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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Development of the Angioedema Control Test—A patient-reported outcome measure that assesses disease control in patients with recurrent angioedema

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Abstract

Background: Recurrent angioedema (AE) is an important clinical problem in the context of chronic urticaria (mast cell mediator–induced), ACE-inhibitor intake and hereditary angioedema (both bradykinin-mediated). To help patients obtain control of their recurrent AE is a major treatment goal. However, a tool to assess control of recurrent AE is not yet available. This prompted us to develop such a tool, the Angioedema Control Test (AECT).

Methods: After a conceptional framework was developed for the AECT, a list of potential AECT items was generated by a combined approach of patient interviews, literature review and expert input. Subsequent item reduction was based on impact analysis, inter-item correlation, additional predefined criteria for item performance, and a review of the item selection process for content validity. Finally, an instruction section was generated, and an US-American-English version was developed by a structured translation process.

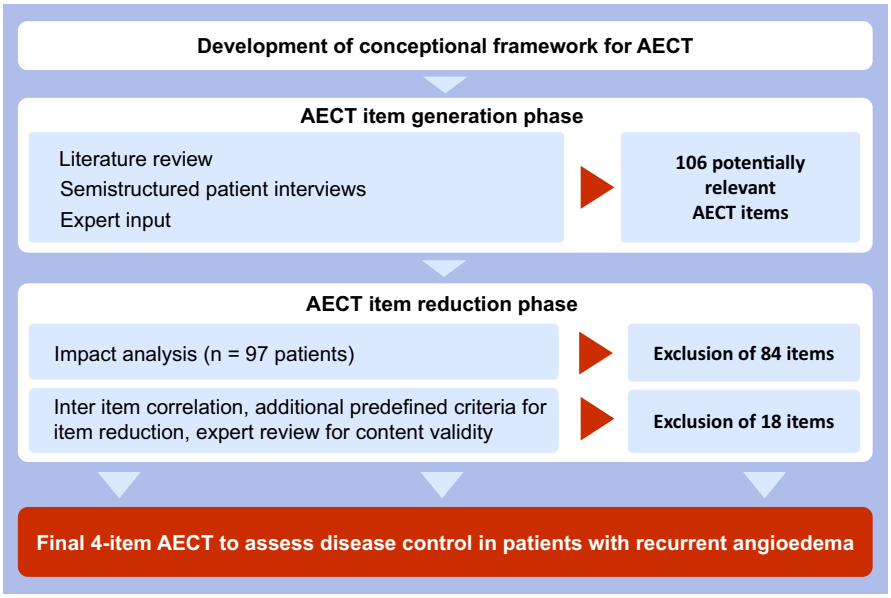
Results: A 4-item AECT with recall periods of 4 weeks and 3 months was developed based on 106 potential items tested in 97 patients with mast cell mediator-induced (n = 49) or bradykinin-mediated recurrent AE (n = 48). Eighty-four items were excluded based on impact analysis. The remaining 22 items could be further reduced by a method-mix of inter-item correlation, additional predefined criteria for item performance and review for content validity.

Conclusions: The AECT is the first tool to assess disease control in recurrent AE patients. Its retrospective approach, its brevity and its simple scoring make the AECT ideally suited for clinical practice and trials. Its validity and reliability need to be determined in future independent studies.

KEYWORDS

AECT, angioedema, development, disease control, impact analysis, item selection

Abbreviations: AAS, Angioedema Activity Score; AE, angioedema; AECT, Angioedema Control Test; AE-QOL, Angioedema Quality of Life Questionnaire; CSU, chronic spontaneous urticarial; CU, chronic urticarial; HAE, hereditary angioedema; PROM, patient-reported outcome measure; VRS, verbal rating scale.



GRAPHICAL ABSTRACT

After a conceptional framework was developed for the AECT, 106 potentially relevant questions were identified during the item generation phase. The subsequent item reduction process, based on a combined approach of impact analysis and additional methods, selected a final set of 4 questions. The final 4-item-AECT is easy-to-administer, easy-to-complete, and easy-to-score which makes it ideally-suited for clinical practice and trials.

Abbreviation: AECT, angioedema control test

1 | INTRODUCTION

Recurrent angioedema (AE) is a frequent and highly relevant group of disorders in dermatology, allergology and otorhinolaryngology, but also in general and emergency medicine. Two major forms of recurrent AE can be distinguished, (a) mast cell mediator–induced recurrent AE, most commonly observed in chronic spontaneous urticaria (CSU), and (b) bradykinin-mediated recurrent AE, for example in the context of hereditary or acquired angioedema due to C1-INH deficiency (HAE-C1-INH or AAE-C1-INH), hereditary angioedema (HAE) with normal C1-INH, or the intake of medication with effects on the contact system (eg, ACE inhibitors).[1,2] Angioedema (AE) and wheals may also occur as a symptom in the context of anaphylaxis and acute urticaria. However, in this case AE is usually not recurrent but only occur as single episodes.

Assessing the disease status in recurrent AE patients is not a trivial task. AE in recurrent AE almost always occurs unpredictably. AE frequency and severity vary considerably, from uncomplicated AE of the distal extremities to life-threatening laryngeal or severely painful abdominal AE attacks. The signs and symptoms of recurrent AE are usually absent when patients consult their physicians during regular appointments. Accordingly, it is difficult for physicians to reliably assess the disease status of recurrent AE patients. As of yet, the only tools available to determine the current disease situation in recurrent AE patients are the Angioedema Activity Score (AAS),[3] which measures disease activity, and the Angioedema Quality of Life Questionnaire (AE-QoL),[4] which assesses the impact of recurrent AE on the patient's life.

The AAS works as a daily diary and requires a certain level of patient compliance to yield reliable results.[5-8] It is a useful tool in clinical studies, but has limitations in daily routine care: (a) it works as a prospective tool, and accordingly, no AAS result can be obtained during a first patient contact; (b) its evaluation requires some practice and more time than is usually available in routine patient care.

The AE-QoL is a retrospective patient-reported outcome measure (PROM) that determines the extent and the pattern of recurrent AE-related quality of life impairment. Like the AAS, the AE-QoL proved to be a useful tool in clinical studies, but has limitations with regard to its application in daily care[5-9]: (a) its score calculation is rather complex so that its result is usually not immediately available during the patient consultation, that is when treatment decisions need to be made, (b) the interpretation of its results and changes requires experience.

More importantly, the AAS and the AE-QoL measure disease activity and impact, respectively, but not disease control. Recurrent AE often results in patients being controlled by their disease. The burden and unpredictability of attacks that comes with having recurrent AE result in reduced control or a loss of control in virtually all areas of patients' life including their partnerships and family life and planning, performance at school and work, career and lifestyle choices including travel, sports and leisure activities, sleep and relaxation, and mental health. In turn, disease control is a major treatment goal in recurrent AE management. Recurrent AE patients expect from their treating physicians' treatment and guidance that helps them to control their disease and to stop their lives from being controlled by their disease. For recurrent AE due to chronic urticaria, all recommended treatments are symptomatic

and aimed at the prevention of swellings, and the current international guideline recommends the use of PROMS to assess and monitor disease control.[10] The current international guideline for HAE recommends "that patients are evaluated for long-term prophylaxis at every visit" and that "disease burden and patient preference should be taken into consideration".[11] This guideline also recommends the use of PROMs to assess and monitor patients. However, a tool to assess disease control in patients with recurrent AE is not yet available.

This prompted us to develop a novel, retrospective PROM for recurrent AE to quantify and monitor disease control, the Angioedema Control Test (AECT). The aim of the development process was to generate a PROM that is as straightforward and as short as possible, easy to administer and fast to complete, as well as easy and fast to evaluate and to interpret.

2 | METHODS

The development of the AECT consisted of two main phases, item generation as well as item reduction and selection. The methods applied followed current recommendations for PROM development.[12]

2.1 | Item generation

The first step of the item generation phase was to convene an expert working group to (a) generate a conceptual framework for the AECT, (b) to contribute to the development of potential AECT items including their answer options and the definition of recall periods, (c) to define methods and criteria for the reduction and selection of AECT items, (d) to review the reduction process of AECT items for content (face) validity and (e) to define criterion measures of angioedema control (anchors) to be used during the validation of the AECT.

In a second step, an unselected list of potential AECT items and answer options was generated by means of semi-structured patient interviews, literature review and expert opinion from the expert working group. Answer options had to (a) be understandable and appropriately worded, (b) have similar intervals between response choices (to enable subjects to clearly identify the individually best

TABLE 1 Patient sample characteristics

	AECT item generation phase (patient interviews)			AECT item selection phase (patient study)		
	All patients	Mast cell mediator–induced recurrent AE	Bradykinin-mediated recurrent AE	All patients	Mast cell mediator–induced recurrent AE	Bradykinin-mediated recurrent AE
Patient, n (%)	25 (100%)	9 (36%)	16 (64%)	97 (100%)	49 (51%)	48 (49%)
Gender						
Female	16 (64%)	7 (78%)	9 (56%)	58 (60%)	31 (63%)	27 (56%)
Male	9 (36%)	2 (22%)	7 (44%)	39 (40%)	18 (37%)	21 (44%)
Age						
≤20 y	1 (4%)	1 (11%)	–	1 (1%)	–	1 (2%)
21-40 y	9 (36%)	3 (33%)	6 (38%)	28 (29%)	9 (18%)	19 (40%)
41-60 y	8 (32%)	2 (22%)	6 (38%)	35 (36%)	18 (37%)	17 (35%)
61-80 y	7 (28%)	3 (33%)	4 (25%)	32 (33%)	22 (45%)	10 (21%)
>80 y	–	–	–	–	–	
Unknown	–	–	–	1 (1%)	–	1 (2%)
Disease duration						
0-2 y	–	–	–	15 (15%)	12 (24%)	3 (6%)
>2-10 y	–	–	–	25 (26%)	23 (47%)	2 (4%)
>10 y	–	–	–	54 (56%)	13 (27%)	41 (85%)
Not assessed/Unknown	25 (100%)	9 (100%)	16 (100%)	3 (3%)	1 (2%)	2 (4%)
Disease severity[a]						
Mild	3 (12%)	2 (78%)	1 (6%)	–	–	–
Moderate	17 (68%)	7 (22%)	10 (63%)	–	–	–
Severe	5 (20%)	–	5 (31%)	–	–	–
Unknown	–	–	–			

Abbreviations: AE, angioedema; AECT, Angioedema Control Test.

[a]Physician global assessment.

(A)

Angioödemkontrolltest (AECT)

Name: _____ Datum: ____ . ____ . _____

Geburtsdatum: ____ . ____ . _____

Anleitung: Sie haben wiederkehrende Schwellungen (Angioödeme). Angioödeme sind flüchtige, viele Stunden bis wenige Tage anhaltende, tief sitzende Schwellungen der Haut oder Schleimhäute, z.B. der Lippen, Augenlider, der Zunge, Hände oder Füße. Manche Patienten leiden auch unter Angioödemen im Bauchinnenraum. Diese sind oft nicht sichtbar aber schmerzhaft. Bei anderen Patienten können neben Angioödemen auch Quaddeln an der Haut auftreten.

Mit den folgenden vier Fragen soll Ihre aktuelle Krankheitssituation erfasst werden. Bitte wählen Sie aus den fünf Antwortmöglichkeiten jeweils diejenige aus, die für Sie *am besten zutrifft*. Bitte beantworten Sie *alle Fragen* und wählen Sie *für jede Frage nur eine Antwort* aus.

1. Wie oft hatten Sie in den letzten 3 Monaten Angioödeme?

   O sehr oft O oft O gelegentlich O selten O gar nicht

2. Wie sehr war Ihre Lebensqualität in den letzten 3 Monaten durch Angioödeme beeinträchtigt?

   O sehr stark O stark O mittelmäßig O kaum O gar nicht

3. Wie sehr hat Sie die Unvorhersagbarkeit von Angioödemen in den letzten 3 Monaten belastet?

   O sehr stark O stark O mittelmäßig O kaum O gar nicht

4. Wie gut waren Ihre Angioödeme in den letzten 3 Monaten durch Ihre Therapie unter Kontrolle?

   O gar nicht O kaum O mittelmäßig O gut O sehr gut

(B)

Angioedema Control Test (AECT)

Patient name: _____ Date: (dd mmm yyyy): ___ ___ _____

Date of birth (dd mmm yyyy): ___ ___ _____

Instructions: You have recurrent swelling referred to as angioedema. Angioedema is a temporary swelling of the skin or mucous membranes which can occur in any part of the body but most commonly involves the lips, eyes, tongue, hands and feet and which can last from hours to days. Some patients develop abdominal angioedema, which is often not visible but painful. Some forms of swelling can also be associated with hives also known as urticaria.

The following four questions assess your current state of health. For each question, please choose the answer from the five options that *best fits your situation*. Please answer *all questions* and please provide *only one answer to each question*.

1. In the last 3 months, how often have you had angioedema?

   O very often O often O sometimes O seldom O not at all

2. In the last 3 months, how much has your quality of life been affected by angioedema?

   O very much O much O somewhat O a little O not at all

3. In the last 3 months, how much has the unpredictability of your angioedema bothered you?

   O very much O much O somewhat O a little O not at all

4. In the last 3 months, how well has your angioedema been controlled by your therapy?

   O not at all O a little O somewhat O well O very well

FIGURE 1 A, Angioedema Control Test (AECT)—German version. B, AECT—American-English Translation [Color figure can be viewed at wileyonlinelibrary.com]

matching response), (c) allow for, but not favour, extreme answers and (d) not require patients to consult any records.

In total, 25 patients were included in the semi-structured patient interviews until saturation was reached, that is until the performance of additional interviews was not likely to add further aspects relevant for item generation (mean age in years ± SD: 46.9 ± 15.9, median: 51; CSU: n = 9, mean age in years ± SD: 45.0 ± 17.1, median: 52; HAE: n = 16, mean age in years ± SD: 47.6 ± 15.7, median: 46.5; Table 1). During these interviews, all patients were asked to describe in their own words:

- The recurrent AE signs and symptoms they are experiencing or have experienced in the past
- What it means for them to suffer from recurrent AE
- What bothers them the most with regard to their recurrent AE
- What questions best to be asked in order to determine how well their recurrent AE is currently under control.

In addition, all patients were asked, which recall period is sufficient and appropriate in order to determine reliable information on the current level of AE control. Eligible for inclusion were all adult patients with mast cell mediator–mediated or bradykinin–mediated recurrent AE.

The literature review was performed on already existing outcome measures in the field of recurrent AE, data on the signs and symptoms of recurrent AE, and data on the impact of recurrent AE on patients' lives. We also assessed published information on how to best measure disease control in conditions with a pattern of unpredictable symptom occurrence and high variability of disease activity, that is conditions that are comparable to recurrent AE such as asthma, chronic urticaria and migraine.

2.2 | AECT item reduction and selection phase

The aim of the item reduction and selection phase was (a) to delete all items of the unselected list of potential AECT items with low relevance and importance for the patients, (b) to delete all redundant items in favour of items with equal or better properties, (c) to delete as many questions as possible in order to minimize the burden for patients (respondent burden), but also to keep as many items as required to maintain a high level of content validity.

In order to achieve these aims, recurrent AE patients were recruited at the AE specialist centre of the Department of Dermatology and Allergy, Charité—Universitätsmedizin, into the AECT item selection study, after approval had been obtained from the responsible institutional review board (*ethics vote number: EA1/286/15*). All participants provided written informed consent. Eligible for inclusion were, as in the semi-structured interviews, all adult patients with expert-diagnosed mast cell mediator–mediated or bradykinin–mediated recurrent AE. In the AECT item selection study, participants were asked to answer all potential AECT items of the unselected list of the item generation phase as well as to evaluate each item's understandability by using paper forms. In addition, an impact analysis was performed.

2.2.1 | Impact analysis

For the impact analysis,[13,14] all patients were asked to specify which of the potential AECT items they had experienced during the last year (answer options: "yes" or "no") and to rate the importance of each item (answer options: 1 = "not important" to 5 = "extremely important"). Each item's "frequency" was then calculated as the percentage of patients who reported to have experienced the item. Each item's "importance" was calculated as the mean of all available importance scores. Subsequently, each item's "impact" (impact score) was computed by the multiplication of "frequency" and "importance."

2.2.2 | Inter-item correlation

An inter-item correlation was performed to identify redundant items by using Spearman rank correlation with the results of all items selected during the impact analysis. The interpretation of the Spearman rank correlation coefficient was as follows: .3-.49 moderate correlation, .5-.69 strong correlation, ≥.7 very strong correlation (indicating redundancy of items).

2.2.3 | Criteria for the deletion of items

The primary criterion for the deletion of items from the unselected list was a low impact score (<1.5 points) in the impact analysis.

Additional criteria for not selecting items for the final AECT were as follows:

- Floor and ceiling effects (items for which a major proportion of patients [>40%] chose response options at the VRS ends, indicating a poor variability of responses)
- Missing responses (items with a considerable number of missing responses [>5%], indicating poor relevance of the item or difficulties of the patients to understand the item content)
- Poor relevance (items that were indicated as relevant by <70% of patients in the impact analysis ["frequency" of <0.7])
- Very strong inter-item correlation (item-item correlation of ≥.7 as a measure of item redundancy [see also above]; items are deleted in favour of alternative items with better properties and/or better face validity for collection of the intended item content)
- Absolute values of the impact score (in case of redundant items with an impact score ≥1.5, the items with lower impact scores were deleted)
- Poor understandability (items marked as poorly understandable by >5% of patients)
- Poor content validity (expert group agrees that an item or item set needs to be deleted or replaced to ensure/maintain the content [face] validity of the final AECT item set)

TABLE 2 Selection, reduction or adjustment of items after impact analysis

Items	Item content	Item domain	Impact score	Discrepancy of impact score (HAE vs CSU)[a]	Inter-item correlation ($r \geq .7$)
1	Suffering from skin swelling (how often)	Signs and symptoms	1.82	–	Item 2
2	Suffering from skin swelling (how much)	Signs and symptoms	1.62	–	Item 1
5	Suffering from skin swelling in the face (how often)	Signs and symptoms	1.54	++ (CSU > HAE)	–
13	Suffering from painful swelling (how often)	Signs and symptoms	1.62	+++ (HAE > CSU)	Items 14, 31, 73
14	Suffering from painful swelling (how much)	Signs and symptoms	1.56	++ (HAE > CSU)	Items 13, 31
31	Impairment of physical fitness (how often)	Quality of life	1.59	+ (HAE > CSU)	Items 13, 14, 47, 49, 50, 73
47	Impairment of work, school or housekeeping (how often)	Quality of life	1.60	–	Items 31, 49, 50, 73
49	Impairment of private life (how often)	Quality of life	1.58	–	Items 31, 47, 50, 73, 74
50	Impairment of private life (how much)	Quality of life	1.55	–	Items 31, 47, 49, 73, 74
73	Impairment of quality of life (how often)	Quality of life	1.94	–	Items 13, 31, 47, 49, 50, 74, 75
74	Impairment of quality of life (how much)	Quality of life	1.98	–	Items 49, 50, 75, 76
75	Suffering from unpredictability of swelling episodes (how much)	Anxiety/Fears	1.87	–	Items 73, 74, 76, 77, 78, 79, 80
76	Feeling insecure (how often)	Anxiety/Fears	1.59	–	Items 74, 75, 77, 78, 79, 80
77	Fear of new swelling episodes (how often)	Anxiety/Fears	1.91	–	Items 75, 76, 78, 79, 80
78	Fear of new swelling episodes (how much)	Anxiety/Fears	1.85	–	Items 75, 76, 77, 79, 80
79	Fear of a worsening of the angioedema disorder (how often)	Anxiety/Fears	1.59	–	Items 75, 76, 77, 78, 80
80	Fear of a worsening of the angioedema disorder (how much)	Anxiety/Fears	1.59	–	Items 75, 76, 77, 78, 79
101	Treatment sufficient to control angioedema complaints (how often)	Effectiveness of therapy	2.69	–	Items 104, 106
102	Treatment not sufficient to control angioedema complaints (how often)	Effectiveness of therapy	1.98	–	–
103	Unplanned intake of medication for swelling episodes (how often)	Effectiveness of therapy	2.08	+ (HAE > CSU)	–
104	Feeling of control over the swelling episodes because of current treatment (how much)	Effectiveness of therapy	2.88	–	Item 101
106	Overall control over recurrent swelling episodes (how well)	–	2.87	–	Item 101

Abbreviations: AE, angioedema; AECT, Angioedema Control Test; CSU, chronic spontaneous urticarial; HAE, hereditary angioedema.

[a]Discrepant impact score between CSU and HAE patients (+ > 0.5, ++ > 1.0, +++ > 1.5, for details also see Table S1)

[b]Additional Reasons for not selecting items for the final AECT: b1) floor responses >40%, b2) ceiling responses >40%, b3) missing values in >5% of patients, b4) frequency <0.7 (<70%).

Additional reasons suggesting deletion of item[b]	Interpretations and expert consensus on the selection, deletion or adjustment of items
–	• Items 1, 2, 5, 13 and 14 comprise of questions best assignable to one domain (signs and symptoms).
–	• Items 1, 5 and 13 on the frequency (how often) of swellings episodes scored higher in the impact analysis as compared to the directly related, redundant items 2, 6 and 14 with a severity rating (how much). Accordingly, the "signs and symptom" item should ask for the frequency.
b1, b4	• The experts decided that it makes sense to only include one item on RA "signs and symptoms" in the final AECT in order to avoid an overrepresentation of the "signs and symptoms" domain in the final AECT.
b1, b4	• The experts concluded that none of the impact analysis suggested items 1, 2, 5, 13 and 14 has the property to serve as an overarching "signs and symptoms" item for CSU and HAE since the items either only ask for skin swelling episodes, skin swelling episodes in the face or painful swelling episodes.
b1, b4	• The experts decided to replace items 1, 2, 5, 13 and 14 by the overarching item: "How often have you had angioedema" that works independent of skin area, body area (dermal, mucosal, intra-abdominal) or pain.
b4	• Items 31, 47, 49 and 50 represent specific items to determine "functioning" and "social" aspects of health-related quality of life impairment due to recurrent AE.
b4	• The experts decided that it makes no sense from the content validity perspective to combine overarching items 73 and 74 and more specific items 31, 47, 49 and 50 in the final AECT and to only keep one overarching item in the final AECT, also having the administrator and respondent burden in mind.
b4	• The impact scores of the overarching quality of life items 73 and 74 are higher as compared to the impact scores of items 31, 47, 49 and 50.
–	• The overarching quality of life items 73 and 74 but not items 31, 47, 49 and 50 reach the additional criterion of frequency >70% (see Table S1).
–	• The impact score was marginally higher for item 74 as compared to item 73. In accordance with this result, the expert group felt that from the content validity perspective it makes more sense to determine information on how much the quality of life is impaired by recurrent AE than to ask for how often quality of life was impaired.
	• The inter-item correlation supported the selection of item 74 for the AECT, since item 74 showed very strong correlations (surrogate for redundancy) with all other items 31, 47, 49, 50 and 73.
–	• Items 75, 76, 77, 78, 79 and 80 represent specific items to determine "anxiety/fears" associated with recurrent AE.
b4	• The experts decided that it makes sense to select only one question from the domain "anxiety/fears" in order to not overrepresent this aspect in the final AECT, also having the administrator and respondent burden in mind.
–	• The experts felt that the unpredictability of recurrent AE attacks is a major driver of anxiety and fears associated with recurrent AE. The unpredictability of attacks goes along with a feeling of being insecure (item 76), the fear of new swelling episodes (items 77 and 78) as well as the fear of a worsening of the recurrent AE disorder in general (items 79 and 80).
–	• The impact scores of items 75, 77 and 78 were higher as compared to items 76, 79 and 80.
	• Items 75, 77 and 78 but not items 76, 79 and 80 reached the additional criterion of frequency >70% (see Table S1).
b4	• The experts regarded item 75 to best capture information on the "anxiety/fears" domain.
	• The inter-item correlation supported the selection of item 75 for the AECT, since item 75 showed very strong correlations (surrogate for redundancy) with all other items 76, 77, 78, 79 and 80 of the "anxiety/fears" domain
b4	
b2, b3	• Items 101, 102, 103 and 104 represent specific items to determine "effectiveness of treatment" for recurrent AE.
b2, b3, b4	• The experts felt a major redundancy between items 101, 102, 103, 104 and item 106, although the latter does not address "effectiveness of treatment" specifically. This feeling was backed by the very strong inter-item correlation between item 101 and items 104 and 106.
b3, b4	• The experts decided that it makes sense to select only one item from the domain "effectiveness of treatment" in order to not overrepresent this aspect in the final AECT, also having the administrator and respondent burden in mind.
	• The impact scores of items 104 and 106 were higher as compared to items 101, 102 and 103.
b3	• All items 101, 102, 103 and 104 but not 106 exhibited additional criteria for not selecting items (ie, floor effects, ceiling effects, missing items, frequency <70%).
–	• The experts felt from the content validity (face validity) perspective that item 106 is not a suitable item to capture "effectiveness of treatment" but due to its overarching nature also not a suitable item for the AECT in general.
	• The experts decided to replace items 101, 102, 103, 104 and 106 by a new item combining the content of items 101 and 106: "how well has your angioedema been controlled by your therapy",

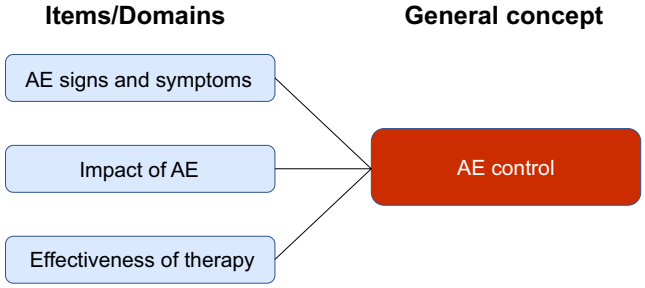


FIGURE 2 Conceptional framework of the Angioedema Control Test (AECT) [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Final formatting of the AECT

After the item reduction and selection phase were completed, the selected item set was used as the final AECT in a following validation study. In addition, an instruction section was generated by the expert group. The aim of the instruction section was to ensure that the AECT can be used as a self-administered questionnaire, that is that all patients are able to fully understand and correctly complete the AECT without further help of any other person. Subsequently, cognitive debriefing interviews were performed with three recurrent AE patients in order to verify the clarity and readability of the instruction section as well as of the selected item set and their response options.

2.4 | Development of an American-English version

To generate a US-American-English version of the AECT, two independent forward translations to US-American-English were performed by native US-American-English speakers bilingual in the source language German. Both forward translations were reconciled and then reviewed and edited by an US-American AE expert. Subsequently, a back-translation was performed by a German native speaker bilingual in the target language and the backward translation was compared with the original German AECT and a final US-American-English consensus version was generated.

2.5 | Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics Version 22; IBM Corporation). The statistical methods applied are described in the respective Methods and/or Results sections of this manuscript.

3 | RESULTS

This work resulted in the generation of the 4-item Angioedema Control Test (AECT; Figure 1A). We also developed, in a structured translation process, an US-American-English version of the AECT (Figure 1B). In the following, the results of the item generation and item selection process are described.

3.1 | Conceptional framework

As a result of the development of the conceptional framework of the AECT (Figure 2), its main purposes were defined to be (a) the detection of the overall level of recurrent AE control and (b) the detection of changes in angioedema control over time, for example before and after the adjustment of therapy. Recurrent AE control was defined as the level of control over recurrent AE (its signs and symptoms as well as its impact) that is achieved by the current treatment strategy (effectiveness of treatment). The target group of the AECT was defined as all patients with recurrent AE including patients with mast cell mediator–induced recurrent AE and patients with bradykinin-mediated recurrent AE. Accordingly, it was regarded as critical to include patients with both recurrent AE subtypes in the AECT development process. The type of assessment done with the AECT was defined as being retrospective to make sure that AECT results are available directly after administration and because a retrospective assessment has proven useful in other already available and well-established disease control tests.[14,15]

3.2 | AECT item generation

As the result of the item generation phase, an unselected list of 106 potential AECT items was created based on the combined approach of patient, literature and expert input (Table S1). Answer options were generated as 5-point verbal rating scales (VRS). The format of the 5-point (VRS) was regarded, by the expert group, to best allow for an appropriate, balanced set of options that does not bias the direction of responses towards one end of the scale (with a classical middle option, two extreme options and two intermediate options). Another basis for the decision to use a 5-point VRS was that this scale has been found to work well in already existing disease control tests.[14,15] The score range of all answer options was defined to be similar for all items (0-4 points) to ensure equally weighted item scores, with low item scores indicating response options associated with poor disease control and high item scores indicating response options associated with well-controlled recurrent AE.

Finally, the recall period was defined based on the expert and patient input to be 3 months. However, the duration of patient suggested recall periods varied widely, and some experts felt that a recall period of 4 weeks is sufficient in many patients. Therefore, it was decided by the expert group to include two AECT versions in a subsequent validation study, one with a recall period of 4 weeks and another with a recall period of 3 months.

TABLE 3 Inter-item correlation of items selected by the impact analysis (analysis of all patients, n = 97)

Items	1	2	5	13	14	31	47	49	50	73	74	75	76	77	78	79	80	101	102	103	104	106
1	1.00	.80	.55	.57	.56	.54	.54	.60	.53	.67	.57	.40	.39	.39	.36	.31	.32	.37	.46	.52	−.24	−.44
2	.80	1.00	.49	.49	.40	.50	.49	.55	.55	.64	.57	.40	.39	.38	.35	.31	.36	.41	.41	.40	−.32	−.48
5	.55	.49	1.00	.31	.25	.39	.36	.39	.42	.49	.52	.50	.46	.37	.42	.47	.47	.45	.45	.23	−.54	−.52
13	.57	.49	.31	1.00	.93	.71	.69	.69	.67	.72	.61	.57	.49	.54	.54	.50	.51	.30	.39	.61	−.23	−.38
14	.56	.40	.25	.93	1.00	.70	.63	.63	.63	.68	.58	.56	.49	.53	.52	.45	.45	.26	.36	.56	−.16	−.35
31	.54	.50	.39	.71	.70	1.00	.76	.74	.73	.71	.67	.57	.54	.58	.54	.53	.53	.36	.53	.58	−.25	−.41
47	.54	.49	.36	.69	.63	.76	1.00	.84	.80	.74	.68	.51	.49	.57	.52	.50	.48	.29	.54	.57	−.27	−.43
49	.60	.55	.39	.69	.63	.74	.84	1.00	.91	.80	.72	.55	.53	.54	.50	.52	.49	.37	.44	.53	−.35	−.42
50	.53	.55	.42	.67	.63	.73	.80	.91	1.00	.81	.77	.65	.63	.62	.58	.59	.58	.40	.43	.54	−.44	−.48
73	.67	.64	.49	.72	.68	.71	.74	.80	.81	1.00	.91	.70	.68	.64	.63	.58	.58	.40	.43	.55	−.39	−.50
74	.57	.57	.52	.61	.58	.67	.68	.72	.77	.91	1.00	.75	.72	.66	.65	.62	.61	.42	.44	.46	−.42	−.48
75	.40	.40	.50	.57	.56	.57	.51	.55	.65	.70	.75	1.00	.83	.81	.83	.79	.78	.38	.40	.47	−.40	−.43
76	.39	.39	.46	.49	.49	.54	.49	.53	.63	.68	.72	.83	1.00	.76	.75	.74	.72	.39	.38	.40	−.45	−.38
77	.39	.38	.37	.54	.53	.58	.57	.54	.62	.64	.66	.81	.76	1.00	.96	.82	.79	.31	.41	.49	−.31	−.35
78	.36	.35	.42	.54	.52	.54	.52	.50	.58	.63	.65	.83	.75	.96	1.00	.84	.82	.32	.36	.44	−.33	−.35
79	.31	.31	.47	.50	.45	.53	.50	.52	.59	.58	.62	.79	.74	.82	.84	1.00	.96	.29	.37	.42	−.38	−.33
80	.32	.36	.47	.51	.45	.53	.48	.49	.58	.58	.61	.78	.72	.79	.82	.96	1.00	.31	.37	.46	−.39	−.33
101	.37	.41	.45	.30	.26	.36	.29	.37	.40	.40	.42	.38	.39	.31	.32	.29	.31	1.00	.51	.17	−.81	−.73
102	.46	.41	.45	.39	.36	.53	.54	.44	.43	.43	.44	.40	.38	.41	.36	.37	.37	.51	1.00	.38	−.51	−.57
103	.52	.40	.23	.61	.56	.58	.57	.53	.54	.55	.46	.47	.40	.49	.44	.42	.46	.17	.38	1.00	−.17	−.30
104	−.24	−.32	−.54	−.23	−.16	−.25	−.27	−.35	−.44	−.39	−.42	−.40	−.45	−.31	−.33	−.38	−.39	−.81	−.51	−.17	1.00	.66
106	−.44	−.48	−.52	−.38	−.35	−.41	−.43	−.42	−.48	−.50	−.48	−.43	−.38	−.35	−.35	−.33	−.33	−.73	−.57	−.30	.66	1.00

Note: Values represent the Spearman's rank correlation coefficient. Spearman's rank correlation coefficients ≥.7 indicate very strong correlations that may be interpreted as a marker of redundancy and are highlighted in grey.

3.3 | AECT item selection

In total, 97 recurrent AE patients took part in the AECT item selection study (mean age in years ± SD: 50.5 ± 15.5, median: 49.5). Of these, 49 had mast cell mediator–induced recurrent AE (mean age in years ± SD: 55.4 ± 14.6, median: 54) and 48 had bradykinin-mediated recurrent AE (mean age in years ± SD: 45.4 ± 15.3, median: 43; Table 1).

The impact analysis, as the primary method to reduce items, excluded 84 items, based on a low impact score of <1.5, in all of which additional deletion criteria also applied (Table S1). None of the 22 remaining items was marked as poorly understandable by >5% of patients. Separate impact analyses for patients with mast cell mediator–induced and bradykinin-mediated recurrent AE (Table S2a,b) showed that the former exhibit higher impact scores for items addressing AE in the face, impairment of appearance due to AE, and itching of AE. Patients with bradykinin-mediated recurrent AE had higher impact scores for items addressing intra-abdominal AE, painful AE and impairment of physical fitness due to AE.

The 22 items with an impact score ≥1.5 were found by the expert group to be attributable to four domains: "signs and symptoms," "quality of life," "anxiety/fear" and "effectiveness of treatment" (Table 2). In order to further reduce the item set, an inter-item correlation was done (Table 3). Very strong correlations were identified primarily between items previously assigned to the same domains, further supporting the domain structure and providing a basis for the deletion due to redundancy inside the domains (documented in Table 2). No major differences with regard to the direction and overall pattern of the correlations were detected between both recurrent AE patient groups (Table S3a,b).

The use of the impact score and discrepancies between the two recurrent AE patient groups, of the inter-item correlation, positivity of additional predefined criteria for the deletion of items as well as a review for content (face) validity by the expert group with regard to single item content but also the overall composition of items led to a selection of a final set of 4 AECT items. Details on the decisions for deleting, keeping order modifying single items are documented in Table 2.

4 | DISCUSSION

In all patients with recurrent AE, a repeated assessment of the disease status is critical to evaluate whether the current treatment is still sufficient or not. Recurrent AE disease activity can vary strongly over time, and insufficiently controlled disease goes along with an increased risk for life-threatening AE episodes and major impairment of patients' quality of life.[6,16-21] On the other hand, an adjustment of treatment may increase treatment costs, for example when a CSU patient's therapy is changed from an antihistamine to omalizumab or when a prophylaxis with a C1 inhibitor or lanadelumab is initiated in HAE patients.[22,23] Accordingly, the assessment of disease control in recurrent AE should be performed by using a valid and reliable approach. This ensures that changes in treatment are done in the right (undertreated) patients and that the reasons for keeping or changing a therapy are well-documented. Here, we report the development of a tool that makes this possible, the AECT, the first PROM to instantly assess angioedema control in recurrent AE patients.

After the development of a conceptual framework for the AECT, 106 items were generated by a combined approach of different methods ensuring that all important perspectives (of patients and experts) were adequately considered. We regarded it as critical to not preselect any contents for the 106 item long list of the item generation phase to avoid missing any unexpected aspects important to patients. In the subsequent AECT item selection study, patient input was again critical. The results of the impact analysis served as the primary criterion for item deletion. A mix of additional criteria made it possible to extract only the most important items (contents) from the remaining 22 items after the impact analysis and to reduce the total number of items to only four. This final set of four AECT items was found to be well in line with the initially developed conceptual framework, with three items clearly attributable to the domains "signs and symptoms," "impact" and "effectiveness of treatment," respectively. The 4th item addresses the important aspect of unpredictability, which correlates strongly with anxiety and fears of recurrent AE patients (inter-item correlation analysis).

Notably, the content of the four selected items resembles the contents and item number identified in the development process of the Urticaria Control Test (UCT), which has been proven to be well suited for the assessment of disease control in patients with chronic urticaria. Chronic urticaria shares important characteristics with recurrent AE, such as the unpredictable occurrence of signs and symptoms and the high variability of disease activity. Finally, the selection of only 4 items for the final AECT ensures a low administrator and patient (respondent) burden, which is of paramount importance for the broad acceptance and implementation of PROMs in daily patient care.

It was the aim to develop an overarching control test that works equally well in all types of recurrent AE. However, there are some evident clinical differences between the two main disease groups included in this work, mast cell mediator–mediated recurrent AE, for example in CSU patients, and bradykinin-mediated recurrent AE, for example in patients with HAE. While HAE but not CSU patients frequently suffer from painful abdominal attacks, CSU patients' AE sometimes presents with an itch component. Accordingly, special attention was given to equal relevance and importance of all finally selected items for both disease groups by the expert working group. Fortunately, the predefined criteria for item deletion only led to remaining items with comparable relevance and importance for CSU and HAE patients.

This report does not provide answers on the validity and reliability of the AECT and its results. In addition, a clear cut-off value still needs to be established for the identification of patients with poorly vs well-controlled recurrent AE, which is critical for guiding treatment decisions. Finally, the smallest score change that is meaningful for patients (minimal clinically important difference) needs to be identified in order to enable an adequate

interpretation of AECT score changes over time, for example before and after treatment adjustment. All of this will be addressed by an ongoing validation study.

Since it was difficult to determine the best suitable recall period from the patients' perspective but also from the experts' view, the AECT validation study will also address and answer this question by carrying two AECT versions, one with a recall period of 4 weeks and another with a recall period of 3 months.

The limitations of this work include that (a) only CSU and HAE patients took part in the item generation and selection phases but no recurrent AE patients of other causes, for example ACE-inhibitor–associated AE. Accordingly, it cannot be fully excluded that item selection would have been different in the missing patient groups. (b) Although most criteria of the item reduction were predefined and transparent, the review for content (face) validity always carries a subjective component, so that it cannot be excluded that a different expert working group may have decided slightly differently with regard to the finally selected items. (c) While a higher proportion of female patients in this study was expected based on the known female preponderance among recurrent AE patients, it may also have caused a gender bias in the AECT questionnaire. Therefore, it is important to consider and examine potential gender differences in AECT results and clinimetric properties in future validation studies. (d) Finally, no children or adolescents were included in this work, which makes it unclear if the AECT item set is equally well suited for children and adolescents.

In conclusion, the final 4-item AECT is the first PROM to assess disease control in recurrent AE patients. Its retrospective approach, its brevity and its simple scoring ensure a low administrator and patient burden and allow for its application in daily patient care and clinical trials. Validation studies are needed to further characterize the AECT validity, the AECT reliability and to define relevant cut-off values.

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CONFLICT OF INTEREST

Karsten Weller reports grants from Shire, nonfinancial support from Moxie, during the conduct of the study; personal fees from Novartis, personal fees from Moxie, personal fees from Shire and personal fees from CSL Behring, outside the submitted work. Tamara Donoso reports grants from Shire, during the conduct of the study. Markus Magerl reports grants from Shire/part of Takeda, during the conduct of the study, personal fees from CSL Behring, personal fees from Shire/part of Takeda, personal fees from Novartis, personal fees from BioCryst, personal fees from KalVista and personal fees from Pharming, outside the submitted work. Emel Aygören-Pürsün reports grants and personal fees from Shire/Takeda, during the conduct of the study, personal fees from Adverum, personal fees from BioCryst, grants and personal fees from CSl Behring, personal fees from KalVista and personal fees from Pharming, outside the submitted work. Petra Staubach reports personal fees and nonfinancial support from Takeda, personal fees and nonfinancial support from Shire, personal fees and nonfinancial support from CSL Behring, grants, personal fees and nonfinancial support from Novartis and personal fees from Pfleger, outside the submitted work. Inmaculada Martinez-Saguer has nothing to disclose. Tomasz Hawro reports grants from Shire, during the conduct of the study. Sabine Altrichter reports grants from Shire, during the conduct of the study, grants and personal fees from AstraZeneca, nonfinancial support from Moxie, grants and nonfinancial support from Allakos, grants and nonfinancial support from Novartis, outside the submitted work. Karoline Krause reports grants from Shire, during the conduct of the study, grants from Shire, grants and personal fees from Novartis, other from MOXIE, outside the submitted work. Frank Siebenhaar reports grants from Shire, nonfinancial support from Moxie, during the conduct of the study, grants and personal fees from Novartis, grants and personal fees from Allakos, grants and personal fees from Blueprint, personal fees from Glenmark, personal fees from Pediapharma, personal fees from Uriach, outside the submitted work. Martin Metz reports grants from Shire, during the conduct of the study, personal fees from Moxie, personal fees from Novartis, personal fees from Sanofi, nonfinancial support from Shire, outside the submitted work. Torsten Zuberbier reports grants from Shire, during the conduct of the study; personal fees from Bayer Health Care, personal fees from FAES, personal fees from Novartis, personal fees from Henkel, grants from Novartis, grants from Henkel, personal fees from AstraZeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer Health Care, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from HAL, personal fees from Leti, personal fees from Meda, personal fees from Menarini, personal fees from Merck, personal fees from MSD, personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, personal fees from Henkel, personal fees from Kryolan and personal fees from L'Oreal, outside the submitted work. Denise Freier reports grants from Shire, during the conduct of the study. Marcus Maurer reports grants and personal fees from Shire, grants and personal fees from Moxie, during the conduct of the study, grants and personal fees from Allakos, grants from AstraZeneca, grants and personal fees from BioCryst, grants and personal fees from CSL Behring, grants and personal fees from FAES, grants and personal fees from Genentech, grants and personal fees from KalVista, grants and personal fees from Novartis, grants and personal fees from Leo Pharma, grants and personal fees from Moxie, grants and personal fees from MSD,

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AUTHOR CONTRIBUTIONS

Karsten Weller has made substantial contributions to conception and design, to acquisition of data, to analysis and interpretation of data, and he has been involved in drafting the manuscript. Tamara Donoso has made substantial contributions to acquisition of data, to analysis and interpretation of data, and she has been involved in drafting the manuscript. Markus Magerl has made substantial contributions to conception and design, to acquisition of data, to analysis and interpretation of data, and he has been involved in drafting the manuscript. Emel Aygören-Pürsün has made substantial contributions to acquisition of data, and she has been involved in revising the manuscript critically for important intellectual content. Petra Staubach has made substantial contributions to acquisition of data, and she has been involved in revising the manuscript critically for important intellectual content. Inmaculada Martinez-Saguer has made substantial contributions to acquisition of data, and she has been involved in revising the manuscript critically for important intellectual content. Tomasz Hawro has made substantial contributions to acquisition of data, to analysis and interpretation of data, and he has been involved in revising the manuscript critically for important intellectual content. Sabine Altrichter has made substantial contributions to acquisition of data, and she has been involved in revising the manuscript critically for important intellectual content. Karoline Krause has made substantial contributions to acquisition of data, and she has been involved in revising the manuscript critically for important intellectual content. Frank Siebenhaar has made substantial contributions to acquisition of data, and he has been involved in revising the manuscript critically for important intellectual content. Martin Metz has made substantial contributions to acquisition of data, and he has been involved in revising the manuscript critically for important intellectual content. Torsten Zuberbier has made substantial contributions to acquisition of data, and he has been involved in revising the manuscript critically for important intellectual content. Denise Freier has made substantial contributions to acquisition of data, and she has been involved in revising the manuscript critically for important intellectual content. Marcus Maurer has made substantial contributions to conception and design, to acquisition of data, to analysis and interpretation of data, and he has been involved in drafting the manuscript. All authors gave final approval of the version to be published, and all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. Buttgereit T, Maurer M. Classification and pathophysiology of angioedema. *Hautarzt*. 2019;70(2):84-91.
2. Magerl M, Brasch J, Forster U, et al. Diagnostics and exclusion of hereditary angioedema: a standardized approach for the practice. *Hautarzt*. 2012;63(7):567-572.
3. Weller K, Groffik A, Magerl M, et al. Development, validation, and initial results of the Angioedema Activity Score. *Allergy*. 2013;68(9):1185-1192.
4. Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012;67(10):1289-1298.
5. Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. *Front Med (Lausanne)*. 2017;4:212.
6. Weller K, Siebenhaar F, Hawro T, Altrichter S, Schoepke N, Maurer M. Clinical measures of chronic urticaria. *Immunol Allergy Clin North Am*. 2017;37(1):35-49.
7. Aygoren-Pursun E, Bygum A, Grivcheva-Panovska V, et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. *N Engl J Med*. 2018;379(4):352-362.
8. Nordenfelt P, Nilsson M, Lindfors A, Wahlgren CF, Bjorkander J. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2017;38(6):447-455.
9. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA*. 2018;320(20):2108-2121.
10. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
11. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy*. 2018;73(8):1575-1596.
12. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes*. 2006;4:79.
13. Juniper EF, Guyatt GH, Streiner DL, King DR. Clinical impact versus factor analysis for quality of life questionnaire construction. *J Clin Epidemiol*. 1997;50(3):233-238.
14. Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol*. 2014;133(5):1365-1372.
15. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65.
16. Bygum A, Aygoren-Pursun E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. *Acta Derm Venereol*. 2015;95(6):706-710.
17. Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013;111(5):329-336.

18. Engel-Yeger B, Farkas H, Kivity S, Veszeli N, Kohalmi KV, Kessel A. Health-related quality of life among children with hereditary angioedema. *Pediatr Allergy Immunol*. 2017;28(4):370-376.
19. Kuman Tuncel O, Gokmen NM, Demir E, Gulbahar O, Pirildar S. The impact of hereditary angioedema on quality of life and family planning decisions. *Int J Psychiatry Med*. 2019;54(6):377-394.
20. Mendivil J, Murphy R, Janssen E, Aygören-Pürsün E, Devercelli G, Boysen H. *Burden of Hereditary Angioedema: Findings from a Multinational Patient Survey in EU, Canada, and Australia*. Lissabon, Portugal: EAACI; 2019.
21. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2014;35(2):185-190.
22. Aygoren-Pursun E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014;9:99.
23. Zuraw BL. Cost-effectiveness of prophylactic medications for the treatment of hereditary angioedema due to C1 inhibitor deficiency: a real-world U.S. perspective. *J Manag Care Spec Pharm*. 2019;25(2):148-151.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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