutes to complete, has been translated into more than 20 languages, and has been found to be more reliable in ill patients than healthy patients.²⁴ Additionally, although the intention was to use the survey in the general population to assess general health, many believe that the survey is not suited for this.^{50,51} Other limitations include questionable test-retest reliability, a low sensitivity to change, and difficult interpretation of score changes. The NHP is well documented in regard to its validation and use in the clinical setting.^{44,45,48,52}

EuroQOL Five Dimensions questionnaire (EQ-5 D)

The EQ-5 D^{53,54} is a generic instrument measuring health status that was developed by the EuroQOL group, established in 1987 and comprising international, multidisciplinary researchers. The aim of the EuroQOL group was to create a generic instrument that could measure HRQOL, was simple and easy to complete, could be used in conjunction with other HRQOL measures, could be disseminated easily, was relevant to people of any age and any health state, and could be standardized to facilitate data collection.^{53–56} The instrument consists of five items and a visual analog scale (VAS) assessing the following domains: Mobility, daily activities, self-care, psychological functioning, social and role performance, and pain or other health problems.

Each question consists of 3 levels, and thus 243 different states are possible. The EQ-5 D generates a single index value for each state ranging from 0 to 100. A less commonly used U. S.-based scoring algorithm was also developed. The strengths of this instrument include ease of use (approximately 1 minute to complete) and translation into greater than 20 languages, and it has been shown to have responsiveness, reliability, and internal validity.⁵⁷

The EQ-5 D has been found to be less sensitive to differences associated with less morbidity, including certain skin diseases.⁵⁸ Overall, the EQ-5 D has been significantly validated,^{59–61} and is most commonly used in clinical and observational trials in the United Kingdom and Europe.⁵⁵ Numerous AD studies have used the EQ-5 D instrument to measure general QOL.^{36,62–64} The baseline AD severity in these studies has ranged from mild to severe, and the resulting EQ-5 D index values have correlated with different disease severities; however, the EQ-5 D has had more recent utility in clinical trials assessing moderate-to-severe AD, where it has shown correlating responsiveness to improvement in AD.^{62,63} Additionally,

the EQ-5 D is used frequently in cost-effectiveness modeling for various disease states and is a reliable estimator of quality adjusted life years (QALYs) in these studies.^{65–69}

Dermatology-specific instruments

Skindex-29

The Skindex-29^{70,71} was developed in 1997, aims to assess QOL in different populations, and should detect QOL changes over time. The Skindex-29 contains 29 items over the following domains: Clinical manifestations, emotions, and functioning.

The Skindex-29 also contains one additional item inquiring about side effects. The overall score is expressed on a 100-point scale, with higher scores equating to a lower QOL. The Skindex-29 has been widely validated and has been shown to have high internal consistency, test-retest reliability, construct validity, content validity, and responsiveness^{70–73}; however, limitations of the questionnaire include the presence of various score interpretations,^{12,74–77} item bias,¹² and an approximate response time of 5 minutes.⁷⁰ Shorter versions, including the Skindex-16 and Skindex-17, have thus been developed and validated.^{78,79} One consideration concerns the Skindex-29 regarding score interpretation.⁸⁰ Of the two main valid scoring approaches, the Nijsten system⁷⁴ uses a distribution-based approach, whereas the Prinsen system^{75–77} uses an anchor-based approach, both methods to assign clinical meaning to instrument scores. The distribution-based approach uses the statistical characteristics of the results to express the effect magnitude, whereas the anchor-based approach seeks to use a global scale as the basis to determine the self-reported difference that will best measure the significance of change.^{81,82} The Nijsten banding includes the following: <5 = very little, 6–15 = mild, 18–36 = moderate, >37 = severe. The clarified Prinsen banding includes the following: 0–24 = none, 25–31 = mild, 32–43 = moderate, >44 = severe.

One study, comparing the Dermatology Life Quality Index (DLQI)⁸³ and Skindex-29 scoring systems, found that the Prinsen system correlated better with the Hongbo⁸⁴ DLQI banding system compared with the Nijsten system.¹² A review of HRQOL-related instruments recommended that the Skindex-29, for which translations exist for greater than 20 languages, be used as the dermatology-specific instrument of choice.⁸⁵ The Skindex-29 has also been used extensively in AD clinical studies of various interventions.^{86–89} Additionally, some studies have found the Skindex instruments to be a better indicator of severity for and more responsive to the emotions domain.^{90,91}

Dermatology Life Quality Index (DLQI)

The DLQI tool, developed in 1994, is one of the most commonly used assessments in dermatology and clinical

trials.^{83,85,92} It measures the impact that skin disease has on the lives of adult patients. The DLQI is a 10-item questionnaire with each item scored from 0 to 3, with a total score ranging from 0 (best) to 30 (worst) that assesses the following domains: Skin clinical manifestations, feelings of embarrassment, day-to-day activities, working, and social life.

The interpretation of the DLQI score is as follows: 0 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, 21-30 = extremely large effect.

For general inflammatory skin conditions, a change in DLQI score of at least four points was found to be clinically important. We recently performed an interpretability study and confirmed that these bands are indeed optimal in adults with AD.⁹³ Although the instrument is dermatology specific and not disease specific, it is highly specific for assessing QOL changes in AD patients.^{94,95} The DLQI has been an extensively validated dermatology-specific questionnaire and has been translated into more than 40 languages.^{83,95-97} The DLQI has also been found to be sensitive to change and have high internal consistency, construct validity, and test-retest reliability.^{83,95,96,98,99} Additional strengths include ease of use, as it takes approximately 1-3 minutes to complete,¹⁰⁰ and that it has been found to correlate with disease severity and the SCORing Atopic Dermatitis (SCORAD) assessment in AD patients.¹⁰¹ The DLQI has been shown to be more of a functional instrument and has shown responsiveness to changes in social, emotional, and physical function.^{14,35,37} It is one of the most frequently used instruments in AD studies.^{5,102} Limitations of the DLQI include inadequate assessment of mild disease, item bias, and a unidimensional nature. Additionally, some studies have showed differential reporting in AD studies by sex when using the DLQI.^{103,104}

Children's Dermatology Life Quality Index (CDLQI)

The CDLQI questionnaire was developed in 1995 to measure QOL in children aged 4-16 years with skin disease to assess how their skin disease affects their lives. It is the most commonly used questionnaire for assessing QOL in children affected by skin disease. Like the DLQI, the CDLQI is a 10-item questionnaire with each item scored from 0 to 3; thus, the total score also ranges from 0 (best) to 30 (worst). The child completes the questionnaire with adult assistance if needed, and the domains covered include itching, sleep loss, friendships, bullying, school performance, sports participation, and enjoyment of vacation.

The validated severity banding for CDLQI scores is as follows: 0 = no effect on child's life, 2-6 = small effect, 7-12 = moderate effect, 13-18 = very large effect, 19-30 = extremely large effect.

A meta-analysis found that, over 38 studies, the mean CDLQI score in children with AD was 8.5 (SD 7.1-9.8), indicating that AD has a moderate effect on QOL in children. The CDLQI has been well validated, takes 1-2 minutes to complete,

and has been shown to have test-retest reliability, internal consistency, content validity, and responsiveness.^{13,105,106}

Like the DLQI, the CDLQI is also commonly used in AD studies to assess QOL in children.^{102,107} Additionally, a cartoon version was created that was found to be quicker and preferred by both children and parents.¹⁰⁸ Limitations of the CDLQI include questionable correlation with AD severity,^{109,110} as well as an inability to compare results with the DLQI, due to both differences in patient populations and reported correlations.¹¹¹ It also lacks validation of its use in patients aged <4 and >16 years.¹¹²

Pruritus-specific instruments

Visual analog scale (VAS)—pruritus

The VAS-pruritus^{113,114} is a unidimensional instrument that allows patients to mark the intensity of their itch on a 10-cm/100-mm ruler-shaped scale. The end points of the scale are marked with 0 ("no itch") and 10 ("worst imaginable itch"), and thus scoring ranges from 0 to 10. The VAS has been well validated for rating pruritus,^{115,116} as well as other clinical manifestations, most notably pain.¹¹⁷⁻¹¹⁹ A detailed analysis to create a banding system includes the following: 0 = no pruritus, 1-3 = mild pruritus, 4-6 = moderate pruritus, 7-8 = severe pruritus, ≥ 9 points = very severe pruritus.

A decrease of 2-3 points should constitute a minimal clinically important difference (MCID) for clinical itch improvement.^{114,116,120} Another research group,¹²¹ based on the results of a study of Japanese patients, recommended a slightly different banding system as follows: 0 = no pruritus, 1-2 = mild pruritus, 3-6 = moderate pruritus, 7-8 = severe pruritus, ≥ 9 = very severe pruritus.

The VAS has shown convergent validity with good correlation to the numerical rating scale (NRS) and visual response scale (VRS), content validity, and test-retest reliability.^{114,116} Additionally, a recent systematic review by the HOME group found that, of 289 AD RCTs in which itch was assessed, the VAS was the most commonly used measure to assess itch in 220 (76%) of them. The VAS was noted to be more sensitive to change compared with the NRS and VRS; however, the VAS had the most missing data of the three during validation.¹¹⁶ Additionally, it should be noted that as a unidimensional instrument, the VAS only provides information about itch intensity; moreover, there is a dearth of information as to the best practices for VAS-itch, including assessing worst versus average itch intensity, recall period, frequency of assessment, and best time(s) to assess itch.

Numerical rating scale (NRS)—pruritus

The NRS-pruritus^{113,116} is also a unidimensional, visual instrument that allows patients to rate their itch intensity. The NRS consists of 10 visually listed numbers ranging from 0

(“no itch”) to 10 (“worst imaginable itch”) consecutively, and patients choose the number that describes the intensity of their itch. The NRS has been well validated for rating pruritus,^{115,116} as well as pain.¹²² We recently performed an interpretability study and found that the previously reported optimal bands for VAS-itch as listed below were also optimal for NRS-itch⁹³: 0-3 = mild, 4-6 = moderate, 7-10 = severe.

One study determined that a decrease of 2-3 points should constitute an MCID for clinical itch improvement in NRS, similar to the VAS.^{115,120} The NRS has shown convergent validity, with good correlation to the VAS and VRS, and test-retest reliability; it has also been shown that there are less missing data for the NRS compared with the VAS, and that patients indicated preference for the NRS over the VAS.^{115,116} The mentioned systematic review by the HOME group found that, of 289 AD RCTs in which itch was assessed, the NRS, along with the VRS, was the second most commonly used measure to assess itch in 81 (28%) trials; however, the NRS is also a unidimensional instrument and only provides information about itch intensity. Additionally, NRS scores were found to be significantly higher than corresponding VAS scores, and so the scores may not be reliably used interchangeably.^{114,115}

Verbal rating scale (VRS)—pruritus

The VRS-pruritus^{113,116} is also a unidimensional instrument where patients verbally rate the intensity of their itch. The VRS has scoring system variability, as a four-point scale¹¹⁶ (none, mild, moderate, and severe pruritus) and a five-point scale¹¹⁴ (none, mild, moderate, severe, and very severe pruritus) have both been used and validated. The VRS has been well validated and has shown convergent validity, with good correlation to the VAS and NRS, and test-retest reliability.^{114,116} It has also been shown that there are less missing data for the VRS compared with the VAS.¹¹⁴ As mentioned, the VRS, along with the NRS, was found to be the second most commonly used measure to assess itch in 81 (28%) of 289 AD RCTs; however, the VRS also provides information only about itch intensity. Additionally, the scoring system variability limits comparisons between studies, and the limited number of response options can also increase variability and limit sensitivity to change.¹¹⁶

ItchyQOL

ItchyQOL,¹²³ developed in 2008, is the first pruritus-specific QOL instrument and can compare QOL in patients with pruritus of any disease. The ItchyQOL is a 22-item questionnaire comprising the following domains: clinical manifestations, functional limitations, and emotions.

The responses for each item range from 1 (best) to 5 (worst), and the overall score is the average of all the responses. An anchor-based banding system was recently developed based on the cumulative score, rather than the average

score, that was meant to supplement the validated average scoring system.¹²⁴ This banding system is as follows: 0-30 (little), 31-50 (mild), 51-80 (moderate), 81-110 (severe).

In our interpretability study, we found the following banding to have the best correlation with disease severity in patients with AD⁹³: 0-36 = mild, 37-54 = moderate, 55-110 = severe.

The ItchyQOL has shown construct validity, internal consistency, test-retest reliability, responsiveness, and discriminant validity.¹²³ English and German versions exist; however, versions in more than 10 additional languages are being developed. The questionnaire takes approximately 5-10 minutes to complete and has not been as extensively validated due to its recent introduction. Some of the items may be difficult for patients to interpret.

5-D Itch Scale

The 5-D itch scale, developed in 2008, is a multidimensional, pruritus-specific questionnaire that measures the long-term course of a patient's pruritus. The questionnaire was designed to be brief, easy to complete, easy to score, to assess the multidimensional nature of pruritus, to assess QOL, to be effective in multiple disease states, and to detect change over time. It comprises five questions assessing the following itch-related domains: Duration, degree, direction (of symptom change), disability, and distribution (areas involved).

The first three domains (duration, degree, and direction) are scored on a five-point scale (1-5). The score of the disability domain, consisting of four items, is achieved by taking the highest individual score of the four items. The score of the distribution domain, consisting of 16 potential locations, is scored as follows: 0-2 = score of 1, 3-5 = score of 2, 6-10 = score of 3, 11-13 = score of 4, 14-16 = score of 5.

The sum of the score of the five domains is calculated and thus the overall score ranges from 5 (best) to 25 (worst). Although there is no banding set forth by the authors, a recent study explored optimal cut-offs for the 5-D itch scale in a study of chronic hemodialysis patients based on NRS categories.¹²⁵ This proposed banding includes the following: ≤ 8 = NRS score of 0, 9-11 = mild pruritus, 12-17 = moderate pruritus, 18-21 = severe pruritus, ≥ 22 = very severe pruritus.

Our interpretability study found the optimal banding in AD patients to be⁹³ 0-11 = mild, 12-17 = moderate, and 18-25 = severe.

The 5-D itch scale has been shown to have convergent validity, test-retest reliability, and sensitivity to change, and also takes <5 minutes to complete.¹²⁶

Itch Severity Scale (ISS)

The ISS,¹²⁷ developed in 2007, attempts to quantify pruritus severity and the associated burden. The ISS is a pruritus-specific 7-item questionnaire. The sum of each question is calculated, divided by the highest possible score, and multiplied by 3; thus scores can range from 0 (best) to 21 (worst). The creators

determined an MCID of approximately 2 points. The ISS has been shown to be a reliable and valid measure of pruritus severity, correlates strongly with the DLQI, and has shown internal consistency and test-retest reliability. Limitations of the ISS include questionable responsiveness to change and a potential lack of generalizability.¹²⁷

AD-specific instruments

Dermatitis Family Impact (DFI)

The DFI,^{128,129} developed in 1998, assesses the extent of how a child with AD affects the QOL of the child's family. The DFI is a 10-item questionnaire, and with each item scored from 0 to 3, the total score can range from 0 (best) to 30 (worst). The questionnaire is to be completed by a parent or caregiver of the child. The domains assessed include housework, food preparation and feeding, sleep, family leisure activity, shopping, expenditure, fatigue, emotional distress, and relationships.

The DFI, which takes approximately 2 minutes to complete, has been well validated and has been shown to have high test-retest reliability, internal consistency, sensitivity to change, and convergent validity.^{128,130–132} Many studies have also shown the DFI to correlate well with AD severity.^{106,128,130,133} Additionally, one review found the DFI to be the second most common QOL measure used in AD randomized controlled trials (RCTs).¹³⁴

Infant's Dermatitis Quality of Life (IDQoL) Index

The IDQoL,^{135,136} developed in 2001, assesses QOL in infants aged ≤ 4 years suffering from AD. The IDQoL, a 10-item questionnaire completed by the parents, assesses the following domains for the infant/child: Clinical manifestations, difficulties with mood, difficulties with sleep, difficulties with bathing, difficulties with dressing, difficulties with play, difficulties with mealtimes, difficulties with other family activities, and difficulties with treatment.

With each item scored from 0 to 3, the total score can range from 0 (best) to 30 (worst). Of note, there is an additional question scored separately that measures the parents' assessment of the infant's/child's AD severity. The IDQoL has been well validated, takes approximately 2 minutes to complete, and has shown test-retest reliability and sensitivity to change.^{128,136,137} The mentioned review also found the IDQoL to be the fourth-most commonly used scale in AD RCTs; however, there are limited studies assessing its correlation with AD severity.¹³⁸

Childhood Atopic Dermatitis Impact Scale (CADIS)

The CADIS,^{15,139} developed in 2005, was developed primarily to measure the emotional effects of AD on young

children < 6 years of age and their parents. The creators believed that many of the existing questionnaires did not adequately assess the emotional effects of AD. They had originally performed a qualitative study of parents of children affected by AD in 2004, and found that parents' emotions was one of the most common areas of response. The CADIS is a 45-item questionnaire (reduced from an original 62 items) with each item scored on 0–4 scale; thus scores range from 0 to 180. The questionnaire covers five domains: Child clinical manifestations, child activity limitations and behavior, family and social function, parent sleep, and parent emotions.

The CADIS has been shown to have responsiveness, high internal consistency, content validity, construct validity, test-retest reliability, concurrent validity, and discriminative validity.^{139,140} Additionally, the CADIS has been found to correlate with SCORAD and treatment response in AD patients.¹⁴⁰ One of the limitations is that the questionnaire takes approximately 6 minutes to complete¹³⁹; however, a shorter version was recently validated in an Italian study.¹⁴¹

Quality of Life Index for Atopic Dermatitis (QoLIAD)

The QoLIAD,¹⁴² developed in 2004, is a 25-item questionnaire to be used in adults with AD that was developed using a needs-based model approach. This model's premise is that QOL is related more so to whether the needs of an individual are being interfered with rather than actual impairment in ability or function. The creators believed that this approach would better measure overall disease impact compared with other questionnaires that focus more on HRQOL, which is the actual capacity to perform such daily activities. The items are scored on a two-point response system (true/not true); thus, scores can range from 0 (best) to 25 (worst). The questionnaire takes < 5 minutes to complete and has shown test-retest reliability, internal consistency, and construct validity. Additionally, it has been found to correlate with AD severity and flares¹⁴²; however, it has not yet been well validated outside of the original study. Of note, the creators state that the QoLIAD should be used in conjunction with the DLQI, as the DLQI assesses everyday function, whereas the QoLIAD assesses the impact of such impairments.¹⁴²

Parents Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)

The PIQoL-AD,^{143,144} developed in 2004, was also developed using a needs-based model approach. The PIQoL-AD is a 28-item questionnaire that assesses the QOL of parents or caregivers of children ≤ 8 years old with AD. The items follow a two-point response system (true/not true), and thus scores can range from 0 (best) to 28 (worst). Using a combination of anchor-based and distribution-based approaches, it was determined that a change in PIQoL-AD score of 2–3 points is considered meaningful. The questionnaire takes approximately 4–5 minutes to complete and has shown test-retest

reliability, internal consistency, construct validity, and promising responsiveness. It correlates with disease flares and treatment response in the child's AD. There is questionable correlation with the child's AD severity.¹⁴⁴ Additionally, the trials only included patients with moderate and moderate-to-severe AD, and so generalization to parents or caregivers of severe or very severe AD patients may be limited.^{145,146} Because the PIQoL-AD assesses the QOL of the parents or caregivers, the creators also state that the PIQoL-AD should be used in conjunction with other instruments that measure the QOL on the children involved, either the IDQoL or CDLQI.¹⁴⁴

Patient-Oriented Eczema Measure (POEM)

The POEM,¹⁴⁷ developed in 2004, was designed as a PRO to measure frequency of AD activity. The creators believed that this would provide a more holistic assessment of the patient's disease and treatment response. The POEM is a 7-item questionnaire that assesses the frequency of symptom occurrence. Each item is scored on a 5-point scale (0-4), and thus the overall score ranges from 0 (best) to 28 (worst). The MCID for POEM has been stated by two key studies to be 3.4, and approximately 3 in young children. The creators also proposed an anchor-based banding system in 2013 for POEM scores as follows¹⁴⁸: 0-2 = clear/almost clear, 3-7 = mild, 8-16 = moderate, 17-24 = severe, 25-28 = very severe.

We recently performed an interpretability study and confirmed these strata for mild, moderate, and severe classifications in patients with AD.⁹³ The questionnaire has been well validated and shown to have construct validity, convergent validity, divergent validity, internal consistency, sensitivity to change, and test-retest reliability.^{18,147} Additionally, the questionnaire, which takes 1-2 minutes to complete, has been shown to have good correlation with the DLQI and CDLQI instruments.¹⁴⁷ A systematic review assessing AD outcome measure also deemed POEM to be one of the few recommended outcome measurements for AD due to its validation and domain coverage. Of note, POEM was chosen by the HOME group at the fourth international consensus meeting as the preferred core instrument to consistently assess the core domain of clinical manifestations and patient-reported clinical manifestations in future AD trials.^{5,149}

Self-Administered Eczema Area and Severity Index (SA-EASI)

The SA-EASI,¹⁵⁰ developed in 2002, was designed for the caregiver of a child with AD to provide a self-assessment of the child's AD severity. The creators believed that a child's caregiver could accurately assess the child's AD severity with no training. The SA-EASI, consisting of two parts, is structured similar to the Eczema Area and Severity Index (EASI) tool and thus allows for comparisons between the patient's and doctor's evaluations. In the first part, the caregiver estimates the body surface area (BSA) involved using a line-

drawing body silhouette. A proportional score is assigned based on the BSA involved, and this score is multiplied by a multiplier that varies according to body region (weighted by age) and the child's age. The second part consists of five 100-mm-VAS where the caregiver assesses the redness, thickness, dryness, number of scratches, and itchiness of the child's average AD lesion. Using complex equations (described in original article¹⁵⁰), acute and chronic SA-EASI scores are calculated from the first and second parts. The questionnaire has been found to correlate with EASI, AD severity, and BSA involvement; however, there are limitations to the SA-EASI. Poor correlation was found between the VAS ratings of the SA-EASI and the corresponding components of EASI. Correlation with disease severity also varied by sex in the original validation study.¹⁵⁰ Another study found poor correlation between the SA-EASI and parents' perception of severity. Additionally, there are limited data on validation, reliability, and responsiveness.

Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD)

The PO-SCORAD,^{151,152} developed in 2009, was designed for patients with AD to self-assess their AD using subjective and objective criteria. The creators believed that self-assessment could potentially provide for better AD monitoring. The PO-SCORAD is derived from the validated SCORAD assessment,^{153,154} and thus allows for comparisons between the patient's and doctor's evaluations. The PO-SCORAD assesses BSA affected, intensity of AD clinical manifestations (dryness, redness, swelling, oozing/scabs, scratch marks, thickness of skin) rated from 0 to 3, and two 100 mm-VAS assessing itching and trouble sleeping.^{151,152} The questionnaire has been validated, found to correlate with SCORAD in adult and children, and has shown internal consistency.¹⁵³ Additionally, the PO-SCORAD has been found to be one of the best measures to correlate with QOL scales, as it was found to correlate well with the POEM, SCORAD, and DLQI instruments.¹⁰¹ There are limited data on validation due to its recent development.

Discussion

There are numerous instruments that cover a wide variety of domains. In the context of AD, PRO and QOL can be measured with generic HRQOL instruments (applicable in a broad spectrum of conditions), dermatology-specific instruments (applicable in all skin diseases), pruritus-specific instruments (assessing the main symptom of AD), and AD-specific instruments. General health-related instruments are effective in assessing overall global health and providing a broad, "big picture" view of a patient's health. Additionally, they allow comparisons of functioning between a variety of disease groups; however, they often lack in determining specific clinical

manifestations and thus understanding how to alleviate the disease burden. Of these instruments, the SF-36, PROMIS global health short form, NHP, and ED-5 Q have all shown widespread use and validation.

Dermatology-specific instruments offer the advantage of assessing numerous domains affected by a skin condition and are able to capture data from patients suffering from a wide spectrum of dermatologic disorders. The DLQI, CDLQI, and Skindex are commonly used instruments in trials and occasionally in clinical practice. The use of each instrument has been supported in the literature and they can be used to supplement AD-specific questionnaires.

Pruritus-specific instruments are helpful in the setting of AD, as itch is the hallmark of and most commonly reported symptom in AD. Adequate assessment of the harmful impact of itch may allow clinicians and researchers to better understand the true burden of AD. AD-specific instruments offer the advantage of item specificity and perhaps providing a more nuanced understanding of patient clinical manifestations and burden from AD. These instruments are valuable tools in assessing PRO and QOL, and can help guide the therapeutic approach and future research in AD. Nevertheless, their scores cannot easily be compared with other disorders.

In regard to PRO, a systematic review evaluating AD RCT from 1994 to 2001 found that 80/93 (86%) of trials reported at least one patient-reported symptom. A systematic review evaluating reporting of clinical manifestations in AD RCT from 2000 to 2014 found that 295/378 (78%) of trials used outcome measures that included clinical manifestations of AD via 30 different instruments; however, of the 295, only 109 (37%) measured clinical manifestations as stand-alone outcomes. Itch was the most commonly assessed symptom (289/295, 98%) either by itself or as part of a composite instrument (such as SCORAD), and 17 total different clinical manifestations were measured. The most commonly used measure in RCT was VAS-itch (76%), followed by NRS-itch and VRS-itch (28%). Comparing these two systematic reviews shows that symptom reporting in AD studies (86% versus 76%) is still incomplete and heterogeneous, and needs further focus. Additionally, the low proportion of RCT measuring clinical manifestations as stand-alone outcomes warrants improvement.

The HOME consensus group performed a systematic review to identify preferred PRO to be included in a core outcomes set in all AD RCT.⁷ The researchers found that, of 18 PRO, only 5 (the ISS, POEM, PO-SCORAD, SA-EASI, and adapted SA-EASI) had sufficient validation data and the potential to be recommended as an instrument to measure clinical manifestations in future RCT. At the HOME IV meeting, the researchers deliberated between the POEM, PO-SCORAD, and SA-EASI as the preferred PRO for clinical manifestations.⁵ A consensus was reached that POEM should be the preferred instrument to measure patient-reported clinical manifestations and should be recommended for inclusion in the core outcome set in AD RCT.

Use of QOL instruments in AD trials is also lacking and may be even worse than the use of PRO for clinical manifestations. A

systematic review found that of 303 AD trials, approximately 90% included at least one PRO; however, only 63 (21%) assessed QOL using 22 different instruments. A systematic review assessing health outcome measures in 382 AD RCT from 1985 to 2010 found that only 67 (18%) used QOL instruments. Additionally, a systematic review assessed the QOL instruments used in 135 AD RCT from 2010 to 2015 and found that only 45 (33%) used a QOL measure and only 15 (11%) used multiple QOL measures. Twenty-eight different QOL measures were used, indicating the variability in QOL instrument usage. This systematic review highlights the low usage of QOL measures in recent AD RCT, but also shows a promising upward trend in the use of QOL measures in RCT from 1985-2010 to 2010-2015 (18% versus 33%).

Both systematic reviews found that the most frequently used QOL instruments were CDLQI, DFI, DLQI, and IDQOL. Of note, most of the trials were in pediatric cohorts and used QOL assessments specific for children, such as CDLQI, DFI, and IDQOL. There are even fewer RCT in adults that incorporated QOL instruments. The HOME group deemed that no pediatric or adult QOL instruments met their criteria for recommendation to be included in AD RCT,^{9,10} but that the CADIS in children¹⁰ and QoLIAD and DLQI in adults⁹ have the potential to be recommended based on further validation studies. At this time, no QOL instrument is currently recommended for a core outcomes set; however, any QOL instrument used in AD RCT should be valid, reliable, and feasible for use in AD patients.⁵

As concluded by the HOME group, the CADIS in children and the QoLIAD in adults correlate well with AD severity and treatment response. In the clinical setting, these could provide important information for clinicians when trying to optimize AD therapy; however, a limitation of these two instruments is the respondent burden of approximately 5 minutes each. In situations where respondent burden or completion time is a significant influencing factor, the DLQI and CDLQI may serve as better assessments of QOL while still assessing domains affected by dermatologic conditions. An obvious limitation of the DLQI and CDLQI is a lack of AD-specific questions that may hamper a clinician's assessment of patients' AD. Further validation work of the CADIS, QoLIAD, and IDQoL should give a better representation of their feasibility and correlation with treatment response.

Conclusions

Many instruments are available to assess PRO and QOL, each with their strengths and weaknesses. Although the incorporation of PRO and QOL measures in AD RCT has been fairly poor, there is growing awareness and interest in remediating this. POEM has emerged as a preferred measure of AD clinical manifestations, but there is still no preferred QOL outcome. Further research and validation of PRO and QOL instruments is needed for patients with AD.

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