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Treat-to-Target in Atopic Dermatitis: An International Consensus on a Set of Core Decision Points for Systemic Therapies

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Currently no treat-to-target framework to guide systemic treatment in adults with moderate-to-severe atopic dermatitis exists. We sought to reach international consensus through an eDelphi process on a core set of recommendations for such an approach. Recommendations were developed by an international Steering Committee, spanning 3 areas (Guiding Principles, Decision Making, and Outcome Thresholds) and 2 specific time-points; an initial acceptable target at 3 months and an optimal target at 6 months, each based on improvements in patient global assessment plus at least one specific outcome domain. These treat-to-target-orientated recommendations were evaluated by an extended international panel of physicians, nurses and patients. Proposed recommendations were rated using a 9-point Likert scale; for each recommendation, consensus agreement was reached if ≥ 75% of all respondents rated agreement as ≥ 7. Consensus on 16 core recommendations was reached over 2 eDelphi rounds. These provide a framework for shared decision-making on systemic treatment continuation, modification, or discontinuation.

Key words: atopic dermatitis; eDelphi; consensus; surveys and questionnaires; treat-to-target; systemic treatment.

SIGNIFICANCE

Moderate-to-severe atopic dermatitis often requires systemic therapies for disease control. Unlike other conditions, such as psoriasis, at present no treat-to-target framework exists to guide optimal use of systemic therapies in atopic dermatitis. We developed recommendations for such a treat-to-target approach and evaluated these through an eDelphi process with proposals rated by an international panel of physicians, nurses and patients to seek international consensus. After 2 eDelphi rounds, consensus agreement was reached on all recommendations. From this, a clinical algorithm is proposed to guide shared decision-making in a treat-to target approach for systemic treatment in adults with moderate-to-severe atopic dermatitis.

Systemic therapies are an important therapeutic strategy for patients with moderate-to-severe atopic dermatitis (AD) that is not sufficiently controlled by topical therapies. While guidelines list treatment options on the basis of disease severity/activity, they make no recommendation as to treatment order or treatment target, and criteria for the assessment of treatment success are currently not well defined (1, 2). Consequently, decision-making to select a treatment and to guide the assessment of its benefit in individual patients can be complex, and often subjective, and patients may not receive optimal management necessary for disease control.

Treat-to-target is an established strategy in a range of immune-mediated/inflammatory conditions, such as rheumatoid arthritis (RA), spondyloarthopathies, systemic lupus erythematosus, and psoriasis (3–11). In these disease areas, the introduction of biologics led to the development of target-driven treatment algorithms in which specific target goals for treatment response are used to guide decisions to continue, discontinue, or modify treatment(s). This approach provides a framework to support treatment choices made using shared clinical decision-making with patients, including discussion of relevant risks/benefits of existing or alternative treatments.

The use of a similar treat-to-target approach for systemic treatment in AD would seem to be a promising strategy to optimize patient outcomes (12). However, at present, no such framework exists. The objective of this evidence-based expert consensus process was to develop a core set of recommendations for treatment

targets, measures and timing, in order to guide the use of systemic therapies in adults with AD in accordance with recommended guidelines (1, 2).

MATERIALS AND METHODS

To establish treatment targets for AD, a consensus-building study was conducted among dermatologists, dermatology nurses and patient representatives through an eDelphi method. Key aspects of this process are described below (a more detailed description is available in Appendix S1[1]).

In the pre-Delphi phase, the available evidence relevant to disease assessment, patient characteristics, and treatment pathways in moderate-to-severe AD in adults was reviewed, discussed and summarized in a series of meetings. A Steering Committee was then established, comprising experts from across Europe (MdB-W, TB, MD, JH, GG, AP, M-A R, J-F S, SW), Canada (RB, C-HH), Australia (PF, SS) and Japan (NK); members were selected on the basis of experience and expertise in treating AD, publication record, participation in clinical trials on AD, and/or participation in comparable consensus activities, such as HOME (13), and TREAT (14), or AD guideline development. All members of the Steering Committee declared potential conflicts of interest.

The Steering Committee then convened over a series of meetings to establish a core set of candidate statements that could inform a treat-to-target approach; these were then included in a survey questionnaire to be examined in an eDelphi process. This was facilitated by an independent methodology expert appointed to guide the eDelphi process and establish consensus rating and agreement criteria. Eligibilty for inclusion in an international extended panel for the eDelphi process was also established. An overview of the approach is shown in Appendix S1; Fig. S1[1].

eDelphi survey questionnaire development

A list of statements was drafted by the Steering Committee, falling within 3 broad areas pertinent to a treat-to-target approach: Guiding Principles, Decision Making, and Outcome Thresholds. For outcome assessment, a multidimensional approach was adopted, including a range physician-reported and patient-reported outcome measures to provide flexibility and ensure clinical utility; Patient self-reported Global Assessment of disease severity (PtGA), Eczema Area and Severity Index (EASI); SCORing Atopic Dermatitis (SCORAD); Dermatology Life Quality Index (DLQI); Patient-Oriented Eczema Measure (POEM); and Peak Pruritus Numerical Rating Scale (NRS). This broad range of validated instruments reflects the fact that no single outcome assessment tool can capture the entire benefit of a treatment (12), and that physician assessments of clinical signs and patient-oriented assessments are both important (12, 15).

For each instrument, a threshold was proposed for 2 assessment time-points; the initial threshold to be attained at 3 months, and the second to be attained at 6 months, chosen on the basis that they represent an appropriate treatment period for assessing therapeutic response, and align with typical consultation schedule patterns.

eDelphi participants and recruitment

Panel participants were selected to provide representation of key stakeholder groups; physicians and specialist nurses with experience in the management of patients with moderate-to-severe AD, and patients/patient association representatives. In keeping with other similar initiatives, panellists were recruited from a wide

range of countries and geographical locations (3–5, 16, 17). Further details on participant selection are available in Appendix S1[1].

Eligible candidate panel participants were invited directly by Steering Committee by email, explaining the project's aim and methodology and requesting their agreement to participate. Final selection was influenced by the need to achieve a balanced and pragmatic geographical spread. In addition, in part due to recruitment limitations in selecting appropriate nurses and patient representatives, but also with the aim of generating a core dataset that would have the greatest value and acceptance by and for dermatologists, it was agreed that the majority of panellists would be physicians. Following agreement to participate, to avoid any potential influence on subsequent participant responses in the eDelphi, no other communication or educational activities with panel participants occurred prior to formal participation in the eDelphi process.

The final extended panel comprised 87 participants; the 14 members of the Steering Committee (all physicians), 60 additional physicians, 3 nurses, and 10 patient representatives. The panel included members from 28 different countries, representing most of mainland Europe, Australia, Japan, and Canada (Appendix S1; Table SI[1]).

eDelphi process and definition of consensus

The eDelphi questionnaire consisted of core statements accompanied by supporting information; all panel participants received identical questionnaires. Participants were asked to rate each of the statements using a 9-point Likert scale ranging from 1= "strongly disagree" to 9="strongly agree". Consensus on any given statement required 75% or more of all participants to rate their level of agreement as 7, 8, or 9 (a "consensus in" approach). Applying this rule across all participants, rather than to each individual stakeholder group, reduced the risk that a lower level of agreement in the smaller stakeholder group could exert undue influence on the overall result.

For round 1 of the eDelphi, the statements were rated, and results and feedback gathered for analysis. Those statements that met the criteria were considered to be agreed and were not available for voting in subsequent eDelphi rounds. Those statements that failed to reach agreement were reviewed and revised by Steering Committee members, after considering the voting scores and comments, and then submitted for a new eDelphi voting round (Appendix S1; Table SII[1]). In each subsequent voting round, participants were able to view the voting results and anonymized comments for the previous eDelphi round.

Questionnaire distribution, data entry and collection of respondent ratings and feedback, was performed on a dedicated, password-protected, online platform (www.t2tconsensus.com), independently managed by a medical communications agency (IntraMed, Milan, Italy). All participant responses were anonymized (using unique respondent identification numbers), although their stakeholder category was recorded; participant anonymity was maintained throughout the eDelphi process and subsequent discussions. Descriptive data analysis was performed using Microsoft Excel.

In line with similar externally supported consensus projects, the project sponsor was not present during the Steering Committee discussions on statement development, and had no involvement in the conduct of the eDelphi and subsequent consensus process.

RESULTS

eDelphi rounds

A total of 16 statements (and a total of 22 different statement items) were presented and achieved agreement over

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2 eDelphi rounds. The percentages of respondents who indicated agreement (rating 7 or higher on the 9-point Likert scale) for the final agreed statements are presented in **Table I**. For eDelphi round 1 (conducted on 24 June 2019), 57 panellists participated (representing 65.5% of all available panellists), including: 44 physicians (59.5% of panel physicians): 3 nurses (100%); and 10 patients/patient association representatives (100%). Consensus agreement was reached for a total of 11 statements; items 1–5, 7, 9, 10, 11b, 13b and 15b; with aggregated agreement from the overall panel ranging from 77.2 to 98.2% for these statements achieving consensus after round 1 (Table I).

For those statements for which agreement was not achieved (with aggregated agreement ranging from 57.8% to 71.9%), revision and subsequent re-voting was performed. Revisions were related mostly to language framing the proposed statements, and the target threshold values remained unchanged. Statement revisions and additional explanatory notes available for eDelphi round 2 are shown in Appendix S1; Table SII[1].

In round 2 (conducted on 7 August 2019), a total of 52 participants responded (59.8% of all available panellists); 43 physicians (58.1%), 2 nurses (66.7%), and 7 patients/patient association representatives (70%). All remaining statements and items examined in round 2 after revision (6, 8, 11a, 12a, 12b, 13a, 14a, 14b, 15a, 16a, and 16b) met the ≥75% consensus agreement criteria in this second eDelphi round; with aggregated agreement from the overall panel ranging from 75.0% to 90.4% for these statements (Table I). Some variation in agreement across the different panel categories was observed; while all recommendations achieved ≥75% consensus by dermatology and nursing panel participants, a number of

Table I. Results of the eDelphi consensus process: core set of treat-to-target recommendations

Core statement	eDelphi							
	Overall		Physicians		Nurses		Patients/patient associations	
	Agree (%)	Mean voting score	Agree (%)	Mean voting score	Agree (%)	Mean voting score	Agree (%)	Mean voting score
Guiding principles								
1. The objective of systemic therapy is to achieve disease control or at least clinically meaningful improvement of disease activity*	98.2	8.5	97.7	8.6	100	8.3	100	8.4
2. Defining treatment targets is helpful in optimizing management of patients with AD requiring systemic therapy*	89.5	8.0	90.9	8.1	100	8.0	80.0	7.8
3. Response to therapy in AD should be assessed by considering changes in clinical signs, symptoms, quality of life, long-term disease control, and a patient global*	96.5	8.4	95.5	8.3	100	8.7	100	8.6
4. In AD requiring systemic treatment, changes in clinical signs, symptoms, quality of life, long-term disease control, and patient global should be measured using validated instruments*	87.7	8.0	86.4	8.0	66.7	7.3	100	8.5
5. Safety and tolerability of the treatment is an integral part of outcomes assessment, and should be considered at each decision point*	98.2	8.6	100	8.7	100	8.3	90.0	8.4
Decision framework								
6. There should be an initial acceptable target, to be reached by 3 months at the latest**	86.5	7.6	90.7	7.5	100	8.0	57.1	6.6
7. There should be an optimal treatment target to be reached by 6 months*	80.7	7.5	81.8	7.5	100	8.0	70.0	7.0
8. If target outcomes are achieved for patient global *plus at least 1* specific disease domain (signs, symptoms, quality of life), treatment continuation should be considered**	75.0	7.2	76.7	7.2	100	8.5	57.1	7.0
9. If target outcomes are achieved for at least 1 specific disease domain (signs, symptoms, quality of life), but not for patient global, or for patient global only, treatment should be discussed with the patient and optimized*	86.0	7.6	84.1	7.5	100	8.3	90	7.8
10. If none of the treatment targets are achieved, the treatment should be changed*	89.5	8.2	93.2	8.2	100	8.7	70	7.6
Outcome thresholds								
11. a) For EASI, the initial acceptable treatment target is at least EASI 50**	80.8	7.5	86.0	7.6	100	8.5	42.9	6.6
11. b) For EASI, the treatment target at 6 months is EASI 75 or EASI ≤7*	77.2	7.2	77.3	7.3	100	8.3	70.0	6.7
12. a) For SCORAD, the initial acceptable treatment target is at least SCORAD 50**	82.7	7.6	86.0	7.7	100	8.0	57.1	6.7
12. b) For SCORAD, the optimal treatment target at 6 months is SCORAD 75 or SCORAD ≤24**	90.4	7.6	93.0	7.7	100	8.5	71.4	7.0
13. a) For Peak Pruritus NRS (0–10), the initial acceptable treatment target is a reduction of at least 3 points**	78.8	7.4	74.4	7.3	100	8.0	100	7.4
13. b) For Peak Pruritus NRS (0–10), the treatment target at 6 months is an absolute score ≤4*	82.5	7.2	81.8	7.2	100	8.3	80.0	7.0
14. a) For DLQI, the initial acceptable treatment target is a reduction of at least 4 points**	82.7	7.1	81.4	7.1	100	8.0	85.7	7.0
14. b) For DLQI, the optimal treatment target at 6 months is an absolute score ≤5**	80.8	7.3	81.4	7.4	100	8.0	71.4	6.7
15. a) For PtGA (0–4), the initial acceptable treatment target is a reduction of at least 1 point**	84.6	7.1	81.4	7.0	100	8.0	100	7.4
15. b) For PtGA (0–4), the treatment target at 6 months is an absolute score ≤2*	78.9	7.1	77.3	7.4	100	8.0	80.0	6.8
16. a) For POEM, the initial acceptable treatment target is a reduction of at least 4 points**	88.5	7.3	86.0	7.2	100	7.5	100	7.4
16. b) For POEM, the optimal treatment target at 6 months is an absolute score ≤7**	88.5	7.6	90.7	7.7	100	8.5	71.4	6.6

*Statements reaching consensus agreement after eDelphi round 1.
**Statements reaching consensus agreement after eDelphi round 2.
AD: atopic dermatitis; EASI: Eczema Area and Severity Index; SCORAD: SCORing Atopic Dermatitis; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; PtGA: Patient self-reported Global Assessment of disease severity; DLQI: Dermatology Life Quality Index.

statements failed to achieve agreement by patient/patient association representatives.

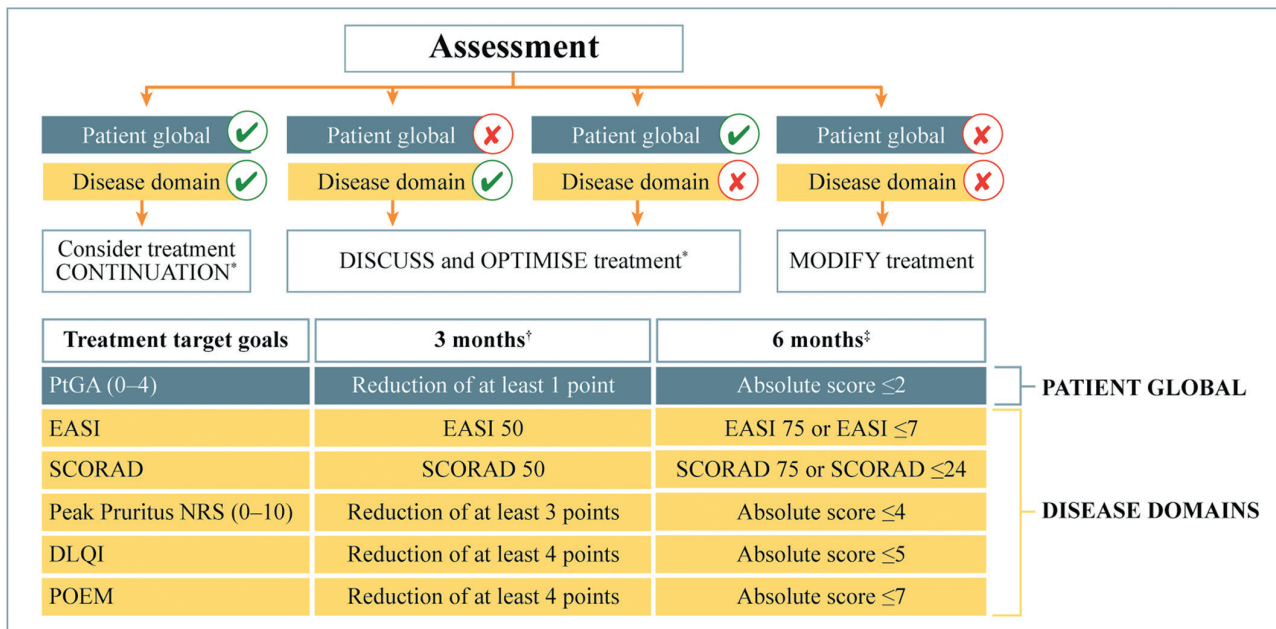### Consensus meeting and round-table discussion

A face-to-face meeting of the Steering Committee was held (in Frankfurt on 25 October 2019), in which the eDelphi survey results were presented. The agreed recommendations consider decision-making at 3 and 6 months, where an initial acceptable target and subsequent optimal treatment target can be used within the context of a clinical algorithm to guide use of systemic therapies in a treat-to target approach for moderate-to-severe AD (**Fig. 1**). This algorithm was discussed and endorsed by the Steering Committee.

In this algorithm, decisions for continuing or changing therapy are based on changes in the patient's global assessment plus changes in at least one specific domain measured with the help of validated outcome assessment instruments (PtGA, EASI, SCORAD, Peak pruritis NRS, DLQI and POEM). Reaching targets in both patient global response plus at least one specific domain target should prompt consideration of treatment continuation.

Failure to reach targets in both patient global assessment and disease domain measures should prompt transition to an alternative treatment. Where only one set of outcome targets is achieved, shared decision-making will guide continuation, modification, or a change of treatment. In addition, as treatment safety and tolerability are cardinal considerations, these should be taken into account at each decision point.

DISCUSSION

Through an eDelphi consensus process involving an international group of practising physicians with long-standing experience in treating patients with moderate-to-severe AD, along with nurses and patient representatives, agreement was reached on a core set of statements related to treat-to-target outcomes in patients with moderate-to-severe AD requiring systemic therapy. Note that our approach assumes that adjunctive use of topical therapies (including topical corticosteroids or topical calcineurin inhibitors) may continue, or indeed evolve. While this may have some impact upon disease

Treatment target goals	3 months†	6 months‡	
PtGA (0–4)	Reduction of at least 1 point	Absolute score ≤2	PATIENT GLOBAL
EASI	EASI 50	EASI 75 or EASI ≤7	
SCORAD	SCORAD 50	SCORAD 75 or SCORAD ≤24	DISEASE DOMAINS
Peak Pruritus NRS (0–10)	Reduction of at least 3 points	Absolute score ≤4	
DLQI	Reduction of at least 4 points	Absolute score ≤5	
POEM	Reduction of at least 4 points	Absolute score ≤7	

* If the treatment is tolerated.
† Indicates an initial acceptable target, to be reached by 3 months at the latest.
‡ Indicates an optimal treatment target to be reached by 6 months.
Patient global: Patient self-reported global assessment
Disease domain: Signs OR symptoms or QOL

Fig. 1. Algorithm for decision-making in treating moderate-to-severe atopic dermatitis (AD) to target with systemic treatments based on the consensus. Relevant targets are shown in the lower panel. Reaching targets in patient global assessment (Patient self-reported Global Assessment of disease severity; PtGA) *plus* at least 1 specific domain target should prompt consideration of treatment continuation; failure to reach target in PtGA and disease domain measure should prompt switching to an alternative systemic agent. Where only 1 set of outcome targets are achieved (i.e. only PtGA or only the disease domain measure) then shared decision-making around treatment continuation, or modification, or switching to an alternative treatment is recommended. All decisions should be made on the basis of acceptable treatment safety and tolerability. QOL: quality of life; EASI: Eczema Area and Severity Index; SCORAD: SCORing Atopic Dermatitis; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; DLQI: Dermatology Life Quality Index.

response, the 3 principal clinical decisions around systemic therapy (treatment continuation; switching to an alternative systemic agent; or shared decision-making on treatment continuation or modification or switching) would still apply.

While decisions on treatment strategies can be made at every consultation, 2 specific decision-points were proposed, at 3 and 6 months, representing time-points where an initial acceptable target, and then an optimal treatment target, should be met. If the targets are not met at these time-points, then treatment should be re-evaluated, and optimization or alternatives considered. These 3- and 6-month time-frames correspond well with typical routine visit schedules and may represent a practical treatment period for assessing therapeutic response. However, these are suggested, and some flexibility is anticipated depending on physician preference and the specific treatments being used.

A range of outcome assessments and instruments were chosen in order to provide flexibility and utility across a range of clinical settings and diverse geographical locations, and to balance observer-only and patient-experienced measures. Despite a lack of a standardized definition on the concept and the wording/phrasing, a satisfactory change in the patient global response (e.g. PtGA) was considered to be important, as it represents the patient's broad perception of disease activity, and is simple and feasible. This is in line with results from a recent research prioritization exercise conducted by the new HOME clinical practice initiative that identified a patient global assessment (PtGA) instrument as being of high importance to investigators, clinicians, and patients in the clinical practice setting (18). However, there was consensus that at the same time, at least 1 specific key domain measured objectively with validated and recommended instruments (18), e.g. SCORAD, EASI, DLQI, Peak Pruritus NRS, or POEM, should show a satisfactory improvement, with the flexibility to use 1 or more, depending on the physician's and the patient's preference.

The threshold targets guiding treatment decisions (Fig. 1) were closely considered during survey development, throughout the eDelphi process, and in subsequent round-table discussions. The targets are based on what was considered to be clinically relevant absolute threshold values or percentage reductions. Many targets recommended for initial assessment at 3 months are reductions that represent acceptable improvements, whereas the later 6-month thresholds were set as the optimal target threshold values. Similar.to our earlier comments on time-points, the outcome tools and target thresholds are suggested; in reality some flexibility may be anticipated. Choice of outcome instrument may, for example, be influenced by physician and patient preference as well as the specific agent used. In principle, the choice of outcome instruments and specific domain to be used for clinical decision-making would be the decision of the treating physician and the patient (on the basis of agreed individual treatment goals). In addition, certain outcome instruments may be preferred, or even necessary when specific agents are being used, either for reimbursement purposes (where for example, it may be necessary to document EASI responses) or where local protocols apply. However, from a response target threshold perspective, we believe that the thresholds we propose could and perhaps should apply to any systemic AD treatment, regardless of the specific systemic agent. While the time-points and treat-to-target thresholds we propose are intended to help guide treatment decisions in the real-life setting, these time-points and targets are consistent with those used in clinical studies.

The recommended treatment target goals have some similarities to those treat-to-target goals developed via consensus for psoriasis, but some differences exist, in part due to different outcome instruments (8–11, 19, 20). Both the long-established European consensus and later Australian consensus defined psoriasis treatment goals on the basis of changes in the Psoriasis Area and Severity Index (PASI) and the DLQI score (8–10). In contrast, the Canadian consensus uses a single outcome instrument, the Physician Global Assessment (PGA) (11). In the USA, the National Psoriasis Foundation also uses a single outcome tool, evaluating body surface area (BSA) changes from baseline at 3 and/or 6 months (19). Most recently, a Belgian consensus publication used a multidimensional approach, where ideal and acceptable treatment targets after 12 weeks were determined using a range of instruments including PASI, PGA and DLQI (20). While, to some extent, our approach and consensus treatment goals in AD align better with this latter multidimensional approach, in general they are broadly consistent with the principles seen in each of these treat-to-target outcomes in psoriasis. Our inclusion of a symptom specific measurement in our AD treat-to-target framework, the Peak Pruritus NRS, reflects the capacity to monitor itch as an important treatment goal from the patients' perspective.

Most treat-to-target initiatives in dermatology generate consensus principally from physicians only. In contrast, the present project also included active involvement of nurses and patient representatives, one of the few to do so, although the recent Belgian treat-to-target consensus in psoriasis also included patient input (20). Although the majority of panel participants were physicians, we believe that including representation from patients and nurses has value in developing treat-to-target aims in AD, even if the numbers were relatively low.

Our consensus initiative has some limitations. Although panel participants were drawn from a wide range of countries, the great majority were from Europe, with smaller numbers from Australia, Canada and Japan. Furthermore, the response rate for the first eDelphi round was 65% of all possible participants, with some subsequent drop-out in round 2 (60% response rate). Anony-

mity was maintained throughout the eDelphi process, which can allow more freedom in participant responses. However, such anonymity does not allow confirmation of specific panelist participation, nor changes in specific participant's voting. Our extended panel recruitment included 3 different stakeholder groups (physicians, nurses and patient groups). While all recommendations achieved consensus in physicians and nursing stakeholder groups, a lower level of agreement was evident for some statements from patient/patient representatives. This may be due to lack of familiarity with the assessment instruments that were proposed, and to the relatively low number of such participants recruited, but it may be that genuine differences in opinion exist. We also accept that the relatively low number of nurse and patient/patient representative participants (in particular that for nurses) is a study limitation.

Another limitation is the absence of long-term target outcomes in the recommendations and treatment algorithm. Clearly these outcomes are important, and their inclusion would be desirable. However, at the time of our initiative, specific validated instruments were not yet available for use in everyday practice. Some instruments have subsequently been validated, such as the Atopic Dermatitis Control Test (ADCT) (21, 22), and Recap of Atopic Eczema (RECAP) (23). Their inclusion could be considered in future updates of this document. Finally, some clinically relevant aspects have not been addressed in the present process. One such example, beyond the scope of the current consensus process, could be how to account for the potential impact of existing or additional adjunctive topical therapies on target outcomes, and how this may influence systemic treatment decisions.

As with many such treat-to-target proposals, the evidence-base for specific recommendations is at present sparse. The aim of this study has been to provide a framework based on expert opinion and informed by extensive clinical experience, and to seek agreement across an extended panel via an eDelphi process. We believe that this represents a starting point and foundation, which can inform and stimulate debate across the wider dermatology community. Use of these recommendations and algorithm may also be a helpful aid to monitoring clinical practice and could be a valuable tool for clinical audit.

ACKNOWLEDGEMENTS

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