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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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What is already known about this topic?

- Comparable, real-life and long-term data on the effectiveness and safety of photo- and systemic therapy in atopic eczema (AE) patients are needed.
- There is a high diversity of outcomes and instruments used in AE research, which require harmonisation 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 photo- and systemic therapies in AE and will provide important information for clinical practice.

- Standardisation of such data collection at the national level will also allow direct data comparisons and pooling across country borders, for instance for the analysis of treatment-related adverse events that require very large patient numbers.

Summary (abstract)

Background

Comparative, real-life and long-term evidence on the effectiveness and safety of photo- and systemic therapy in moderate-to-severe atopic eczema (AE) is limited. Such data must come from well-designed prospective patient registries. Standardisation of data collection is needed for direct comparisons and data pooling.

Objectives

To reach 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 AE patients.

Methods

Proposals for the measurement instruments were based on the recommendations of the Harmonising Outcome Measures for Eczema (HOME) initiative, the existing AE database of TREATgermany, expert opinions and systematic reviews of the literature. The proposals were discussed at multiple face-to-face consensus meetings, one teleconference and via email. The frequency of follow-up visits was determined by an expert survey.

Results

A total of 16 experts from 7 countries participated in the 'how to measure' consensus process and 12 external experts were consulted. 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 the comparability and pooling of data across centres and country borders and enable international collaboration to assess the long-term effectiveness and safety of photo- and systemic therapy used in patients with AE.

Introduction

A significant number of paediatric and adult patients with moderate-to-severe atopic eczema (AE) may require photo- 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 (EMA)^{1,2} while only dupilumab has been approved by the United States (US) Food and Drug Administration (FDA).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 photo- and systemic immuno-modulatory therapies, 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} Since randomized controlled trials (RCTs) have very strict inclusion criteria, important subgroups of patients (for instance those with co-morbidities) 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

In order to harmonise 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 fully harmonise data collection within national AE treatment research registries and prevent heterogeneity.^{13,14}

Materials and Methods

Study design

To establish a core set of measurement instruments ('how to measure') three face-to-face expert consensus meetings, one teleconference (TC) and final discussions via email were arranged. For this process we used the following sources to guide decision making:

1. We used the recommendations from the Harmonising Outcome Measures for Eczema (HOME) initiative where possible, for instance with regard to the capture of clinical signs, patient-reported outcomes and quality of life.¹⁵⁻¹⁷
2. Relevant literature, in particular systematic reviews considering measurement instruments in AE.^{7,13,14,18-20}
3. The existing AE database of TREATgermany²¹ that already included over 100 patients at the start of this study.

4. Personal communications with experts in the field of measurement instruments for specific domain items. (e.g. K. McElhone from the UK psoriasis biologics register (BADBIR), personal communication, May 18, 2017)

5. The current usage of measurement instruments in clinical practice and clinical experience of the participants.

During all meetings feasibility and current common practice were kept in mind.

All meetings were chaired by either Professor Phyllis Spuls or Professor Carsten Flohr. During each session, the evidence for each suggested measurement instrument was presented in form of a Power Point 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): 1. the HOME recommendations, 2. quality of the validation studies and 3. 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 consensus on domain items could not be reached immediately during the meetings, for instance 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 re-discussed at the next consensus meeting. The three face-to-face consensus meetings were audio recorded 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). The results of the survey were discussed and approved in a small group via email.

Participants

Participants were physicians, patients, and non-clinical 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 email) from e.g. the Coronel Institute of Occupational Health and the Medical Psychology Department of the Academic Medical Centre in Amsterdam (AMC) for items considering work and health and items considering treatment adherence.

Definition of consensus

Consensus was predefined both for the 'how' and '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 by TC, the other three by face-to-face meetings in London, Amsterdam and Nantes. A total of 16 participants met (for details see Fig. S2), all members of the TREAT Registry Taskforce, including 11 academic dermatologists, 1 dermatology resident, 1 dermatology PhD student, 1 patient/patient representative, 1 epidemiologist/ methodologist and 1 health economist. A total of 11 experts were consulted for specific items.

During the face-to-face meetings slight alterations were made to the ‘what to measure’ core dataset. In order 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 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 (see Table 1). For all items consensus was reached on the measurement instruments.

Details on specific domain items

Ethnicity. We reviewed all ethnicity classifications we had access to based on a literature search, including the one used by the UK Biobank, the German National Cohort and the British Association of Dermatologists’ Biologic Interventions Register (BADBIR). The classification system shown in Table 1 was made (based on all these reviewed classification systems) and was selected as 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 was 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 (UNESCO) 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 will 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 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 AE are available and reviewed (e.g. the UK Working Party criteria, the Hanifin & Rajka criteria, the refined Millennium Criteria²³). Although in clinical practice a diagnosis of AE is often made without the use of specific diagnostic criteria, the use of validated diagnostic criteria is nevertheless 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. Also, the option 'physician-diagnosed' was added in case no diagnostic criteria were used.

Previous and current photo- 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 to record the cumulative dose of phototherapy. It was decided to add investigational therapies to the registry (both for past and current systemic therapy) even though 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, 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 provides 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 AE 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. Part 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 if certain phenotypical and morphological characteristics are present. For definitions on these characteristics see Figure S3.

Details on physician- and patient-reported domain items

Physician-assessed clinical signs and patient-reported symptoms. For all items HOME recommendations were followed, i.e. the Eczema Area and Severity Index (EASI) was selected for the item 'physician-assessed clinical signs'¹⁵ and the Patient-Oriented Eczema Measure (POEM) for the item 'patient-reported symptoms'.^{16,25,26}

Patient-reported symptoms. At 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 Numerical Rating Scale (NRS)-11 for itch has good reliability and validity and that recall bias increases with the recall period.^{18,27} NRS-11 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 past 24 hours.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 to use 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 standardised definitions.²⁹ As a result, the International Eczema Council (IEC) and Eli Lilly and Company (Lilly) have worked on a validated 5-point investigator global assessment (IGA) scale which was incorporated in the core dataset for this item.³⁰ (<http://www.eczemacouncil.org/research/investigator-global-assessment-scale/>)

Patient global assessment. Little research has been done towards the PGA. This subdomain of the long-term control domain has been discussed during HOME V, but as yet stays undefined.¹⁷ However, since we decided to use the 5-point IGA scale, the 5-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.³¹

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 AE care received, impact of AE on the family, adherence to treatment between appointments. We recommend the use of an adapted PsoSat Questionnaire, a questionnaire that measures the treatment satisfaction in psoriasis patients,³² the Family Dermatology Life Quality Index (FDLQI)³³ 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 AE patients.³⁴ The MARS will be optional until it is validated for AE.

When to measure

Thirteen out of 16 participants (81%) completed the survey. Eight out of 13 (62%) voted for a minimum follow-up frequency of every three months while on therapy; 7 out of 13 participants (54%) voted for an extra visit 4 weeks after baseline. 7 out of 13 participants (54%) voted for a minimum follow-up frequency while off therapy of every 6 months. 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 70 measurement instruments for the 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 photo- and systemic immunomodulatory therapies. By doing so, a complete core dataset is now available for usage by researchers worldwide.

Strengths and limitations

Our recommendations for core domains and domain items for data collection were based on a carefully conducted international Delphi process that over 400 stakeholders (physicians, nurses, patients, methodologists, regulatory body and industry representatives) from over 30 countries contributed to. 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 international consensus on core outcomes based on validation studies and systematic reviews. Experts that 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 regulatory bodies or pharmaceutical industry. However, where required expertise was not available within the group, external experts were consulted. Also, due to the fact that 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, since 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 bigger role than for instance in the HOME initiative.

Recommendations for future work

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 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 AE patients on photo- and systemic therapies across country borders to answer important questions on long-term effectiveness, safety and cost-effectiveness of these therapies, some of which can only be addressed with very large patient numbers (e.g. on rare adverse events). We are working on a standardised 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 RCTs and ultimately aid the standardisation and optimisation 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 (treat-registry-taskforce.org), to extend this collaborative project not just within Europe but also beyond.

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Tables

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

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

Supporting information

Figure S1 – When to measure the domain items, survey

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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, USA, 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 classification 1 – 8: Employed Self-employed Disability pension (unable to work) Retired Student or pupil Engaged on home duties Unemployed 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 UK 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	- UVB (unspecified) if type is unknown - This is only medical history. If current it

		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), c. adverse event (Y N)	should be recorded under 'current AE treatments'
	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 (see Fig. S4) - This is only medical history. If 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 registered for the past year - This is only medical history. If 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 registered for the past year - This is only medical history. If current it should be recorded under 'current AE treatments'
	Hospitalisation for AE	1. Y N 2. Duration (cumulative days)	- Only registered for the past year - This is only medical history. If 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 (see Fig. S4)
	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	1. <30 gram 30-60 gram 60-100 gram >100 gram	- 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 1 st degree relative (parents or children) - According to the patient or physician- diagnosed
Allergic co- morbidity	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 co- morbidity	Malignancies	1. Y N 2. When (year) 3. Type of malignancy (free text)	- MedDRA categories will be used for this item as much as

		4. Active Remission Relapsed	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 (herpes simplex virus (HSV) infection, mollusca contagiosa, etc.) (possibility to select multiple options)	
	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):	- For definitions on these phenotypical

		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)	and morphological characteristics see Figure S3
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 (5-point)	
	Patient-reported symptoms	1. POEM 2. Peak Pruritus NRS (0-10) past 24 hours 3. Peak VAS pain (0-10) past 24 hours (Optional)	
	Patient global assessment	1. PGA 5-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? (5-point likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (5-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	1. FDLQI	- Needs to be filled out

	family		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
	Kidney profile	1. Y N 2. Normal Abnormal 3. Clinically relevant Y N	- Normal/abnormal according to local standards
	Evaluating TPMT level prior to 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	- Same comment(s) as for baseline item

		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)	
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 (5-point)	
	Patient-reported symptoms	1. POEM 2. Peak Pruritus NRS scale (0-10) past 24 hours 3. Peak VAS pain (0-10) past 24 hours (Optional)	
	Patient global assessment	1. PGA 5-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
	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? (5-point likert scale) 2. How satisfied are you with the treatment received for your AE since the last visit? (5-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 Hospitalisation or prolonged hospitalisation of existing hospitalisation Persistent or significant disability Congenital anomaly Important medical event which requires medical intervention Not applicable (possibility to select multiple options) 4. Relatedness: Not related Doubtful Possible Probable Very likely Definite 5. 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)	

Abbreviations: AAD, American Academy of Dermatology; AE, Atopic Eczema; BB-UVB, Broad-band 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; HIV, Human immunodeficiency virus; HOME,

Harmonising Outcome Measures for Eczema; IDQoL, Infant's Dermatitis Quality of Life Index; IgE, Immunoglobulin E; ISCED, International Standard Classification of Education; JDA, Japanese Dermatological Association; MARS, Medication Adherence Report Scale; MedDRA, Medical Dictionary for Regulatory Activities; NB-UVB, Narrow-band ultraviolet B; NRS, Numerical Rating Scale; PGA, Patient Global Assessment; 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; UK, United Kingdom; USA, United States of America; 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.

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 three months
Follow-up frequency while off therapy	Every 6 months
Visit window	1 Month

Figure S1 – When to measure the domain items, survey

1. What should be the minimum follow up frequency for registry data entry while on therapy, starting from baseline?

- ☐ 4 Wks, 3 months and then every 3 months ☐ 3 Months, 6 months and then every 6 months
- ☐ Every 3 months ☐ Every 6 months
- ☐ 4 Wks, 3 months, 6 months and then every 6 months
- ☐ Other (please specify)

2. What should be the minimum follow up frequency for registry data entry, while off therapy (after discontinuation of therapy)?

- ☐ Every 3 months ☐ 6 Months, 12 months and then annually
- ☐ 3 Months, 6 months and then every 6 months ☐ Annually
- ☐ Every 6 months
- ☐ Other (please specify)

3. Should we define a visit window?

- ☐ Yes
- ☐ No

4. If yes, what should be the visit window for follow up visits while on therapy?

- ☐ +/- 1 week
- ☐ +/- 2 weeks
- ☐ +/- 1 month
- ☐ Other (please specify)

5. If yes, what should be the visit window for follow up visits while off therapy (after discontinuation of therapy)?

- ☐ +/- 1 week ☐ +/- 2 months
- ☐ +/- 2 weeks ☐ +/- 3 months
- ☐ +/- 1 month
- ☐ Other (please specify)

Figure S2 – Overview of attending participants

MEETING	Academic dermatologist	Dermatology resident	Dermatology PhD student	Patient/ patient representative	Epidemiologist/ methodologist	Health economist
Teleconference	6	1	1	-	1	-
London	10	1	1	1	1	1
Amsterdam	4	1	1	1	1	-
Nantes	6	1	-	-	1	-

Figure S3 - Definitions on phenotypical and morphological characteristics

CONSENSUS	
Pompholyx:	Vesicular eczema
Discoid eczema:	≥ 5 Circular patches in total, ≥ 2cm diameter each
Nodular prurigo:	≥ 5 Palpable nodules of the skin from long-term scratching (usually on the legs or arms), ≥ 1cm diameter each
Follicular eczema:	Widespread eczematous hair follicle involvement, more commonly seen in darker skin types
Ichthyosis:	Widespread fine scale predominantly affecting the non-flexural areas of the limbs and body
Keratosis pilaris:	Thickening around the base of hair follicles over upper arms, thighs or cheeks
Erythroderma:	≥ 90% BSA (Body Surface Area) involvement

Figure S4 - Average treatment (maintenance) dose

CONSENSUS		
Ciclosporin:		Oral corticosteroids:
< 2.5 mg/kg/day		< 0.5 mg/kg/day
2.5 – 3.5 mg/kg/day		0.5 – 1.0 mg/kg/day
3.6 – 4.5 mg/kg/day		> 1.0 mg/kg/day
4.6 – 5.0 mg/kg/day		Unknown
> 5.0 mg/kg/day		
Unknown		
Azathioprine:		Dupilumab:
< 1 mg/kg/day		< 300 mg every other week
1 – 2 mg/kg/day		300 mg every other week
2.1 – 3 mg/kg/day		300 mg every week
> 3 mg/kg/day		> 300 mg every week
Unknown		Other – please specify
		Unknown
Methotrexate (adults):	Methotrexate (children):	Omalizumab:
< 5 mg/week	< 0.1 mg/kg/week	< 300 mg every four weeks
5 – 10 mg/week	0.1 – 0.2 mg/kg/week	300 mg every four weeks
11 – 15 mg/week	0.21 – 0.3 mg/kg/week	> 300 mg every four weeks
16 – 20 mg/week	0.31 – 0.4 mg/kg/week	Other – please specify
21 – 25 mg/week	> 0.4 mg/kg/week	Unknown
> 25 mg/week	Unknown	
Unknown		
Mycophenolate acid (adults):	Mycophenolate acid (children):	
< 1 g/day	< 30 mg/kg/day	
1 – 1.5 g/day	30 – 40 mg/kg/day	
1.6 – 2 g/day	41 – 50 mg/kg/day	
> 2 g/day	> 50 mg/kg/day	
Unknown	Unknown	