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TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries*

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Summary

Background Comparative, real-life and long-term evidence on the effectiveness and safety of phototherapy and systemic therapy in moderate-to-severe atopic eczema (AE) is limited. Such data must come from well-designed prospective patient registries. Standardization of data collection is needed for direct comparisons and data pooling.
Objectives To reach a consensus on how and when to measure the previously defined domain items of the TREatment of ATopic eczema (TREAT) Registry Taskforce core dataset for research registries for paediatric and adult patients with AE.
Methods Proposals for the measurement instruments were based on recommendations of the Harmonising Outcome Measures for Eczema (HOME) initiative, the existing AE database of TREATgermany, systematic reviews of the literature and expert opinions. The proposals were discussed at three face-to-face consensus meetings, one teleconference and via e-mail. The frequency of follow-up visits was determined by an expert survey.
Results A total of 16 experts from seven countries participated in the 'how to measure' consensus process and 12 external experts were consulted. A consensus was reached for all domain items on how they should be measured by assigning measurement instruments. A minimum follow-up frequency of initially 4 weeks after commencing treatment, then every 3 months while on treatment and every 6 months while off treatment was defined.
Conclusions This core dataset for national AE research registries will aid in the comparability and pooling of data across centres and country borders, and enables international collaboration to assess the long-term effectiveness and safety of phototherapy and systemic therapy used in patients with AE.

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Conflicts of interest:
Conflicts of interest statements can be found in the Appendix.

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What's already known about this topic?

- Comparable, real-life and long-term data on the effectiveness and safety of phototherapy and systemic therapy in patients with atopic eczema (AE) are needed.
- There is a high diversity of outcomes and instruments used in AE research, which require harmonization to enhance comparability and allow data pooling.

What does this study add?

- Our taskforce has reached international consensus on how and when to measure core domain items for national AE research registries.
- This core dataset is now available for use by researchers worldwide and will aid in the collection of unified data.

What are the clinical implications of this work?

- The data collected through this core dataset will help to gain better insights into the long-term effectiveness and safety of phototherapy and systemic therapy in AE and will provide important information for clinical practice.
- Standardization of such data collection at the national level will also allow direct data comparisons and pooling across country borders (e.g. in the analysis of treatment-related adverse events that require large patient numbers).

A significant number of paediatric and adult patients with moderate-to-severe atopic eczema (AE) may require phototherapy or systemic immunomodulatory therapy at some point during their life. For adults, ciclosporin, and recently dupilumab, are currently the only systemic therapies that are approved by the European Medicines Agency,[1,2] while only dupilumab has been approved by the U.S. Food and Drug Administration.[3] For children, there are no approved systemic therapies, although our European and North American treatment surveys show that they are regularly prescribed.[4,5] While there is some evidence on the short-term effectiveness of phototherapy and systemic immunomodulatory therapy, there is a clear lack of head-to-head comparison trials and a paucity of data on the long-term effectiveness and safety of such treatments.[6,7] As randomized controlled trials have very strict inclusion criteria, important subgroups of patients (e.g. those with comorbidities) are commonly excluded and therefore evidence in real-life populations is missing. All of this requires data collection from well-defined patient cohorts.[8–10]

To harmonize data collection for such observational cohorts, the TREatment of ATopic eczema (TREAT) Registry Taskforce initiated a consensus exercise to develop a core set of domains and domain items for AE treatment research registries. After an international Delphi study and consensus meeting, the core dataset ('what to measure') was agreed on, consisting of 19 domains with 69 corresponding domain items (49 at baseline and 20 at follow-up).[11,12]

As the next step in this consensus-finding process, we performed a consensus exercise to define how and when to measure the core domain items to harmonize data collection fully within national AE treatment research registries and prevent heterogeneity.[13,14]

Patients and methods

Study design

To establish a core set of measurement instruments ('how to measure'), three face-to-face expert consensus meetings, one teleconference and final discussions via e-mail were arranged. For this process we used the following sources to guide decision making: (i) recommendations from the Harmonising Outcome Measures for Eczema (HOME) initiative were used where possible (e.g. regarding the capture of clinical signs, patient-reported outcomes and quality of life);[15–17] (ii) relevant literature, in particular systematic reviews considering measurement instruments in AE;[7,13,14,18–20] (iii) the existing AE database of TREATgermany,[21] which already included over 100 patients at the start of this study; (iv) personal communications with experts in the field of measurement instruments for specific domain items [e.g. K. McElhone (British Association of Dermatologists Biologics and Immunomodulators Register; BADBIR), personal communication]; and (v) the current use of measurement instruments in clinical practice and clinical expertise of the participants. During all meetings, feasibility and current common practice were kept in mind.

All meetings were chaired by either P.I.S. or C.F. During each session, the evidence for each suggested measurement

instrument was presented in the form of a PowerPoint presentation and written handouts, followed by whole group discussions. These discussions were iterative and continued until full consensus was achieved. Voting was done by a show of hands and was therefore not anonymous. Whenever possible, validated measurement instruments were selected. If multiple validated instruments were available, decisions were based on (in order of importance): (i) HOME recommendations; (ii) quality of the validation studies; and (iii) the feasibility and, in particular, the potential to be used in different countries, and the number of available translations of the measurement instrument. In case the consensus on domain items could not be reached immediately during the meetings (e.g. due to a lack of evidence), items were assigned to participating TREAT members for further investigation, taking into account their areas of expertise. These items were then rediscussed at the next consensus meeting. The three face-to-face consensus meetings were audiorecorded for reference at the next meetings.

To define when the domain items should be measured ('when to measure'), in September 2017 we conducted an online survey among all participants using SurveyMonkey software. Options put to the vote were based on current clinical practice (Fig. S1; see Supporting Information). The results of the survey were discussed and approved in a small group via e-mail.

Participants

The participants were physicians, patients and nonclinical researchers (i.e. health economists, epidemiologists/methodologists) from the TREAT Registry Taskforce with an interest in AE and/or AE measurement instruments. We also consulted external experts through personal communications (mostly e-mail) from, for example, the Coronel Institute of Occupational Health and the Medical Psychology Department of the Academic Medical Centre in Amsterdam for items considering work and health, and items considering treatment adherence.

Definition of consensus

Consensus was predefined both for the 'how to measure' and for the 'when to measure'. Consensus for the 'how to measure' was achieved when 100% of the participants present during the consensus meeting agreed on the measurement instrument. Consensus on the follow-up frequency and the visit window ('when to measure') was achieved when the majority of the participants voted for one of the options.

Results

How to measure

In March, May and June 2017 four consensus meetings were held. The first was done by teleconference and the other three were by face-to-face meetings in London, Amsterdam and Nantes. A total of 16 participants met, all members of the TREAT Registry Taskforce, including 11 academic dermatologists, one dermatology resident, one dermatology PhD student, one patient/patient representative, one epidemiologist/methodologist, and one health economist (Fig. S2; see Supporting Information). A total of 12 experts were consulted for specific items.

During the face-to-face meetings, slight alterations were made to the 'what to measure' core dataset. To make the core dataset as feasible as possible some domain items were merged with others. The items 'medical history', 'follow-up (FU) safety bloods', 'adverse events that cause stop or switch of therapy or change in dosage' and 'probability of relationship with treatment' are now captured as part of the other items (for details see Table 1). Additionally, the items 'other significant illnesses' and 'other medication relevant for AE treatment response' were added as they were not previously captured in the 'what to measure' core dataset. After these alterations, the final 'what to measure' core dataset consists of 70 items (50 baseline items and 20 follow-up items; Table 1). For all items, consensus was reached on the measurement instruments.

Details on specific domain items

Ethnicity

We reviewed all ethnicity classifications that we had access to, based on a literature search, including the one used by the U.K. Biobank, the German National Cohort and BADBIR. The classification system shown in Table 1 was made (based on all these reviewed classification systems) and was selected because this system allows patients and physicians to choose from an extensive list of ethnicities. The option to select and specify two ethnicities is given as well. To capture migration, country of birth of patient and parents were also added.

Educational status

Educational status is an important predictor of health and disease.[22] For this item, the International Standard Classification of Education (ISCED) system was chosen. The ISCED has, for instance, been adopted by the United Nations Educational, Scientific and Cultural Organization General Conference and consists of definitions that have been agreed on internationally. Further, it facilitates the comparison of education systems from different countries. The group agreed that each country would translate this classification to its national educational classification.

It was decided to record the highest completed educational level (from the parent or child in case of a child or from the patient themselves if an adult).

Use of validated diagnostic criteria

Both the quality of the gathered data and the feasibility of the registry were considered. Many lists of diagnostic criteria for

Table 1 Core dataset of domains, domain items and measurement instruments to be captured in national atopic eczema treatment registries

Domains	Domain items	How to measure	Comments
Demographics	Date of birth	1. Date	
	Date of enrolment into registry	2. Date	
	Gender	1. Male, female, other	
	Ethnicity	1. Country of birth of patient and parents 2. Ethnicity of patient (possibility to select two options): White (Europe, Russia, Middle East, North Africa, U.S.A., Canada, Australia), Black-African, Afro Caribbean, African American, Asian-Chinese, South Asian (India, Pakistan, Sri Lanka, Nepal, Bhutan, Bangladesh), Asian—other (Korea, China north of Huai River), Japanese, Hispanic or Latino, mixed—please specify, other—please specify	
	Educational status	1. ISCED classification (for both adults and children): ISCED 0: Early childhood education ISCED 1: Primary education ISCED 2: Lower secondary education ISCED 3: Upper secondary education ISCED 4: Post-secondary non-tertiary education ISCED 5: Short-cycle tertiary education ISCED 6: Bachelor's or equivalent level ISCED 7: Master's or equivalent level ISCED 8: Doctoral or equivalent level	This item will be assessed repeatedly Use the highest completed education level; from child or parents if a child or from the patient themselves if adult Will have to be translated for each country to its national educational classification
	Current occupation or education	1. Eurostat classifications 1–8: 1. employed, 2. self-employed, 3. disability pension (unable to work), 4. retired, 5. student or pupil, 6. engaged on home duties, 7. unemployed, 8. other—please specify	This item will be assessed repeatedly
AE diagnosis	How diagnosis AE is established	1. Clinically Y/N 2. Histopathology Y/N	
	Use of validated diagnostic criteria	1. Physician diagnosis alone, Hanifin & Rajka Criteria, U.K. Working Party Diagnostic Criteria, AAD/Eichenfield Criteria, Refined Millennium Criteria, Schultz-Larsen Criteria, Kang and Tian Criteria, Diepgen Criteria, Danish Allergen Research Centre Criteria, Saeki's JDA Criteria	Each country can decide which of these criteria they want to give as options
	Date of onset AE	1. Year	
Past AE treatments	Phototherapy	1. Y/N 2. NB-UVB, BB-UVB, UVB (unspecified), UVA, UVA1, UVAB, PUVA (oral or other), other (possibility to select multiple options) 3. How many courses (numerical), cumulative dose (J/cm^{-2}) (optional), when (start year) (optional), number of treatments within a course (numerical) (optional), outcome: a. effect (excellent (clearance), good, moderate, poor), b. reason to stop (insufficient response, loss of treatment response (after initial good response), side-effects, cumulative dose, disease remission, other) (select one option), c. adverse event (Y/N)	UVB (unspecified) if type is unknown This is only medical history. If (also) current it should be recorded under 'current AE treatments'

(continued)

Table 1 (continued)

Domains	Domain items	How to measure	Comments
	Systemic therapy	1. Y/N 2. Ciclosporin, azathioprine, methotrexate, mycophenolate acid, systemic corticosteroids, dupilumab, omalizumab, other—please specify, investigational medication—please specify (possibility to select multiple options) 3. How many courses (numerical), when (start month + year) (optional), duration (free text), average treatment (maintenance) dose (optional), outcome: a. effect (excellent (clearance), good, moderate, poor), b. reason to stop (insufficient response, loss of treatment response (after initial good response), side-effects, cumulative dose, disease remission, other), c. adverse event (Y/N)	With definitions for average treatment (maintenance) dose (Fig. S4; see Supporting Information) This is only medical history. If (also) current it should be recorded under 'current AE treatments'
	Topical treatments for AE	1. Y/N 2. Corticosteroids, calcineurin inhibitors, tar ointments, crisaborole, other (possibility to select multiple options)	Only to be registered for the past year This is only medical history. If (also) current it should be recorded under 'current AE treatments'
	Day hospital care treatments for AE (outpatient)	1. Y/N 2. Duration (cumulative treatment days)	Only to be registered for the past year This is only medical history. If (also) current it should be recorded under 'current AE treatments'
	Hospitalization for AE	1. Y/N 2. Duration (cumulative days)	Only to be registered for the past year This is only medical history. If (also) current it should be recorded under 'current AE treatments'
Current AE treatments	Phototherapy	1. Y/N 2. NB-UVB, BB-UVB, UVA, UVA1, UVAB, PUVA (oral or other), other 3. Start date, cumulative dose (J/cm^{-2}), stop date	
	Systemic therapy	1. Y/N 2. Ciclosporin, azathioprine, methotrexate, mycophenolate acid, systemic corticosteroids, dupilumab, omalizumab, other—please specify, investigational medication—please specify (possibility to select multiple options) 3. Start date, start dose, current dose, stop date	With definitions for average treatment (maintenance) dose (Fig. S4; see Supporting Information)
	Topical treatments	1. Y/N 2. Corticosteroids, calcineurin inhibitors, tar ointments, crisaborole, other (possibility to select multiple options) 3. Classification of steroids and calcineurin inhibitors (optional) 4. Frequency ('how many times a week do you use it?') (optional)	If classification is registered use the national official potency classification
	Amount of topical creams/ointments used per week (g)	1. <30, 30–60, 60–100, >100	This is exclusive additive-free, bland emollients
Family history of AE or allergic diseases	Family history of AE or allergic diseases	1. Y/N 2. Atopic eczema, asthma, allergic rhinoconjunctivitis, atopic eye disease, eosinophilic oesophagitis, other (possibility to select multiple options)	Y if first-degree relative (parents or children) According to the patient or physician-diagnosed

(continued)

Table 1 (continued)

Domains	Domain items	How to measure	Comments
Allergic comorbidities	Asthma	1. Physician diagnosed Y/N	
	Allergic rhinoconjunctivitis	1. Physician diagnosed Y/N	
	Atopic eye disease	1. Physician diagnosed Y/N	
	Eosinophilic oesophagitis	1. Physician diagnosed Y/N	
	Food allergies	1. Do you have a food allergy currently? Y/N 2. If yes, is at least one food allergy diagnosed by a doctor? Y/N 3. If yes, how was this diagnosis made? Double-blind placebo-controlled oral food challenge, open food challenge, skin prick tests, scratch tests, positive food allergen-specific IgE test, other (e.g. atopy patch test), unknown	
	Contact allergies	1. Have you ever been tested for contact allergies with patch tests? Y/N, unknown 2. If yes, what was the outcome? Positive, negative, unknown	
Other past and current comorbidities	Malignancies	1. Y/N 2. When (year) 3. Type of malignancy (free text) 4. Active, remission, relapsed	MedDRA categories will be used for this item as much as possible
	Serious infections	1. Y/N 2. When (year) 3. Type of infection (free text) 4. Active, latent, resolved (cured)	MedDRA categories will be used for this item as much as possible Includes 'medical history' (tuberculosis, HIV, hepatitis B or C); original item of domain baseline assessments
	Other significant illnesses	1. Y/N 2. When (year) 3. Type of illness (free text) 4. Active, remission, resolved (cured), relapsed	MedDRA categories will be used for this item as much as possible
Current concomitant medication (i.e. other than specific AE medication)	Antihistamines	1. Y/N 2. Oral, topical	
	Antibiotics	1. Y/N 2. Oral, topical	
	Other medication relevant for AE treatment response	1. Y/N 2. Which (free text)	Includes 'immunotherapy' Relevant according to judgement of treating physician
	Immunosuppressives for other inflammatory diseases	1. Y/N 2. Which (free text) 3. Indication: inflammatory bowel disease, rheumatoid arthritis, other—please specify 4. Start date, stop date 5. Current dose (free text)	
Baseline general AE questions	Exposures that trigger disease flares	1. Y/N 2. Stress, infection, weather conditions, sweating/exercise, exposure to aero-allergens, other (possibility to select multiple options)	
	Episodes of skin infection	1. Y/N 2. Bacterial skin infection (folliculitis, impetigo, etc.), viral skin infection (HSV infection, molluscum contagiosum, etc.) (possibility to select multiple options)	

(continued)

Table 1 (continued)

Domains	Domain items	How to measure	Comments
	Days lost from usual activities (e.g. work, study)	1. Y/N 2. Days per month (free text)	Average number of days in the past 3 months
Baseline physical examination	Fitzpatrick skin type	1. I, II, III, IV, V, VI	
	Skin examination	1. Flexural eczema: select involved areas (individual patches have to be ≥ 1 cm): skin folds around the eye(s), neck (front), flexures of the arm(s), flexures of the leg(s), front of ankle(s), not applicable 2. Non-flexural eczema: select involved areas (individual patches have to be ≥ 2 cm and, excluding the face, on both sides): face, extensor of elbows, arms, extensor of knees, legs, hands, not applicable 3. Presence of (Y/N): (history of) pompholyx, discoid eczema, nodular prurigo, follicular eczema, ichthyosis, keratosis pilaris, palmar hyperlinearity, erythroderma, skin infection (if Y: bacterial/viral/fungal, sample taken Y/N)	For definitions on these phenotypical and morphological characteristics see Figure S3 (see Supporting Information)
Baseline physician- and patient-reported domains	Physician-assessed clinical signs	1. EASI 2. SCORAD (optional)	Objective or full SCORAD. If the full SCORAD is used, the objective and subjective SCORAD need to be reported separately
	Investigator/physician global assessment	1. vIGA-AD™ scale (five-point)	
	Patient-reported symptoms	1. POEM 2. Peak pruritus NRS (0–10) past 24 h 3. Peak VAS pain (0–10) past 24 h (optional)	
	Patient global assessment	1. Patient Global Assessment five-point	
	Generic quality of life score	1. EQ-5D (version 5L and Y)	Adults EQ-5D-5L; children EQ-5D-Y; caregivers (proxies) EQ-5D-Y and EQ-5D-5L Awaiting the index score for the EQ-5D-Y
	Skin-specific quality of life score	1. DLQI, CDLQI, IDQoL	DLQI > 16 years; CDLQI 4–16 years; IDQoL < 4 years
	Patient-reported satisfaction with AE care received	1. How satisfied are you with the care received for your AE since the last visit? (five-point Likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (five-point Likert scale)	The wording may change in the future if a validated measurement tool becomes available Satisfaction with care is broad and includes for instance satisfaction with treatment, physician and the hospital
	Impact of AE on the family	1. FDLQI	Needs to be filled out within the visit window (according to the patients visit) by adult family members or the partner of the patient Preferably the FDLQI is answered by the same person every time
Baseline investigations	Full blood count	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Normal/abnormal according to local standards
	Liver function	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Normal/abnormal according to local standards

(continued)

Table 1 (continued)

Domains	Domain items	How to measure	Comments
	Kidney profile	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Normal/abnormal according to local standards
	Evaluating TPMT level before azathioprine use	1. Y/N, not applicable 2. Low or absent, intermediate, normal or high	
Baseline management	Main reasons for choosing specific treatment (systemic or phototherapy)	1. Existent comorbidities and/or results of baseline investigations including abnormal laboratory results, patient age, anticipation of pregnancy and other family planning issues for both males and females, history of prior systemic therapies (incl. response), drug safety and side-effect profile, therapeutic profile: a. speed of onset, b. magnitude of effect, c. better long-term control after drug is stopped, accessibility of the treatment (including licensing), patient preferences, other (possibility to select 3 options)	
	Relative contraindication (s) for selected treatment	1. Y/N 2. Which (free text)	
Follow-up general AE questions	Days lost from usual activities	1. Y/N 2. Days per month (free text)	Average number of days since the last visit
	Change in diagnosis after enrolment	1. Y/N 2. CTCL, other	
	Date of death and relation to AE	1. Date, not applicable 2. Not related, doubtful, possible, probable, very likely, definite	
Follow-up physical examination	Skin examination	1. Flexural eczema: select involved areas (individual patches have to be ≥ 1 cm): skin folds around the eye(s), neck (front), flexures of the arm(s), flexures of the leg(s), front of ankle(s), not applicable 2. Non-flexural eczema: select involved areas (individual patches have to be ≥ 2 cm and, excluding the face, on both sides): face, extensor of elbows, arms, extensor of knees, legs, hands, not applicable 3. Presence of (Y/N): (history of) pompholyx, discoid eczema, nodular prurigo, follicular eczema, ichthyosis, keratosis pilaris, palmar hyperlinearity, erythroderma, skin infection (if Y: bacterial/viral/fungal, sample taken Y/N)	Same comment(s) as for baseline item
Follow-up physician- and patient-reported domains	Physician-assessed clinical signs	1. EASI 2. SCORAD (optional)	Same comment(s) as for baseline item
	Investigator/physician global assessment	1. vIGA-AD™ scale (five-point)	
	Patient-reported symptoms	1. POEM 2. Peak pruritus NRS scale (0–10) past 24 h 3. Peak VAS pain (0–10) past 24 h (optional)	
	Patient global assessment	1. Patient Global Assessment five-point	
	Generic quality of life score	1. EQ-5D (version 5L and Y)	Same comment(s) as for baseline item
	Skin-specific quality of life score	1. DLQI, CDLQI, IDQoL	Same comment(s) as for baseline item

(continued)

Table 1 (continued)

Domains	Domain items	How to measure	Comments
	Reporting of disease control	–	HOME results showed that for now this should be registered by repeated measurements of clinical signs, symptoms, quality of life and a patient global instrument (a specific instrument is not yet defined by HOME)
	Adherence to treatment between appointments	1. MARS (optional)	To be adjusted for AE, until then optional
	Patient-reported satisfaction with AE care received	1. How satisfied are you with the care received for your AE since the last visit? (five-point Likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (five-point Likert scale) 3. PsoSaT (optional)	PsoSat to be adjusted for AE Further comment(s) same as for baseline item
	Impact of AE on the family	1. FDLQI	Same comment(s) as for baseline item
Follow-up investigations	Full blood count	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Previously captured as 'safety bloods' Further comment(s) same as for baseline item
	Liver function	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Previously captured as 'safety bloods' Further comment(s) same as for baseline item
	Kidney profile	1. Y/N 2. Normal, abnormal 3. Clinically relevant Y/N	Previously captured as 'safety bloods' Further comment(s) same as for baseline item
Follow-up adverse events	Severe adverse events	1. Y/N 2. Diagnosis (free text) 3. In case of a serious adverse event: death, life-threatening, hospitalization or prolonged hospitalization of existing hospitalization, persistent or significant disability, congenital anomaly, important medical event that requires medical intervention, not applicable (possibility to select multiple options) 4. Relatedness: not related, doubtful, possible, probable, very likely, definite 5. Action: Stop, switch of therapy, change in dosage, not applicable	MedDRA categories will be used for this item as much as possible Severe according to judgement of treating physician
Follow-up management	Reason for switching therapy	1. Efficacy, inefficacy, adverse event(s), interaction with other medication, child wish, patient request, other, not applicable (possibility to select multiple options)	
	Reason for discontinuation of therapy	1. Efficacy, inefficacy, adverse event(s), interaction with other medication, child wish, patient request, other, not applicable (possibility to select multiple options)	

AAD, American Academy of Dermatology; AE, atopic eczema; BB-UVB, broadband ultraviolet B; CDLQI, Children's Dermatology Life Quality Index; CTCL, cutaneous T cell lymphoma; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol five-Dimensional; FDLQI, Family Dermatology Life Quality Index; HSV, herpes simplex virus; HOME, Harmonising Outcome Measures for Eczema; IDQoL, Infant's Dermatitis Quality of Life Index; ISCED, International Standard Classification of Education; JDA, Japanese Dermatological Association; MARS, Medication Adherence Report Scale; MedDRA, Medical Dictionary for Regulatory Activities; N, no; NB-UVB, narrowband ultraviolet B; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure; PsoSat, Psoriasis Satisfaction questionnaire; PUVA, psoralen and ultraviolet A; QoLIAD, Quality of Life Index for Atopic Dermatitis; SCORAD, SCORing Atopic Dermatitis; TPMT, thiopurine methyltransferase; UVA, ultraviolet A; UVAB, ultraviolet A plus ultraviolet B; UVB, ultraviolet B; VAS, visual analogue scale; vIGA-AD, Validated Investigator Global Assessment scale for Atopic Dermatitis; Y, yes.

AE are available and reviewed (e.g. the U.K. Working Party criteria, Hanifin and Rajka criteria, refined Millennium Criteria).[23] Although in clinical practice a diagnosis of AE is often made without the use of specific diagnostic criteria, nevertheless the use of validated diagnostic criteria is desirable within the context of national AE treatment research registries. During the consensus exercise, we decided to give national registries the option to decide which validated diagnostic criteria they would like to use. In addition, the option 'physician diagnosed' was added in case no diagnostic criteria were used.

Previous and current phototherapy and systemic therapy

In addition to recording the type, dose and outcome of past therapies, we also recommend to capture the number of treatment courses, the average treatment (maintenance) dose and whether adverse events associated with these treatments occurred. Where available, we also recommend recording the cumulative dose of phototherapy. It was decided to add investigational therapies to the registry (both for past and current systemic therapies), although during the initial Delphi exercise, this was voted out.

Current topical treatments

The question was whether or not to register the potency of corticosteroids as the classification differs between countries. For feasibility reasons it was therefore decided to recommend registration of the potency using the known national classification system, but this is not mandatory.

Malignancies, serious infections and other significant illnesses

While only past malignancies and past serious infections were voted in during the Delphi exercise, the knowledge of current malignancies, infections and other comorbidities provide us with important information for safety and subgroup analyses. Thus, these items were added. The item 'medical history' (tuberculosis, HIV, hepatitis B or C), which was previously voted in during the Delphi exercise, is now captured as part of the item 'past serious infections'.

Other medication relevant for an atopic eczema treatment response

Although not voted in during the 'what to measure' Delphi process, this item has been added, as such therapies (e.g. immunotherapy or aeroallergens) might need to be considered as a confounder of the response to AE treatments.

Days lost from usual activities

Some of the costs of AE are associated with decreased productivity or days lost from work.[24] Registration of the days lost from work is important to register for health technology assessment and cost-effectiveness research. However, this would bias results towards those patients in productive areas. Hence, the name of this item was changed to 'days lost from usual activities'.

Skin examination

Treatment response might be influenced by the phenotype of AE. Therefore, we suggest to document whether certain phenotypical and morphological characteristics are present. For definitions on these characteristics see Figure S3 (see Supporting Information).

Details on the physician- and patient-reported domain items

Physician-assessed clinical signs and patient-reported symptoms

For all items, HOME recommendations were followed, that is, the Eczema Area and Severity Index was selected for the item 'physician-assessed clinical signs'[15] and the Patient-Oriented Eczema Measure (POEM) was selected for the item 'patient-reported symptoms'.[16,25,26]

Patient-reported symptoms

At the fifth meeting of HOME (HOME V) it was agreed that the inclusion of intensity of itch should be investigated, as the POEM only measures frequency of itch.[17] Schoch *et al.* and Phan *et al.* found that the 11-point numerical rating scale (NRS) for itch has good reliability and validity and that recall bias increases with the recall period.[18,27] The 11-point (NRS) was therefore added to the item 'patient-reported symptoms' and after consultation with external experts it was decided to register the peak itch for the previous 24 h.[28]

Reporting of disease control

For this item, which is analogous to the long-term control domain as defined by HOME, HOME V has recommended the use of repeated measurements of the long-term control subdomains: clinical signs, symptoms, quality of life and a patient global instrument.[17]

Investigator/Physician Global Assessment

Futamura *et al.* concluded that global assessments are often used in AE research but comparisons are hard because there are no standardized definitions.[29] Therefore, the International Eczema Council and Eli Lilly and Company have worked on a validated five-point Investigator Global Assessment (IGA) scale, which was incorporated in to the core dataset for this item.[30,31]

Patient global assessment

Little research has been done towards the patient global assessment (PGA). This subdomain of the long-term control domain has been discussed during HOME V, but as yet stays undefined.[17] However, as we decided to use the five-point IGA

scale, the five-point PGA for the item 'patient global assessment' was chosen.

Skin-specific quality-of-life score

For this item, during the HOME IV (adults) and HOME V (children) meetings it was concluded that there is currently no measurement instrument that can be recommended.[16,17,19,20] Considering feasibility and the most commonly used instruments, it was decided to use the Dermatology Life Quality Index (DLQI), the Children's DLQI (CDLQI) and the Infants' Dermatitis Quality of Life Index (IDQoL). Further validation work on the DLQI was recently published by Patel *et al.*[32]

Generic quality-of-life score

Feasibility, access to different languages and the high degree of usage were the main reasons to choose the EQ-5D-5L (adults) and the EQ-5D-Y (children) as the preferred measurement instruments for this item.

Patient-reported satisfaction with atopic eczema care received, impact of atopic eczema on the family and adherence to treatment between appointments

We recommend the use of an adapted Psoriasis Satisfaction questionnaire (PsoSat), a questionnaire that measures the treatment satisfaction in patients with psoriasis,[33] the Family Dermatology Life Quality Index[34] and the Medication Adherence Report Scale (MARS), which was originally developed for the adherence with oral medication in asthma but can be easily adapted for patients with AE.[35] The MARS will be optional until it is validated for AE.

When to measure

Thirteen of 16 participants (81%) completed the survey. Eight of 13 (62%) voted for a minimum follow-up frequency of every 3 months while on therapy; seven of 13 participants (54%) voted for an extra visit 4 weeks after baseline. Seven of 13 participants (54%) voted for a minimum follow-up frequency of every 6 months while off treatment. The recommended visit window for patients both on and off therapy was set at +/− 1 month (58% and 50%). An overview is shown in Table 2.

Discussion

This consensus study identified measurement instruments for all domain items previously agreed on during our Delphi study for AE research registries that capture data on adults and children with moderate-to-severe AE on phototherapy and systemic immunomodulatory therapy. By doing so, a complete core dataset is now available for usage by researchers worldwide.

Our recommendations for core domains and domain items for data collection were based on a carefully conducted international Delphi process, in which over 400 stakeholders (physicians, nurses, patients, methodologists, regulatory body and industry representatives) from over 30 countries contributed.[11,12] The results of this Delphi directly fed into the 'how to measure' recommendations presented here.[12] In addition, proposals for the measurement instruments were based on the recommendations from the HOME initiative. Although primarily meant for clinical trials and not specifically for research registries, the HOME recommendations represent an international consensus on core outcomes based on validation studies and systematic reviews. The experts who participated in the HOME initiative participated in this study as well, allowing us to benefit from their expertise. Further, a patient and experts in the field of AE and/or AE measurement instruments were involved, which strengthened our recommendations and provided insight into important aspects that will play a role during implementation of the core dataset.

As for potential limitations, the final decisions on the 'how to measure' were made by a relatively small group for feasibility reasons, which did not include representatives from the regulatory bodies or pharmaceutical industry. However, where required expertise was not available within the group, external experts were consulted. In addition, because observational studies need large numbers of patients, this core dataset will need to be implemented in many research facilities. Although this might prove to be a challenge, we think that, as many of the items from the core dataset are already registered in clinical practice, this will not become a problem. Although we had a very experienced patient representative, who also was the Chair of the Dutch Association for People with Atopic Dermatitis, it would have been desirable to include more patient representatives in this consensus process. Finally, for a number of domain items no underlying systematic reviews of the evidence were available. This meant that, in this study, expert opinion played a larger role than, for example, in the HOME initiative.

As a next step, the feasibility of the core dataset and the proposed follow-up frequencies need to be tested. As part of such feasibility work, it is important to keep in mind that our recommendations apply to research registries, rather than record keeping in routine clinical practice. We are also

Table 2 When to measure the domain items for national atopic eczema treatment registries

Category	When to measure
Follow-up frequency while on therapy	4 weeks, 3 months and then every 3 months
Follow-up frequency while off therapy	Every 6 months
Visit window	+/−1 month

encouraged that the larger TREATgermany dataset appears feasible to local investigators in its current form.[21]

This core dataset will allow the international dermatology community to generate, compare and pool data of patients with AE on phototherapy and systemic therapy across country borders to answer important questions on long-term effectiveness, safety and cost-effectiveness of these therapies; which can only be addressed with very large patient numbers (e.g. on rare adverse events). We are working on a standardized data collection/storage platform to facilitate uniform data collection, pooling and analyses. In the long-term, we hope that our recommendations and the analyses generated by national treatment registries will complement the more short-term results from randomized controlled trials and ultimately aid the standardization and optimization of patient management.

As the uptake of this core dataset by new national AE registries is vital, we encourage colleagues to contact us through our website (https://treat-registry-taskforce.org), to extend this collaborative project not just within Europe but also beyond.

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Appendix

Conflicts of interest: A.D.I. has served as a consultant to AbbVie, Anacor, Chugai Pharma, Pfizer, Regeneron, Roche/Genentech, Sanofi Genzyme and UCB Pharma. C.J.A. has received institutional funding and consultancy fees from Dr Wolff GmbH. C.F. is Chief Investigator of the U.K.–Irish Atopic Eczema Systemic Therapy Registry (A*STAR) and his department has received funding from Sanofi for investigator-led research. C.V. has advised and given lectures for AbbVie, LEO Pharma, Novartis and Sanofi Genzyme, and has been involved in the PO-SCORAD development. D.W. has acted in a consultancy capacity for Janssen and Novartis. J.S. has received institutional funding for investigator-initiated research from ALK, Novartis, Pfizer and Sanofi, and is Chief Investigator for the German AE registry, TREATgermany. L.F.E. has served as a consultant to Anacor/Pfizer, LEO Pharma, Eli Lilly and Company, Roche/Genentech and Sanofi/Regeneron. M.D. has been a speaker, advisory board member and/or investigator for AbbVie, CK-Care Foundation, La Roche Posay Foundation, LEO Pharma, Meda Pharma, Pierre Fabre Laboratories, Regeneron and Sanofi Genzyme. M.A.M.-H. is an advisory board member for Sanofi. P.I.S. has served as a consultant to AbbVie, Anacor, LEO Pharma, Novartis and Sanofi, has received independent research grants from LEO Pharma and Schering-Plough, has been involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of AE, and is Chief Investigator of the Dutch AE registry, TREAT NL. S.B. has received research grants from La Fondation pour la Dermatite Atopique and Pierre Fabre Laboratories, has received personal fees from Bioderma, Ferring, La Roche Posay Laboratoire Dermatologique, Novalac and Sanofi Genzyme, and has received nonfinancial support from AbbVie, Janssen and Novartis. S.W. has served as a consultant and/or lecturer to Novartis, Pfizer and Sanofi Genzyme, has received independent research grants from Biogen, Novartis, Pfizer, La Roche Posay Foundation and Sanofi Genzyme, and has been involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of AE.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. When to measure the domain items, survey.

Fig S2. Overview of attending participants.

Fig S3. Definitions on phenotypical and morphological characteristics.

Fig S4. Average treatment (maintenance) dose.