Original Article

Psychometric Field Study of Hereditary Angioedema Quality of Life Questionnaire for Adults: HAE-QoL

Nieves Prior, MD, PhD[a], Eduardo Remor, PhD[b], Elia Pérez-Fernández, MSc[c], Magdalena Caminoa, MD[d], Carmen Gómez-Traseira, MD[d], Francisco Gayá, MSc[e], Anne Aabom, MD[f], Werner Aberer, MD[g], Stephen Betschel, MD[h], Isabelle Boccon-Gibod, MD[i], Laurence Bouillet, MD, PhD[i], Anette Bygum, MD, PhD, DSc[f], Dorottya Csuka, PhD[j], Henriette Farkas, MD, PhD, DSc[j], Maria Gomide, MD[k], Anete Grumach, MD, PhD[k], Iris Leibovich, RN, MA[l], Alejandro Malbran, MD[m], Dumitru Moldovan, MD, PhD[n], Eniko Mihaly, MD[n], Krystyna Obtulowicz, MD[o], Cecilia Perpén, SC[m], Adriane Peveling-Oberhag, MD[p], Grzegorz Porebski, MD[o], Celine Rayonne Chavannes, MBA[h], Avner Reshef, MD[l], Petra Staubach, MD, PhD[p], Michaela Wiednig, MD[g], and Teresa Caballero, MD, PhD[d,q] *Madrid, Spain; Odense, Denmark; Graz, Austria; Toronto, Canada; France; Budapest, Hungary; Brazil; Tel Hashomer, Israel; Tìrgu-Mureş Romania; Krakow, Poland; and Mainz, Germany*

What is already known about this topic? Although there has been an increasing interest in health-related quality of life (HRQoL) in hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) in recent years, only generic questionnaires (eg, SF-36) have been used, as no disease-specific HRQoL questionnaire was available.

What does this article add to our knowledge? This is the first disease-specific HRQoL questionnaire in C1-INH-HAE. It has been developed in an international setting following published guidelines regarding development and cross-cultural adaptation. It shows good reliability and validity evidence.

How does this study impact current management guidelines? C1-INH-HAE experts recommend measuring HRQoL annually and specially when assessing the need for long-term prophylaxis. The measurement of HRQoL with a disease-specific questionnaire allows assessing specific concerns and indicators related to the disease in contrast with generic ones available.

BACKGROUND: Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) may affect health-related quality of life (HRQoL). A specific HRQoL questionnaire for adult patients with C1-INH-HAE, the HAE-QoL, has recently been developed in Spain.

OBJECTIVE: The objective of this study was to perform a cross-cultural validation and psychometric study of the HAE-QoL in an international setting.

METHODS: Cross-cultural adaptation of the Spanish HAE-QoL draft version and an international rating phase with experts were performed. The resultant version of the HAE-QoL, a clinical questionnaire, and Short Form 36-item Health Survey Version 2.0 (SF-36v2) were pilot tested internationally. Item reduction was based on both descriptive and exploratory factor analysis. Psychometric properties were assessed.

RESULTS: Cross-cultural adaptation of the HAE-QoL was performed in 18 countries. The draft version of the HAE-QoL was pilot tested in 332 patients, and accurate data were obtained from 290 patients from 11 countries. The reduction process resulted in a new version with 25 items and 7 dimensions (treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, and mental health). Strong psychometric properties were observed (Cronbach's α 0.92; test-retest reliability 0.87). Convergent validity showed mild to moderate correlations with SF-36v2 physical and mental component summaries (0.45 and 0.64, respectively) and with SF-36v2 dimensions ($P < .004$). HAE-QoL scores discriminated significantly among severity groups (median: asymptomatic 133.5 vs severe 84.0; $P < .001$); between patients with and without long-term prophylaxis (median: 101 vs 90; $P = .001$); and between patients with and without psychiatric and/or psychological care (median: 74 vs 103; $P \leq .001$).

CONCLUSIONS: The HAE-QoL, currently available in 18 languages, showed good reliability and validity evidence. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Disease-specific; Quality of life; Hereditary angioedema; C1 inhibitor; Questionnaire; Validation studies; Psychometric; Adults; HAE-QoL; SF-36v2*

Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disorder characterized by recurrent episodes of subcutaneous and submucosal angioedema affecting various body sites, most frequently

Abbreviations used

AE-QoL- Angioedema quality of life questionnaire
C1-INH-HAE- Hereditary angioedema due to C1 inhibitor deficiency
CHI- Corrected homogeneity index
CQ- Clinical questionnaire
EFA- Exploratory factor analysis
GLS- Generalized least squares
HRQoL- Health-related quality of life
ICC- Intraclass correlation coefficient
LTP- Long-term prophylaxis
PAF- Principal axis factoring
SF-36v2- Short Form 36-item Health Survey Version 2.0

gastrointestinal mucosa, face, limbs, and larynx.[1,2] Its estimated prevalence is 1:50,000-1:100,000 inhabitants.[3-5]

This disease is associated with a significant and multifaceted disease burden.[6] Several aspects of C1-INH-HAE can significantly impair a patient's health-related quality of life (HRQoL), such as unpredictability of attacks, which are frequently disabling, disfiguring, painful, and even potentially fatal.[1,7-9] Other factors found to burden patients include delay in diagnosis,[3,4] unnecessary medical procedures, treatment with ineffective drugs,[2,10] and severe side effects from some medications administered as maintenance therapy.[11,12] It is currently well recognized that the effect of disease on HRQoL is an important facet to consider when assessing the general burden of disease and measuring the response to treatment.[13,14] Evidence of the effect of C1-INH-HAE or its treatment on HRQoL has been documented using generic instruments.[15-20]

In this report, we describe the development and psychometric evaluation of HAE-QoL, a multidimensional and specific HRQoL questionnaire for adult patients with C1-INH-HAE. The purpose is to provide a discriminant and evaluative tool to complement evaluations based on generic measures, thereby focusing on aspects that are both relevant and specific to patients living with C1-INH-HAE who are not covered by generic questionnaires.

METHODS

Process validation was performed according to methodologies described in published guidelines and previous HRQoL studies.[21-29] An outline of the development process is shown in Figure E1, available in this article's Online Repository at www.jaci-inpractice.org.

Development of draft version (phase I)

The development of the initial version of the HAE-QoL included a national multicenter study performed in Spain. After review of published medical literature and semistructured interviews with

[a]Allergy Department, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain
[b]Faculty of Psychology, Universidad Autónoma, Madrid, Spain
[c]Research Unit, Hospital Universitario Fundación Alcorcón, Madrid, Spain
[d]Allergy Department, Hospital La Paz Institute for Health Research (IdiPaz), Madrid, Spain
[e]Research Unit, Hospital La Paz Institute for Health Research Institute (IdiPAZ), Madrid, Spain
[f]Department of Dermatology and Allergy Centre and OPEN Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark
[g]Department of Dermatology, Medical University, Graz, Austria
[h]Division of Allergy and Clinical Immunology St. Michael's Hospital, Toronto, Canada
[i]National Reference Centre for Angioedème (CREAK), Internal Medicine Department, Grenoble University Hospital Joseph Fourier University of Medicine, Grenoble, France
[j]National Angioedema Center 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[k]Faculty of Medicine ABC, Sao Paulo, Brazil
[l]Allergy, Clinical Immunology and Angioedema Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel
[m]Unidad de Alergia, Asma e Inmunología Clínica, Buenos Aires, Argentina
[n]Department of Allergology-Immunology, Mures County Hospital, Tirgu-Mureş Romania
[o]Department of Clinical and Environmental Allergology, Jagiellonian University, Krakow, Poland
[p]Department of Dermatology, University Medical Center Mainz, Mainz, Germany
[q]Biomedical Research Network on Rare Diseases (CIBERER, U754), Madrid, Spain

Conflicts of interest: N. Prior has received research support from FIS (Fondo Investigaciones Sanitarias) (Spanish Government, PI 060843) and Fundación SEAIC (Sociedad Española de Alergología e Inmunología Clínica); is employed by Hospital Universitario Severo Ochoa; has received lecture fees from Shire; and has received travel support from Shire and CSL Behring. E. Pérez-Fernández has received consultancy fees and payment for participation in review activities from IdiPAZ. C. Gómez-Traseira has received research support from FIS (Spanish Government, PI 060843); is employed by Hospital Universitario La Paz; has received lecture fees from Shire; and has received travel support from Shire and CSL Behring. A. Aabom states that the expenses for the translation of the quality of life questionnaire were paid from Spain, and according to the manuscript, funding was given from FIS PI 060843 y Fundacion SEAIC, CSL Behring, and JErine AG (Shire), HAEI (International Patient Organization for Hereditary Angioedema due to C1 inhibitor deficiency); has received lecture fees from Shire Pharmaceuticals; and has received travel support from Shire Pharmaceuticals, ViroPharma, and SOBI (Swedish Orphan Biovitrum AB). S. Betschel reports grants and personal fees from CSL, personal fees from Shire, personal fees from Viropharma, personal fees from Baxter, personal fees from Novartis, and personal fees from Canadian Blood Services, outside the submitted work. L. Bouillet is on the boards for Shire, Behring Ingelheim, and Pharming; has received consultancy fees from hire; has provided expert testimony for Shire, Behring Ingelheim, and Novartis; has received research support from Behring Ingelheim and shire; has received lecture fees from Shire, Behring Ingelheim, Novartis, and Genzyme; and has received travel support from Shire and Behring Ingelheim. A. Bygum has received research support from FIS (Spanish Government, PI 060843); is on the Advisory Board for CSL Behring; has received consultancy fees from Viropharma; has received research support from Shire and SOBI; has received lecture fees from Shire, CSL Behring, and Viropharma; and has received travel support from CSL Behring and Shire. D. Csuka has received travel support from Shire Human Genetic Therapies, Inc., Viropharma, and CSL Behring. H. Farkas is on the CSL Behring and Shire Advisory Boards. A. Grumach is on the board for Shire; has received consultancy and lecture fees from Shire and CSL Behring; and has received research support from Shire. D. Moldovan has received research and travel support from CSL Behring, Pharming, and Shire. A. Peveling-Oberhag has received lecture fees from Novartis and Roche. T. Caballero has received research support from FIS (Spanish Government, PI 060843) and Fundación SEAIC; is on the boards for Viropharma and Shire; has received consultancy fees from Shire, Viropharma, CSL Behring, and SOBI; is employed by the Hospital Universitario La Paz; has received lecture fees from Shire and Viropharma; and has received travel support from Shire and CSL Behring. The rest of the authors declare that they have no relevant conflicts.

Received for publication July 11, 2015; revised December 1, 2015; accepted for publication December 21, 2015.

Available online ■■

Corresponding author: Nieves Prior, MD, PhD, Allergy Department, Hospital Universitario Severo Ochoa, Av. De Orellana, 28911 Leganés, Madrid, Spain. E-mail: nivprior@gmail.com.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.12.010

patients with C1-INH-HAE and experts, a theoretical model of the questionnaire was constructed and evaluated by another group of experts and patients, resulting in the HAE-QoL v.1.1. We employed a 6-month recall period, and questions were based on a 5- or 6-point Likert scale depending on the kind of question. The details of this phase were previously published.[30] The HAE-QoL dimension scores were calculated by taking the sum of the individual item scores. No imputation of missing values was performed.

Internationalization of the questionnaire (phase II)

The international validation study followed standardized research design, with identical steps, conditions, and format (written information was given on the procedure) in every country, as recommended.[31]

Ethical approval was granted by the Research Ethics Committee of Hospital Universitario La Paz (Madrid) and local Ethics Committees as required.

Cross-cultural adaptation. The Spanish version of the HAE-QoL v.1.1 and a supplementary clinical questionnaire (CQ) were culturally adapted *a priori* to a chosen common language (American English) using the standard method for linguistic validation.[31-33] This involved forward-backward translations of the Spanish version, by 2 native American English translators, only one of whom had knowledge about C1-INH-HAE, as well as 2 Spanish C1-INH-HAE experts well versed in English. Sequential consensus meetings among translators and experts were held to discuss conceptual equivalence, and led to agreement on version (HAE-QoL v.1.1 in American English).

International expert rating phase. A standardized form was used to assess content validity of the HAE-QoL v.1.1 in American English in participating countries, as well as wording, relevance of the items, and adequate dimension assignment. Qualitative comments from the international experts were also taken into account to assure culturally relevant input. Criteria for deletion, modification, or change in dimension were an agreement rate over 20% or significant qualitative comments.

The resultant HAE-QoL v.1.2 in American English was subsequently adapted for culturally diverse samples following the same forward-backward methodology for each of the target languages spoken in participant countries.

Pilot study and psychometric analysis (phase III)

International pilot study. The HAE-QoL v.1.2 was tested in a sample of patients from different countries for assessing suitability, data quality, scaling assumptions and psychometric characteristics, and determining the need to delete questions.

Participating patients signed an informed consent form. Inclusion criteria for patients were that they were 18 years old or older and had a confirmed laboratory diagnosis of C1-INH-HAE (types I and II). Exclusion criteria were cognitive disabilities and/or lack of fluency in the target language.

As there is no validated C1-INH-HAE clinical severity score available, an *ad hoc* severity score was designed for classifying patients with C1-INH-HAE (see Table I) based on the literature review and personal experience, and taking into account aspects considered in other nonvalidated severity scores.[10]

A convenience sample of patients, heterogeneous regarding sex, age, level of studies, geographical origin, and severity of the disease, was recruited.

TABLE I. Ad hoc C1-INH-HAE severity score

Severity score	Criteria
Asymptomatic	No angioedema episodes and no long-term prophylactic treatment
Mild	No life-threatening angioedema episodes and no long-term prophylactic treatment and ≤3 episodes/last 6 mo
Moderate	No life-threatening angioedema episodes and • ≤6 episodes/last 6 mo with long-term prophylactic treatment (exclude maintenance treatment with pdC1INH) or • 4-12 episodes/last 6 mo without long-term prophylactic treatment
Severe	Life-threatening angioedema episodes and/or • 6 episodes/last 6 mo with long-term prophylactic treatment and/or • Maintenance treatment with pdC1INH and/or • >12 episodes/last 6 mo without long-term prophylactic treatment

C1-INH-HAE, Hereditary angioedema due to C1 inhibitor deficiency; *pdC1INH*, plasma-derived C1 inhibitor concentrate.

In the first phase, a questionnaire package containing the HAE-QoL v.1.2, an *ad hoc* demographical and CQ specifically designed for this study, and the generic Short Form 36-item Health Survey version 2.0 (SF-36v2)[34] were distributed, with recommendations about providing an adequate setting and how to administer the questionnaires without interruption. Reliability was assessed by administering the HAE-QoL v.1.2 1 month later to 50% of the sample according to the same fulfillment recommendations. A shorter CQ retest was also designed to assess significant changes in personal situation or clinical stability during that period. Clinical stability was defined, based on the research group personal criteria, as the absence of all the following features in the last month: increase and/or decrease in frequency or severity of angioedema attacks, significant change in treatment or need of withdrawal due to adverse effects, initiation of self-administration of specific medication, and requirement of intubation or tracheotomy. Besides, it was considered that no other personal situations that could impact answers were present in the last month, that is, deaths or severe family events related or not to C1-INH-HAE, requirement of psychological or psychiatric assistance, treatment or appearance of new medical disorders (related or not to the disease), and pregnancy for women.

Pilot testing data analysis. Completed questionnaires were sent to Hospital Universitario La Paz (Madrid, Spain) for centralized data management. Data entry was repeated to double check for accuracy, using a program designed to detect inconsistencies. Discrepancies were evaluated by 3 researchers.

Analysis involved (a) descriptive statistics about data quality (percent missing, minimum and maximum scores, mean, standard deviation, skewness, kurtosis, ceiling and floor effects, item-total correlation, and internal consistency coefficient); (b) exploratory factor analysis (EFA) was applied to each dimension; (c) item reduction based on descriptive and EFA results; and (d) psychometric analysis to assess reliability and validity evidence. Floor and

TABLE II. Participation in the different phases of the international validation

Country	Expert rating phase	Cross-cultural adaptation	Pilot study			
			No. of patients	First phase (HAE-QoL, CQ, SF-36v2)	Retest phase	Reason for deletion
Argentina	No	√	19	16	UC	3/19 uncompleted data. 0/16 retest (only CQ retest fulfilled)
Austria	√	√	21	18	UC	3/21 deleted because of <18 y. 0/18 retest (only CQ retest fulfilled)
Brazil	√	√	35	34	17	1 deleted because of <18 y
Canada	√	√	22	21	13	1/21 deleted because of no confirmed diagnosis of C1-INH-HAE
China	√	√	No participation			
Denmark	√	√	28	27	UC	1/28 deleted because of diagnosis of acquired angioedema 0/27 retest (only CQ retest fulfilled)
France	√	√	29	UC	UC	None of both CQ fulfilled.
Germany	√	√	43	42	28	1/43 deleted because of diagnosis of HAE without C1-INH deficiency
Hungary	√	√	38	38	21	1/22 retest deleted because the first part of CQ retest was incomplete
Israel		√	10	9	UC	1 deleted because page 6 from HAE-QoL was missing
Italy	√	√	No participation			
Macedonia	√	√	No participation			
Netherlands	√	No	No participation			
United Kingdom	√	√	No participation			
Panama	√	√	No participation			
Poland	√	√	23	22	10	1/23 deleted because of wrong fulfillment of HAE-QoL 1/11 retest deleted because of wrong fulfillment of CQ
Romania	√	√	20	19	7	
Spain	√	√	44	44	28	1/29 retest deleted because of CQ retest unfulfilled
Total	15 experts 14 countries	17 countries	332	290	124	

C1-INH-HAE, Hereditary angioedema due to C1 inhibitor deficiency; *CQ*, clinical questionnaire; *QoL*, quality of life; *SF-36v2*, Short Form 36-item Health Survey Version 2.0; *UC*, uncompleted.

ceiling effects were assessed and considered to be present if more than 15% of respondents had the lowest or highest possible scores, respectively.[25,35]

To shorten the instrument, a first wave of item reduction was performed. An item was deleted if it fulfilled at least one of the following criteria: >10% of *missing values*; a *correlation homogeneity index (CHI)* < 0.3, or if its omission led to an *increase in Cronbach's α coefficient*. Afterwards, a second item reduction wave was carried out with EFA, which was also used to examine the underlying structure of the dimensions. Generalized least-squares (GLS) or principal axis factoring (PAF) extraction methods were used, followed by an Oblimin rotation allowing factors to be correlated. Criteria for determining the number of factors were based on a goodness-of-fit test with root mean square error of approximation less than 0.05 (good adjustment) or failing, between 0.05 and 0.08 (acceptable adjustment).[36] Two criteria were used for item deletion: a factor loading less than 0.4 and selection of the 4 items with the highest loadings in each factor (a maximum of 4 items per dimension had been decided *a priori* to achieve a shorter version).

Internal consistency reliability of HAE-QoL total and dimension scores was assessed by calculating the Cronbach α coefficient.[37] Values between 0.70 and 0.95 were considered optimum.[25]

Test-retest reliability was measured by means of intraclass correlation coefficient (ICC) in a group of subjects considered stable with regard to their personal situation and clinical condition during retest period. ICC was considered acceptable if $\geq$0.7.[25]

Convergent validity was assessed by calculating the Pearson correlation coefficient between HAE-QoL and SF-36v2 raw scores, and association was deemed to exist if >0.4. Construct validity was assessed by means of predefined hypothesis regarding the clinical criterion and discriminant ability between known groups regarding severity. The Kruskal-Wallis test for several independent samples was

used, and *post hoc* analysis was adjusted by Bonferroni correction. Using the clinical criterion, we hypothesized that patients with symptoms, long-term prophylaxis (LTP) treatment, need for psychological and/or psychiatric care or intubation and/or tracheotomy requirement would score lower on the HAE-QoL than the patients without these conditions. The Mann-Whitney *U* test and Student *t* test were used for comparisons. Known-group validity was considered supported if clinically differentiable patient groups had significantly different HAE-QoL scores in expected ways. The in-house disease severity score previously described (Table I) was used to classify patients. The Kruskal-Wallis test and *post hoc* comparisons were carried out.

All tests were deemed 2-tailed and those with a *P* value less than 0.05 were considered statistically significant. All data input and statistical analysis were performed using the statistical package SPSS 20.0 (IBM Corp, Armonk, NY).

RESULTS

Internationalization of the questionnaire

Cross-cultural adaptation resulted in HAE-QoL v.1.1 in American English.

International expert rating phase. A total of 15 C1-INH-HAE experts from 14 countries (of 18 countries invited) participated (response rate: 77.7%). As a result of the agreement rate and qualitative comments, no items were deleted or added. A single item was reworded based on one expert's qualitative comment. Regarding relevance for C1-INH-HAE, experts unanimously agreed on relevance for all but 7 items, which 93.3% of experts considered relevant. Dimension reassignment was required for 3 items because of qualitative comments (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The resultant HAE-QoL v.1.2 contained 44 items and 9 dimensions.

New cross-cultural adaptation. Participant countries helped create versions in the following languages (in alphabetical order): Danish, English (for Canada, the USA, and the UK), French (for Canada and France), German (for Austria and Germany), Hebrew, Hungarian, Italian, Macedonian, Mandarin Chinese, Polish, Portuguese (for Brazil), Romanian, and Spanish (for Argentina and Spain).

Pilot study and psychometric analysis

A total of 332 patients from 12 countries were enrolled in the study. Responses were collected initially during the patients' visit to the health clinic and via a follow-up mailing. There was sufficient data completion for 290 patients from 11 countries. Information about participation in the different stages and reasons for patient exclusion in the pilot study are shown in Table II. Characteristics of the patients included in the pilot study are shown in Table III.

Of the entire pool of 44 items contained in the HAE-QoL v.1.2, 34 were applicable to all patients. This "General pool of items" was used to perform the psychometric analysis. Items that had been formulated for a subgroup of patients (eg, patients under LTP treatment or women) were not included in the psychometric study. After content analysis, the 34 "General pool" items were regrouped into 4 new domains (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

TABLE III. Characteristics of international pilot study sample

Characteristics	n (%)	N total
Mean age (SD)	41.5 ± 14.6	290
Gender (male/female)	90 (31)/200 (69)	290
Type HAE		270*
Type I	232 (85.9)	
Type II	38 (14.1)	
HAE severity†		274
Asymptomatic	8 (2.9)	
Mild	65 (23.4)	
Moderate	89 (32.6)	
Severe	112 (41.8)	
Intubation/tracheotomy requirement	34 (11.8)	287
Maintenance treatment	146 (51.8)	282
Attenuated androgens	105	
Antifibrinolytics	21	
pdC1INH	18	
Others	2	
Psychiatric/psychological care or treatment requirement (in last 6 mo)	31 (11.1)	279
Type of residence		284
Rural/semiurban (<25,000 inhabitants)	125 (43.1)	
Urban (>25,000 inhabitants)	159 (54.8)	
Level of education (%)		290
No schooling/primary school/grade school	72 (24.8)	
High school/further studies	218 (75.2)	

C1-INH-HAE, Hereditary angioedema due to C1 inhibitor deficiency; *pdC1INH*, plasma-derived C1 inhibitor concentrate.
*Physicians included patients with confirmed C1-INH-HAE laboratory diagnosis. However, the clinical questionnaire was filled by patients and some of them did not know if they had type I or II C1-INH-HAE.
†According to in-home severity score (see Table I).

Item reduction process

In the first wave, 4 items were deleted: 1 had 20.7% missing values and 3 had a CHI < 0.3 (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

After EFA, a 2-factor solution most closely approached every one of the 4 draft dimensions except the "Treatment difficulties" dimension in which a 1-factor solution adjusted best.

The GLS extraction method was used except in the "Emotional role and social functioning" dimension in which PAF was required.

Items with loading less than 0.4 were deleted. In the "Perceived control over illness" dimension, the 4 items with the highest loadings were selected. On the basis of the content of maintained items, the final dimensions were renamed (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

The final version of the HAE-QoL includes 25 items and 7 dimensions: treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social

TABLE IV. HAE-QoL v.2.0 (final version) scale structure and descriptive analysis

Subscale	No of items	Min value	Max value	Floor effect (%)	Ceiling effect (%)	Cronbach's α	ICC
Treatment difficulties	4	4	23	0	13.8	0.71	0.72
Physical functioning and health	4	4	23	0.7	15.2	0.85	0.82
Disease-related stigma	3	3	15	0.7	20.7	0.71	0.76
Emotional role and social functioning	4	4	20	1.0	20.0	0.85	0.90
Concern about offspring	2	2	10	9.3	23.1	0.63	0.70
Perceived control over illness	4	4	20	6.5	8.6	0.88	0.78
Mental health	4	4	24	2.8	11.7	0.88	0.77
Total HAE-QoL	25	25	135	0	3.4	0.92	0.87

HAE-QoL, Hereditary angioedema quality of life; *ICC*, intraclass correlation coefficient.

TABLE V. HAE-QoL convergent validity with SF-36v2

	SF-36v2									
Subscales HAE-QoL	Physical functioning	Role physical	Bodily pain	General health	Vitality	Social functioning	Role emotional	Mental health	PCS	MCS
Treatment difficulties	0.38	0.50	0.55	0.42	0.43	0.50	0.44	0.48	0.38	0.50
Physical functioning and health	0.40	0.60	0.58	0.52	0.46	0.52	0.43	0.50	0.40	0.60
Disease-related stigma	0.35	0.51	0.50	0.47	0.39	0.49	0.40	0.43	0.35	0.51
Emotional role and social functioning	0.42	0.59	0.56	0.51	0.50	0.59	0.45	0.50	0.42	0.59
Concern about offspring	0.17	0.30	0.36	0.33	0.28	0.30	0.27	0.30	0.17	0.30
Perceived control over illness	0.39	0.55	0.54	0.50	0.44	0.44	0.47	0.46	0.39	0.55
Mental health	0.42	0.57	0.58	0.54	0.51	0.54	0.49	0.58	0.42	0.57
Total HAE-QoL	0.45	0.64	0.64	0.58	0.53	0.59	0.52	0.57	0.45	0.64

HAE-QoL, Hereditary angioedema quality of life; *MCS*, mental component summary; *PCS*, physical component summary; *SF-36v2*, Short Form 36-item Health Survey Version 2.0.

Pearson correlation coefficient: All correlations were statistically significant with $P < .001$ except correlation between *Perceived control over illness* and *Physical function* that was $P = .004$.

functioning, concern about offspring, perceived control over illness, and mental health.

Psychometric analysis of the final version (version 2.0): HAE-QoL

CHI for individual items ranged from 0.43 to 0.77. Items missing data varied between 0.3% and 5.2%.

Regarding HAE-QoL dimensions, no floor effect was observed (the percentage of patients scoring the lowest possible value ranged from 0% in the "Treatment difficulties" dimension to 9.3% in the "Concern about offspring" dimension). Additional information is provided in Table IV.

The HAE-QoL showed good-to-excellent internal consistency; Cronbach's α coefficient for the total score was 0.92 and for the individual dimensions ranged from 0.63 to 0.88.

Retest phase was completed in 128 patients. Accurate data were obtained for 124 patients, but only 37 of them were considered clinically stable. Total ICC was 0.87 (95% CI, 0.77-0.93), indicating excellent reliability and ranging from 0.70 to 0.90 in the different dimensions (Table IV).

Convergent validity with SF-36v2 showed statistically significant mild-to-moderate correlations among the HAE-QoL dimensions and the SF-36v2 dimensions (range: 0.17-0.64). The HAE-QoL total score correlated well with the SF-36v2 physical and mental component summaries 0.45 and 0.64, respectively. Results are shown in Table V.

Regarding construct validity, 3 of 4 predefined hypotheses were confirmed. Hypothesis of lower HRQoL regarding intubation or tracheotomy requirement was only statistically significant different in the "Perceived control over illness" dimension (for more details, see Table VI).

Data about known-groups validity are displayed in Figure 1. All dimension scores and the total score varied significantly by severity. *Post hoc* comparisons showed that subjects with severe disease had dimension and total HAE-QoL scores significantly lower (worse) for all dimensions compared with those with mild C1-INH-HAE or asymptomatic patients (Table VII).

Regarding respondent burden, the average time needed to complete the HAE-QoL instrument in the pilot study (ie, the 44 item version) was 26 minutes (range: 5-180 minutes) with a median of 19 (interquartile range: 12.5-30).

The range of total HAE-QoL scores is 25-135. Higher scores indicate better HRQoL or less impairment for a particular dimension.

DISCUSSION

This large international study includes the design and validation of the first disease-specific HAE-QoL questionnaire for assessing HRQoL in adult patients with C1-INH-HAE.

As a chronic, disfiguring, and potentially fatal disease, C1-INH-HAE can affect almost all aspects of a patient's life.[6] Some studies addressing QoL issues in the C1-INH-HAE population have been published in the recent years[5,15-20,38,39]; however, the HRQoL questionnaires used were generic, as no

TABLE VI. Construct validity regarding external clinical criterion

Subscales HAE-QoL	Asymptomatic*			Intubation/tracheotomy ever in life*			Long-term prophylaxis (LTP)†			Psychiatric-psychological care/treatment*		
	No n = 282 Median (P25-P75)	Yes n = 8 Median (P25-P75)	*P*	No n = 253 Median (P25-P75)	Yes n = 34 Median (P25-P75)	*P*	No n = 136 Mean ± SD	Yes n = 146 Mean ± SD	*P*	No n = 248 Median (P25-P75)	Yes n = 31 Median (P25-P75)	*P*
Treatment difficulties	18.5 (14-21)	23 (17.2-23)	.03	19 (14.5-22)	19.5 (12.7-21)	.27	18.4 ± 4.4	17.2 ± 4.5	.02	20 (15-22)	15 (10-18)	<.001
Physical functioning and health	17 (12-21)	23 (23-23)	<.001	18 (13-21)	16.5 (11-20.2)	.46	17.2 ± 5.3	15.8 ± 5.1	.02	18 (14-21)	12 (8-16)	<.001
Disease-related stigma	12 (9-14)	15 (15-15)	<.001	12 (9-14)	12 (8.7-14)	.99	11.9 ± 3.3	10.6 ± 3.3	.001	12 (9-14)	9 (6-12)	<.001
Emotional role and social functioning	15.5 (11-18)	20 (20-20)	<.001	16 (11-19)	15.5 (10-17.5)	.47	15.6 ± 4.4	14 ± 4.4	.002	16 (11.2-19)	12 (8-15)	<.001
Concern about offspring	7 (4-9)	10 (7.5-10)	.01	7 (4-10)	6.5 (5-8)	.42	7 ± 2.8	6.2 ± 2.8	.02	7 (5-10)	4 (2-8)	.001
Perceived control over illness	11.5 (8-16)	20 (18.2-20)	<.001	13 (8-17)	10 (5-14.2)	.04	13.3 ± 5.1	11.2 ± 4.9	<.001	13 (8-17)	7 (4-13)	<.001
Mental health	17 (12-21)	24 (19.5-24)	.001	17 (12-21)	16.5 (8-20.2)	.20	17.3 ± 5.5	15.5 ± 5.7	.006	18 (13-21)	12 (7-16)	<.001
Total HAE-QoL	97 (74-116.25)	133.5 (119.5-135)	<.001	99 (77-118)	95.5 (64.75-111)	.24	100.8 ± 25.9	90.4 ± 25	.001	102.5 (78-119.75)	74 (52-87)	<.001

HAE-QoL, Hereditary angioedema quality of life.
*Mann-Whitney test.
†Student *t* test.

disease-specific tools were available. It is important to consider that generic HRQoL questionnaires are usually not as sensitive as disease-specific ones.[14,40] Thus, a specific questionnaire, such as HAE-QoL, should provide a better picture of the multifaceted nature of HRQoL in C1-INH-HAE as it focuses on domains that are most relevant to patients. HAE-C1-INH experts recommend that HRQoL be measured on an annual basis[41] and World Allergy Organization C1-INH-HAE guidelines state that HRQoL should be considered when assessing the need for prophylaxis.[42] The HAE-QoL could be useful in this regard.

The HAE-QoL was developed according to standard questionnaire development guidelines and methodologies.[21-29] Although new documents such as ISOQOL recommendations[43] and COSMIN checklist[44] have been published after this study was underway, the HAE-QoL meets most of the recommended standards.

The methodology we followed was based on a patient-centered perspective, which helped to ensure content validity, one of the most important measurement properties.[25,43] In addition, questionnaires should be acceptable to patients, easy to understand, and complete, and results from the pilot study on missing answers and time needed to complete the questionnaire demonstrate that the HAE-QoL meets these requirements.

This work also followed recommendations in the literature[31] regarding cross-cultural adaptation methodology. For international conceptualization, that is, taking into account other countries' aspects or points of view, a mixed approach was decided. A sequential approach for cross-cultural adaptation of the HAE-QoL v.1.0 was followed by a parallel approach by which pilot testing was performed in an international field study. All of the information provided by patients from all of the participant countries was used for the psychometric analysis taking into account published requirements.[31]

Psychometric analysis results were highly acceptable. The HAE-QoL showed good internal consistency for each dimension and for overall total scores. The test-retest reliability over 4 weeks was excellent (>0.70 for all dimension and total scores). The 4-week retest interval was enough to avoid the effect of recall bias and the possibility that patient health status would change because only stable patients had been selected.

Floor and ceiling effects were examined to ensure that the questionnaire had the ability to cover the full range of severity in patients and discriminate between subjects. Although the ceiling effect is present in 3 of 7 dimensions (the effect in the "Physical functioning and health" dimension is practically insignificant), it should be taken into account that we adopted a very strict definition of this effect, in comparison to other studies in which the threshold was as high as 60%.[45]

As there is no gold standard for measuring HRQoL, data were compared with the SF-36v2, a tool known to be psychometrically sound and widely used in validation processes. Although Terwee et al[25] recommended values ≥0.7 for concurrent validity, other experts deemed convergent validity exists when there is substantial correlation (>0.40).[45,46] In our study, correlations obtained between the HAE-QoL total and dimension scores, on one hand, and the SF-36v2 domains and physical and mental component scores, on the other, were all statistically significant. They were mostly mild to moderate, indicating a certain agreement between the 2 instruments. The greatest correlations were seen between pain and physical role domains, as well as with the mental component summary. The lack of strong

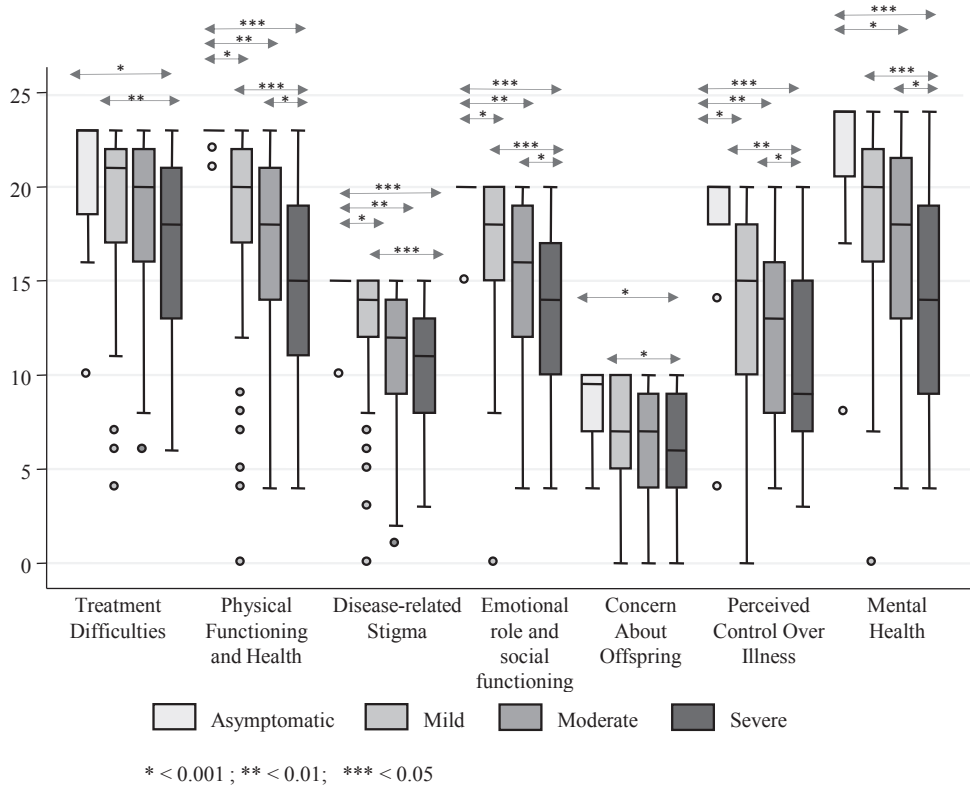

FIGURE 1. Discriminant validity.

TABLE VII. Discriminant validity

Subscales HAE-QoL	Asymptomatic n = 8	Mild n = 65	Moderate n = 89	Severe n = 112	*P* values *post hoc* 2-by-2 comparisons					
					S-A	S-Mi	S-Mo	Mo-A	Mo-Mi	Mi-A
Treatment difficulties	23 (17.25-23)	21 (16-22)	20 (15-22)	16 (13-21)	**.03**	**.002**	.08	.37	1	1
Physical functioning and health	23 (23-23)	20 (16.5-22.5)	18 (13-21)	15 (10.25-19)	**<.001**	**<.001**	**.04**	**.001**	.14	**.03**
Disease-related stigma	15 (15-15)	14 (11-15)	12 (9-14)	10.5 (8-13)	**<.001**	**<.001**	.32	**.001**	.14	**.03**
Emotional role and social functioning	20 (20-20)	17 (15-20)	16 (11-18.5)	14 (10-17)	**.001**	**<.001**	**.02**	**.001**	.21	**.04**
Concern about offspring	10 (7.5-10)	8 (5-10)	7 (4-9)	6 (4-8)	**.02**	**.05**	1	.07	.62	.48
Perceived control over illness	20 (18.25-20)	15 (10-17.5)	13 (8-16.5)	9 (7-15)	**<.001**	**.001**	**.03**	**.004**	.95	**.03**
Mental health	24 (19.5-24)	19 (14.5-22)	17 (12-21)	15 (9-19)	**<.001**	**<.001**	**.01**	**.02**	.78	.14
Total HAE-QoL	133.5 (119.5-135)	110 (91-122.5)	96 (80-118)	84 (65.25-107.75)	**<.001**	**<.001**	**.02**	**.002**	.20	.06

A, Asymptomatic; *HAE-QoL*, hereditary angioedema quality of life; *Mi*, mild; *Mo*, moderate; *S*, severe.
Mean (P25-P75).
Statistically significant *P* values typed in bold.

correlations might be due to the fact that SF-36v2 is a generic instrument and the HAE-QoL is specific for patients with C1-INH-HAE.

HAE-QoL scores were highly sensitive for most groups depending on health status, as hypothesized. Thus, symptomatic patients, patients under LTP treatment or under psychiatric and/or psychological care or treatment, had significantly lower (worse) scores than patients without such constraints. Interestingly, the *a priori* limiting factor of intubation or tracheotomy showed no statistically significant differences, except for the "Perceived control over illness" dimension, which, on the other hand, was to be expected. Nevertheless, it met the recommended quality criteria of ≥75% of the hypotheses confirmed.[25]

The HAE-QoL also discriminated well among subjects based on C1-INH-HAE severity. Subjects with severe expression had statistically significant worse scores compared with those of asymptomatic patients or patients with mild disease, in all dimensions, demonstrating the ability of the HAE-QoL to detect these differences. In contrast, "Concern about offspring" and "Treatment difficulties" dimension scores did not show significant differences among patients with different C1-INH-HAE severity. This suggests that concern about transmission of disease

and problems with treatment exist regardless of the severity of disease. Similar findings regarding concern about disease transmission have also been pointed out by other authors.[39,47] Bouillet et al[16] found a significant decrease in HRQoL measured by SF-36v2 related to annual number of attacks as a disease severity marker. However, no relationship between HRQoL and C1-INH-HAE severity had been found in another study,[20] which might have been due to the lower sensitivity of the SF-36 generic questionnaire or the severity score used, which had not been validated.

The HAE-QoL also discriminates between patients who do or do not receive psychiatric and/or psychological care or treatment. This is a relevant feature as earlier studies have identified mental health disorders associated with C1-INH-HAE.[15,39,48]

An HRQoL questionnaire for angioedema, the angioedema QoL questionnaire (AE-QoL), has been published recently.[49] It cannot be considered a specific HRQoL questionnaire for C1-INH-HAE, as it was designed using data from a heterogeneous sample not limited to patients with C1-INH-HAE. Moreover, it includes aspects that are not relevant for patients with C1-INH-HAE (such as how food affects attacks) and fails to consider other issues, such as the potential for passing this genetic disorder on to children, a key concern of patients with C1-INH-HAE reported in previous studies.[39,47]

One limitation of the study is the failure to detect differences between patients with moderate and mild C1-INH-HAE in any of the dimensions. It could be that the effect of the disease on HRQoL is similar in these groups, or perhaps the tool is unable to discriminate between both groups. It is also worth noting that the sample size of the asymptomatic group was quite small and the *ad hoc* severity scoring system used in this study had yet to be validated. Notwithstanding, this classification was designed based on our combined professional experience, bearing in mind the weaknesses and limitations of other severity scoring systems used in C1-INH-HAE research.

Another possible limitation of the study was the differences in sample size and distribution of participants across countries, in both the test and retest phase. Studies on rare diseases must often be multinational to provide sufficiently large sample sizes. Several countries participated in this study and recruited a large number of patients. Data on patients who were below the age of 18 had not been diagnosed with HAE-C1-INH, or submitted incomplete CQs were not included in the final analysis. In addition, patients had to be stable insofar as not only their C1-INH-HAE clinical status, but also in their personal life (ie, major life events). Data on patients who were not found to exhibit said stability during the first phase of the study or subsequently failed to provide data on which to assess HAE-QoL stability during the retest phase were deleted from the retest sample group. The deletion of data on participants from some countries in the retest phase was intended to reduce potential sampling bias, and consequently we believe that, overall, the data obtained from both phases are reliable for analysis at the end of this process.[43]

The 6-month recall period seems appropriate for evaluating patients with C1-INH-HAE in routine follow-up visits.[50] However, it could also be an obstacle for evaluating specific interventions, and thus validation of a 3-month recall period version is being considered.

Issues pending regarding recommended standards are responsiveness (change over time) and minimal-important difference. Further study is necessary to assess the utility of the HAE-QoL to evaluate these 2 aspects.

Although the development of the HAE-QoL has been a thorough painstaking project, validation should be an ongoing process and continuous evidence of its validity will attest to its applicability in a wide variety of populations and settings.

The HAE-QoL addresses 7 relevant HRQoL domains for adult patients with C1-INH-HAE (treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, and mental health). This reveals the numerous HRQoL domains affecting patients with C1-INH-HAE in addition to what may otherwise have been considered typical health-related outcomes, such as severity of disease or number of episodes per year.

In summary, the HAE-QoL offers a number of advantages. First, it is based on both patients' perceptions of C1-INH-HAE and the point of view of experts, rather than only on criteria perceived by researchers or described in the literature. Secondly, the tool can be employed in an international setting as it has been developed in collaboration with an international multicenter task force. Considering that C1-INH-HAE is a rare disease, cohorts from the different countries allowed achieving a sizeable and heterogeneous sample. Another strength of the study lies in its being a disease-specific questionnaire that makes comparisons among subgroups of patients within the same disease possible. Lastly, the HAE-QoL is a short self-administered questionnaire that is easy to answer and to score.

To the best of our knowledge, this is the first and only disease-specific HRQoL instrument for adult patients with C1-INH-HAE. It is available in 18 languages and has been shown to be a valid, reliable, and consistent instrument that could help care providers to high-quality comprehensive care for adult patients with C1-INH-HAE.

Acknowledgments

The authors would like to thank all participating patients and the following experts who have collaborated to create this questionnaire: C. Andreu, O. Barrera, I. Bobolea, K. Bork, R. Cabañas, A. Campos, V. Cardona, P. Carretero, M. Cicardi, S. Cimbollek, R. De Albuqueruque, F. García, T. González Quevedo, A. Gonzalo, M. Guilarte, V. Grivcheva-Panovska, D. Hernandez, C. Hernando, K. E. Andersen, M. Levi, H. Longhurst, M. C. López Serrano, R. Lleonart, C. Marcos, M. Pedrosa, S. Rodrigues, M. Rubio, A. Sala, M. E. Sanchís, T. Soto, M. A. Tejedor, E. Toledo, A. Zanichelli, and Y. Zhi; Courteney Hightower, Juliette Siegfried, and Sarah Smith for translations; and Fundación SEAIC, FIS (Fondo Investigaciones Sanitarias) (Spanish Government), CSL-Behring, Jerini AG (currently part of Shire), and HAEI for funding this research.

REFERENCES

1. Frank M, Gelfand J, Atkinson J. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med 1976;84:580-93.
2. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine 1992;71:206-15.
3. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol 2005;94:498-503.

4. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survery. Br J Dermatol 2009;161:1153-8.
5. Nordenfelt P, Dawson S, Wahlgren C-F, Lindfors A, Mallbris L, Björkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc 2014;35:185-90.
6. Banerji A. The burden of illness in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2013;111:329-36.
7. Bork K, Meg G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs and course. Am J Med 2006;119:267-74.
8. Zuraw B. Hereditary angioedema. N Engl J Med 2008;359:1027-36.
9. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-inhibitor deficiency. J Allergy Clin Immunol 2012;130: 692-7.
10. Agostoni A, Aygoren-Pursun E, Binkley K, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol 2004;114:S51-131.
11. Cicardi M, Castelli R, Zingale L, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. J Allergy Clin Immunol 1997;99:194-6.
12. Bork K, Pitton M, Harten P, Koch P. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. Lancet 1999;353:1066-7.
13. Guyat G, Feeny D, Patrick D. Measuring health-related quality of life. Ann Intern Med 1993;118:622-9.
14. Testa M, Simonson D. Assessment of quality-of-life outcomes. N Engl J Med 1996;334:835-40.
15. Lumry W, Castaldo A, Vernon M, Blaustein M, Wilson D, Horn P. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010;31:407-14.
16. Bouillet L, Launay D, Fain O, Boccon-Gibod I, Laurent J, Martin L, et al. Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. Ann Allergy Asthma Immunol 2013;111:290-4.
17. Bygum A, Andersen K, Mikkelsen C. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol 2009;19:147-51.
18. Bewtra A, Levy R, Jacobson K, Wasserman R, Machnig T, Craig T. C1-inhibitor therapy for hereditary angioedema attacks: prospective assessments of health-related quality of life. Allergy Asthma Proc 2012;33:427-31.
19. Gomide M, Toledo E, Valle S, Campos R, Franca A, Gomez N, et al. Hereditary angioedema: quality of life in Brazilian patients. Clinics 2013;68:81-3.
20. Aabom A, Andersen KE, Perez-Fernández E, Caballero T, Bygum A. Health-related quality of life in Danish patients with hereditary angioedema. Acta Derm Venereol 2015;95:225-6.
21. Eignor DR. Standards for the development and use of tests: the standards for educational and psychological testing. Eur J Psychol Assess 2001;17:157-63.
22. Krippendorf KL. Content Analysis: An Introduction to Its Methodology. Beverly Hills, CA: Sage; 1980.
23. Arranz P, Remor E, Quintana M, Villar A, Díaz JL, Moreno M, et al. Development of a new disease-specific quality-of-life questionnaire to adults living with haemophilia. Haemophilia 2004;10:376-82.
24. Aaronson N, Alonso J, Burnam A, Lohr KN, Patrick DL, Perrin E, et al. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002;11:193-205.
25. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007;60:34-42.
26. Anastasi A, Urbina S. Psychological Testing. Englewood Cliffs, NJ: Prentice Hall; 1997.
27. Remor E, Arranz P, Quintana M, Villar A, Jiménez-Yuste V, Diaz JL, et al. Psychometric field study of the new haemophilia quality of life questionnaire for adults: the "Hemofilia-QoL". Haemophilia 2005;11:603-10.
28. Ware J, Gandek B. Methods for testing data quality, scaling assumptions and reliability: the IQOLA Project Approach. J Clin Epidemiol 1998;51:945-52.
29. Stead M, Brown J, Velikova G, Al E. Development of an EORTC questionnaire module to be used in health-related quality-of-life assessment for patients with multiple myeloma. Br J Haematol 1999;104:605-11.
30. Prior N, Remor E, Gómez-Traseira C, López-Serrano C, Cabañas R, Contreras J, et al. Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-QoL): Spanish multi-centre research project. Health Qual Life Outcomes 2012;10:82.
31. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res 1993;2:451-9.
32. Beaton D, Bombardier C, Guillemin F, Ferraz M. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine 2000;25:3186-91.
33. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol 1993;46:1417-32.
34. Ware JJ, Kosinski M, Gandek B. SF-36 Health Survey: Manual & Interpretation Guide. Lincoln, RI: Qualimetric; 2002.
35. McHorney C, Tarlov A. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res 1995;4:293-307.
36. Browne M, Cudeck R. Alternative ways of assessing model fit. Sociol Methods Res 1992;21:230-58.
37. Cronbach L. Coefficient alpha and the internal structure of tests. Psychometrika 1951;16:297-334.
38. Kreuz W, Martínez-Saguer I, Aygören-Pürsün E, Rusicke E, Heller C, Klingebiel T. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. Transfusion 2009;49:1987-95.
39. Caballero T, Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Zlatko S, et al. The humanistic burden of hereditary angioedema: results from Burden of Illness Study in Europe. Allergy Asthma Proc 2014;35: 47-53.
40. Patrick D, Deyo R. Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27:S217-32.
41. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein J, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy 2014; 69:602-16.
42. Craig T, Aygören-Pürsün E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organ J 2012;5:182-99.
43. Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res 2013;22:1889-905.
44. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 2010;19:539-49.
45. Rentz A, Flood E, Altisent C, Bullinger M, Klamroth R, Garrido RP, et al. Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia. Haemophilia 2008;14:1023-34.
46. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008;122:139-44. 144.e1-2.
47. Huang S. Results of an on-line survey of patients with hereditary angioedema. Allergy Asthma Proc 2004;25:127-31.
48. Fouche AS, Saunders EFH, Craig T. Depression and anxiety in patients with hereditary angioedema. Ann Allergy Asthma Immunol 2014;112:371-5.
49. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy 2012;67:1289-98.
50. Caballero T, Caminoa M, Prior N, Gómez-Traseira C, Forjaz MJ. Requirements for HAE-C1-INH scoring measurements: results from the Gargnano 2010 survey. Paper presented at: 7th C1 Inhibitor Deficiency Workshop; May 20-22, 2011; Budapest, Hungary. http://www.diamond-congress.hu/haenet2011/img/journal.pdf. Accessed February 20, 2016

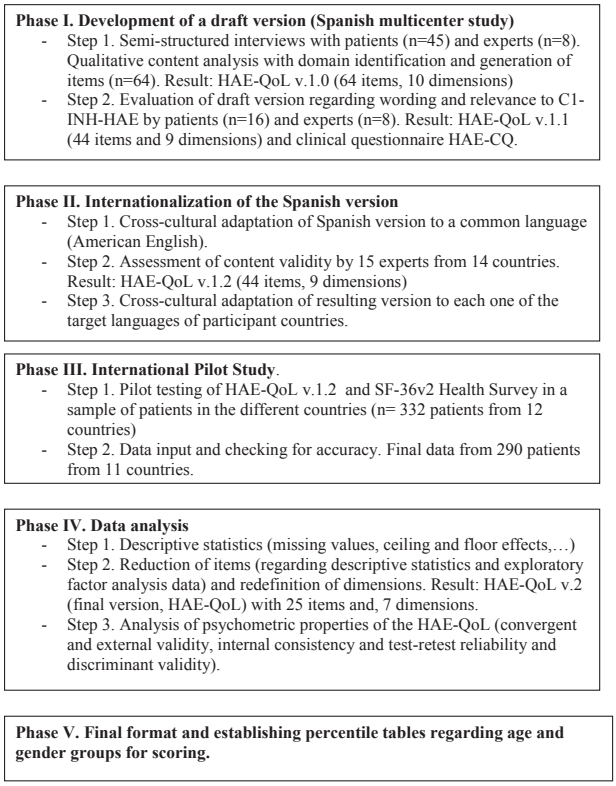

FIGURE E1. HAE-QoL questionnaire development process. C1-INH-HAE, Hereditary angioedema due to C1 inhibitor deficiency; CQ, clinical questionnaire; HAE-QoL, hereditary angioedema quality of life questionnaire; SF-36v2, Short Form 36-item Health Survey Version 2.0.

TABLE E1. Item evolution from international expert rating phase to final version

Item no.	Draft version dimension	International expert rating phase	General pool (GP)/other dimension	GP (34 items) Dimensions (n = 4)	First item reduction wave	EFA No. of factors	Second item reduction wave	Final dimension
1	Social support	SD	GP	Treatment difficulties		1		Treatment difficulties
2	Social support	SD	GP	Treatment difficulties		1		Treatment difficulties
3	Physical role	SD	GP	Physical function and health	Deleted Missing 26.7%			
4	Physical role	SD	GP	Physical function and health		2		Physical function and health
5	Physical role	SD	GP	Physical function and health		2		Physical function and health
6	General health	SD	GP	Physical function and health		2		Physical function and health
7	General health	SD	GP	Physical function and health		2	Deleted No loading in any of 2 factors	
8	Mental health	SD	GP	Mental health		2		Mental health
9	Mental health	SD	GP	Mental health		2		Mental health
10	Mental health	SD	GP	Mental health		2		Mental health
11	Mental health	SD	GP	Mental health		2		Mental health
12	Treatment	Change of dimension: social support	GP	Treatment difficulties		1		Treatment difficulties
13	Treatment	SD	GP	Treatment difficulties	Deleted CHI 0.27			
14	Social support	SD	GP	Treatment difficulties		1		Treatment difficulties
15	Social role	SD	GP	Emotional role and social functioning		2		Emotional role and social functioning
16	Social role	SD	GP	Emotional role and social functioning		2		Emotional role and social functioning
17	Social role	SD	GP	Emotional role and social functioning		2		Emotional role and social functioning
18	Emotional role	SD	GP	Emotional role and social functioning		2		Concern about offspring
19	Emotional role	SD	GP	Emotional role and social functioning		2		Emotional role and social functioning
20	Emotional role	SD	GP	Emotional role and social functioning		2		Concern about offspring
21	Physical role	SD	GP	Physical function and health		2	Deleted Load < 0.4	
22	Physical functioning	SD	GP	Physical function and health		2		Physical function and health
23	Physical role	26.7% agreement on incorrect dimension but no consensus about new dimension, so kept same	GP	Physical function and health		2		Disease-related stigma
24	Physical role	SD	GP	Physical function and health		2		Disease-related stigma
25	Physical role	SD	GP	Physical function and health		2		Disease-related stigma

26.	Mental health	SD	GP	Mental health		2	Deleted Low load	
27	Mental health	SD	GP	Mental health		2		Perceived control over illness
28	Mental health	SD	GP	Mental health		2	Deleted Low load	
29	Mental health	SD	GP	Mental health	Deleted CHI 0.22 + ↑ α			
30	Mental health	SD	GP	Mental health		2		Perceived control over illness
31	Mental health	SD	GP	Mental health		2		Perceived control over illness
32	Mental health	SD	GP	Mental health		2		Perceived control over illness
33*	Treatment	SD	Maintenance treatment					
34*	Esthetics	SD	Attenuated Androgens					
35*	Treatment	SD	Short-term prophylaxis					
36*	Treatment	SD	Maintenance treatment					
37*	Treatment	SD	Maintenance treatment					
38*	Treatment	Rewording due to qualitative comment SD	Maintenance treatment					
39*	Treatment	SD	Acute treatment					
40*	Treatment	SD	Maintenance treatment					
41*	Treatment	Change in dimension: social support (due to qualitative comment)	Home treatment					
42	Social support	SD	GP	Treatment difficulties		1	Deleted Load 0.07	Deleted Load 0.07
43	Treatment	Change in dimension: social support (due to qualitative comment)	GP	Treatment difficulties	Deleted CHI 0.21			
44*	General health	SD	Women					

CHI, Corrected homogeneity index; *EFA*, exploratory factor analysis; *GP*, general pool; *SD*, same dimension.
*Items not included in the final pool and reduction process because they did not apply to all patients (explained in detail in the text).

TABLE E2. General pool items descriptive analysis

General pool N = 290	Item no.	Rate Min-Max	No answer Percent (Total = Yes applicable)	Floor effect (%)	Ceiling effect (%)	Mean	SD	CHI	Alpha if item deletion
Treatment difficulties	1	1-6	1.4	6.9	58.3	4.79	1.73	0.52	0.95
Treatment difficulties	2	1-6	0.7	3.1	68.6	5.30	1.32	0.43	0.95
Treatment difficulties	12	1-6	0.3	18.3	24.1	3.80	1.82	0.62	0.95
Treatment difficulties	13	1-6	0.7	6.2	66.5	5.12	1.54	0.32	0.95
Treatment difficulties	14	1-5	2.1	7.2	46.9	3.78	1.44	0.66	0.95
Treatment difficulties	42	1-5	2.8	0.3	51.7	4.24	1.09	0.12	0.95
Treatment difficulties	43	1-5	4.8	1.4	41.0	3.98	1.26	0.04	0.95
Physical functioning and health	3	1-6	20.7	2.8	27.2	3.53	2.22	0.49	0.95
Physical functioning and health	4	1-6	0.7	8.6	22.1	3.97	1.57	0.77	0.95
Physical functioning and health	5	1-6	1.7	6.5	28.3	4.18	1.65	0.72	0.95
Physical functioning and health	6	1-6	1.4	7.6	59.0	4.85	1.71	0.6	0.95
Physical functioning and health	7	1-6	1.0	5.5	60.7	4.93	1.60	0.53	0.95
Physical functioning and health	21	1-5	1.0	11.0	47.6	3.71	1.50	0.67	0.95
Physical functioning and health	22	1-5	1.4	12.1	34.8	3.44	1.49	0.71	0.95
Physical functioning and health	23	1-5	1.4	11.4	53.8	3.84	1.52	0.54	0.95
Physical functioning and health	24	1-5	3.4	2.4	54.5	4.01	1.35	0.50	0.95
Physical functioning and health	25	1-5	1.0	11.7	28.3	3.36	1.42	0.73	0.95
Social role and emotional functioning	15	1-5	0.3	5.9	37.2	3.72	1.27	0.76	0.95
Social role and emotional functioning	16	1-5	0.7	10.7	31.4	3.43	1.42	0.76	0.95
Social role and emotional functioning	17	1-5	1.4	11.4	29.7	3.33	1.45	0.75	0.95
Social role and emotional functioning	18	1-5	2.8	15.5	56.9	3.73	1.68	0.45	0.95
Social role and emotional functioning	19	1-5	2.4	3.1	64.8	4.26	1.25	0.56	0.95
Social role and emotional functioning	20	1-5	5.2	24.8	26.2	2.80	1.68	0.52	0.95
Mental health	8	1-5	1.0	9.0	36.6	4.28	1.74	0.63	0.95
Mental health	9	1-6	0.7	9.7	24.1	4.01	1.65	0.76	0.95
Mental health	10	1-6	1.0	9.3	22.4	3.97	1.65	0.77	0.95
Mental health	11	1-6	1.0	12.8	26.2	3.98	1.76	0.76	0.95
Mental health	26	1-5	0.7	12.4	32.4	3.34	1.46	0.68	0.95
Mental health	27	1-5	1.0	27.6	25.5	2.93	1.61	0.69	0.95
Mental health	28	1-5	1.0	21.4	22.4	3.01	1.51	0.73	0.95
Mental health	29	1-5	3.1	16.2	16.6	2.98	1.41	0.27	0.95
Mental health	30	1-5	1.4	10.7	24.1	3.21	1.39	0.71	0.95
Mental health	31	1-5	1.0	19.7	19.7	2.97	1.47	0.71	0.95
Mental health	32	1-5	0.7	19.3	21.7	3.01	1.47	0.73	0.95

CHI, Corrected homogeneity index.