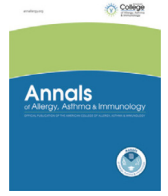




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Development and validation of a US quality of life instrument for hereditary angioedema due to C1 inhibitor deficiency

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ARTICLE INFO

Article history:

Received for publication March 25, 2024.

Received in revised form June 25, 2024.

Accepted for publication July 8, 2024.

ABSTRACT

Background: Hereditary angioedema (HAE) attacks are unpredictable, cause a substantial and enduring burden of illness, and are potentially fatal. Because of issues unique to the US health care system, there is a need for a US-validated, HAE-specific quality of life (QoL) instrument.

Objective: To develop and validate a US HAE-specific QoL instrument according to US Food and Drug Administration guidelines and established methodologies.

Methods: We generated 41 QoL-related items likely relevant to US patients with HAE due to C1 inhibitor (C1INH) deficiency (HAE-C1INH) and performed a 10-patient pilot study to refine the question wording. A total of 415 US patients with HAE-C1INH completed the initial 41-item instrument online, thereby providing data for item reduction, factor analysis, and the assessment of validity and reliability. We used a multiple linear regression to identify the drivers of the total and domain scores. Convergent validity analysis was used to assess the extent to which the HAE-C1INH QoL instrument (HAE-C1INH-QoL) is theoretically related to the angioedema-QoL instrument (AE-QoL).

Results: Item reduction and factor analysis yielded a final instrument of 31 items across 5 domains, and the assessment analysis showed that the HAE-C1INH-QoL is valid and reliable. Attack frequency and severity were statistically significant factors that influenced the total and domain scores. Correlation analysis of the 2 instruments indicated that 8 items of the HAE-C1INH-QoL were not included or well-described in the AE-QoL.

Conclusion: The HAE-C1INH-QoL is the first HAE-specific QoL tool validated in the United States. When compared with the AE-QoL, the items in our instrument are more relevant to US patients with HAE.

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Introduction

Hereditary angioedema (HAE) due to C1 inhibitor (C1INH) deficiency (HAE-C1INH) is a rare genetic disorder characterized by protracted episodes of subcutaneous and submucosal swelling.¹ Attacks most commonly affect the extremities, facial area, and gastrointestinal mucosa.¹ If not treated with targeted HAE therapies, acute swelling episodes can cause significant morbidity and death by asphyxiation owing to airway closure.^{1,2}

Disclaimer: None of the companies cited in the Funding section, nor anyone other than the authors, had any involvement in the project initiation, study design, writing of the manuscript, or the decision to submit for publication.

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<https://doi.org/10.1016/j.anai.2024.07.018>

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HAE attacks are intermittent and unpredictable, increasing the substantial and enduring burden of illness of affected individuals and their caregivers.³⁻⁵ HAE-C1INH impairs quality of life (QoL), both during attacks and in attack-free intervals.³⁻⁵ The aggregate disease burden is magnified by the disproportionately high levels of anxiety and depression experienced by many patients with HAE.^{5,6} Together with the anxiety surrounding unpredictable attacks and the specter of death, individuals continue to express fear of passing HAE onto their children as a consequence of the holistic disease impact endured during their own lives.⁷

QoL instruments are frequently used to assess the burden of living with a disease and the effectiveness of new treatments in clinical trials.⁸ The most widely used instruments for QoL assessment are either generic, providing an overall evaluation of the impacts of health status, or specifically designed to measure aspects of QoL relating to a condition or disease.⁹

Both the United States (US) and international guidelines recommend using HAE-specific QoL instruments as part of a comprehensive management plan.^{10,11} Three instruments have been developed to assess the QoL of patients with recurrent angioedema, namely the angioedema-QoL (AE-QoL), the HAE-QoL, and the Hereditary Angioedema Association-QoLv2 (HAEA-QoLv2).^{6,12,13} Each instrument has individual limitations. For example, the domains of the AE-QoL are based on the broader impact of either histamine or bradykinin-mediated AE and, therefore, do not address the QoL impairment specific to the inherited nature of HAE or the risk of fatal attacks.¹² The HAE-QoL was not validated in the US and does not reflect access to medicine issues unique to the US health care system. The most recent of these assessment tools, the HAEA-QoLv2, is US specific but has yet to be validated.

This manuscript describes a new, US-validated, HAE-specific QoL instrument, the HAE-C1INH-QoL, which uses informative verbal labels to help those affected answer questions. Many QoL instruments employ ordinal scales with simple verbal labels that comprise a few words, such as strongly agree. To more clearly describe the meaning of each answer point on our scale, we chose to use highly explanatory and novel labels that provide (1) additional details for each item in the questionnaire and (2) a descriptive scenario for each answer option.

Methods

In developing the HAE-C1INH-QoL, we used existing information, including guidelines for creating tools that measure patient-reported outcomes,¹⁴ the conceptual framework and measurement properties of the HAEA-QoLv2 described by Busse et al,⁶ the process for developing and validating the AE-QoL described by Weller et al¹² and the development and data analysis phases of the HAE-QoL described by Prior et al.¹³ Based on these inputs, we identified 4 steps, namely (1) development of a conceptual framework and item generation; (2) pilot study; (3) item reduction and factor analysis; and (4) content validation. We submitted the study to the WCG Institutional Review Board Affairs Department, which determined it to be exempt under 45 Code of Federal Regulations § 46.104(d)(2).

Development of a Conceptual Framework and Item Generation

The conceptual framework of the HAE-C1INH-QoL tool began with the HAEA-QoLv2 instrument. As shown in [Table 1](#), we generated a preliminary version of the HAE-C1INH-QoL from the following:

1. The HAEA-QoLv2.⁶
2. Real-world data collected from 737 US patients through a pharmacologic and socioeconomic burden of HAE survey that was conducted by the US HAEA in 2018.⁵
3. Published QoL data relating to patients with HAE¹⁵ and the use of other condition-specific QoL assessment tools.^{16,17}
4. Review and revision of certain HAEA-QoLv1 items excluded from v2.⁶
5. An HAE Expert Group comprising 4 HAE medical professionals and 2 patients from the US HAEA, a nonprofit organization that serves people with HAE and their caregivers.

We also sought expert input (Prof Pelle Guldborg Hansen, Roskilde University, Roskilde, Denmark) on questionnaire techniques to aid in the development of labels to clearly describe the meaning of each answer point.

Pilot Study

The HAEA recruited 10 adult US patients who reported being diagnosed with HAE-C1INH type 1 or type 2 by a health care professional from a pool of members who previously volunteered to participate in research projects. Each patient completed an online preliminary

version of the questionnaire and provided reflective notes on each item. A consultancy conducted a 1-hour, in-depth online (no video, anonymized) interview with participants to obtain additional feedback on (1) the informative label approach and (2) the level of understanding associated with the question and answer options. The HAE expert group collated and reviewed the feedback from the pilot study and incorporated it into an updated version of the HAE-C1INH-QoL.

Item Reduction and Factor Analysis

Members of the HAEA were invited by email to complete and evaluate the items in the updated HAE-C1INH-QoL instrument. Respondent replies provided the basis for the item reduction, factor analysis, and validity and reliability analyses. Respondents identified items that they experienced problems or dissatisfaction with or had concern over during the last year (yes or no) and rated each item on a scale from 1-5, where 1 = not important and 5 = extremely important. Frequency was the proportion of patients who experienced a particular item, and importance was the mean importance score for those who answered yes to experiencing the item.¹⁸ The mean impact score for each item was the product of the frequency and importance. As with the AE-QoL, the benchmark for excluding items was a mean impact score < 1.5.¹²

We performed exploratory factor analysis using principal axis factoring to determine the appropriate domains for the HAE-C1INH-QoL. Single factors (domains) with eigenvalues ≥ 1 were retained according to the Kaiser criterion.¹⁹ After factor extraction, we performed Varimax rotation with Kaiser normalization to improve the interpretability of the factor loading.²⁰ Individual items with a factor loading ≥ 0.5 in a domain were assigned to that domain. To calculate the total and domain scores, we assigned raw scores ranging from 0 to 4 to all item answer options from worst to best, where higher numbers implied better QoL. The raw domain and total scores were standardized using linear transformation into percentage scores (range, 0-100). Scoring guidelines and a scoring Excel template are available in [eTable 1](#). Guidelines on how missing replies were handled can be found in [eTable 2](#).

Concept Validation

After establishing the item and domain structure of the HAE-C1INH-QoL instrument, we assessed its validity and reliability using 4 assessment measures, namely internal consistency, convergent validity, discriminant (known groups) validity, and test-retest reliability. In addition, we reviewed potential floor or ceiling effects by benchmarking against Terwee (>15% indicates the presence of a floor or ceiling effect)²¹ and used multiple linear regression analysis to identify the main influencing factors and to provide more granularity about the discriminant validity within the HAE-C1INH-QoL scores.

Internal consistency measures the homogeneity of items in each domain and the full instrument. We used Cronbach's alpha,²² which is expressed as a number between 0 and 1 and is connected to the interrelatedness of the items and the number of items overall. Higher values generally indicate better internal consistency. When assessing internal consistency, values between 0.70 and 0.95 are considered acceptable.^{22,23}

We assessed convergent validity; that is, the extent to which the instruments should theoretically be related to each other, by calculating the Pearson pairwise correlation (range, -1 to 1) of the total score and domain scores for the HAE-C1INH-QoL instrument and the AE-QoL. We evaluated convergent validity for the entire cohort. We expected a negative correlation because the AE-QoL instrument measures QoL impairment (higher scores = worse QoL) and the HAE-C1INH-QoL instrument measures QoL status (higher scores = better QoL). Correlations between -1 and -0.5 were considered strong.^{24,25}

Table 1
Item Generation

No.	Item (question)	Recall period	Source
1	Your mood	7 d	HAEA-QoLv2
2	Feeling anxious or fearful	7 d	HAEA-QoLv2, Bygum 2015 ¹⁵ and expert input
3	Feeling depressed	7 d	HAEA survey 2018
4	Your mental energy ^a	7 d	HAEA-QoLv2, Brazier 2012 ¹⁶ and expert input
5	Making important life decisions ^b	General	HAEA survey 2018
6	How you feel about yourself	General	HAEA-QoLv2
7	Being a burden to people close to you ^b	1 y	HAEA-QoLv1, Bygum 2015 ¹⁵ and expert input
8	Being a burden to society in general ^c	1 y	Expert input and the HAEA survey 2018
9	That doctors and/or nurses taking care of you do not understand HAE	1 y	HAEA-QoLv2
10	Lack of understanding of HAE from people around you	1 y	HAEA survey 2018
11	Your relationship with friends ^c	General	HAEA-QoLv2
12	Feeling isolated or lonely	7 d	HAEA survey 2018
13	Passing HAE onto your children ^d	1 y	HAEA-QoLv2 and the HAEA survey 2018
14	Finding a partner or maintaining romantic relationships ^c	General	HAEA-QoLv1
15	Your relationships with family members or spouse/partner ^c	General	HAEA-QoLv2
16	Your sexual desire ^c	7 d	Rosen 1997 ¹⁷
17	Your sleep	7 d	HAEA-QoLv2
18	Your physical energy ^a	7 d	HAEA-QoLv2, Brazier 2012 ¹⁶ and expert input
19	Your ability to travel	7 d	HAEA-QoLv2
20	Your job, schoolwork, or other commitments ^c	7 d	HAEA-QoLv1
21	Getting things done at home	7 d	HAEA-QoLv2
22	Doing activities for fun	7 d	HAEA-QoLv2
23	Enjoying life	7 d	HAEA-QoLv2
24	Exercise ^f	7 d	HAEA-QoLv2 and expert input
25	Being active ^f	7 d	HAEA-QoLv2 and expert input
26	Your actions or behavior triggering an attack	1 y	HAEA-QoLv1
27	That others will look at you when you are experiencing excessive swelling	1 y	HAEA-QoLv2, Bygum 2015 ¹⁵ and expert input
28	Willingness to go out in public	1 y	HAEA-QoLv2
29	That your HAE attacks will get worse in the future	1 y	HAEA-QoLv1
30	Experiencing pain from HAE attacks	1 y	HAEA-QoLv1
31	Having your private parts swell from HAE ^b	1 y	HAEA-QoLv1
32	Serious HAE attack for which you would need to go to the emergency room	1 y	HAEA-QoLv2
33	Dying during an HAE attack	1 y	HAEA-QoLv2
34	Treatment will not work for an HAE attack ^b	1 y	HAEA-QoLv2
35	HAE treatment will have adverse effects	1 y	HAEA-QoLv2
36	Having access to your HAE medications in case you need to treat an attack (carrying medication) ⁵	1 y	HAEA-QoLv2
37	Lack of access to medication during an attack (treatment) ⁵	1 y	HAEA-QoLv2
38	Being able to afford the cost of medication	1 y	HAEA-QoLv1
39	Health care payer denying you treatment	1 y	HAEA-QoLv2
40	That manufacturers will no longer make medications that you need	1 y	HAEA-QoLv2
41	Willingness to have medical or dental procedures ^b	General	HAEA-QoLv2

Abbreviations: HAE, hereditary angioedema; HAEA-QoL, US Hereditary Angioedema Association quality of life.

^aItem 1 HAEA-QoLv2 split: 4, 18.

^bItems excluded because factor loadings < 0.5.

^cItems excluded because of mean impact score of < 1.5.

^dItem 37 HAEA-QoLv2 retained as an essential concept.

^eCombines items HAEA-QoLv1 9, 10.

^fItem 12 HAEA-QoLv2 split: 24, 25.

⁵Combines items: HAEA-QoLv2 27, 28, 29; HAEA-QoLv1 30.

We tested discriminant validity, which is the ability of the HAE-C1INH-QoL instrument to distinguish between groups that were known to differ, using the analysis of variance trend test and descriptive analysis (eFigs 1 and 2) to compare group means and SDs. Patients were split into 3 attack groups based on differing attack frequencies in the last 3 months. There is no standard approach to attack frequency groupings. Reviewing the QoL results, we assigned 3 attack frequency groups as follows: attack-free group (0 attacks), nonzero attack frequencies at or below the 95th percentile (1 to 6 attacks); and above 95th percentile attack frequency group (≥ 7 attacks). We assessed self-reported HAE severity on a scale from 0 to 10 (0 = not at all severe; 10 = very severe). Responses were then banded into 5 severity groups. Although there is no standard definition of disease severity, we used this banding to test the tool's ability to differentiate between the groups. Studies that described the HAE burden of illness demonstrated that attack frequency and severity influence QoL.^{3,5,15,26} Therefore, we expected the mean HAE-C1INH-QoL scores to differ between the groups and to decrease as the number of attacks and severity increased.

Finally, we tested the ability of the HAE-C1INH-QoL instrument to yield stable and reproducible scores over a short time period by re-

administering the questionnaire to a subset of 61 patients 3 to 6 weeks after the first completion. We calculated the intraclass correlation coefficient of the total and domain scores from the first and second assessments using a value of > 0.7 as an indicator of good reproducibility.²⁷

Exploratory Analysis: Minimal Clinically Important Difference

A minimal clinically important difference (MCID) is often used to determine the effectiveness and patient satisfaction with a given treatment. MCID is critical for interpreting the significance of results from studies using patient-reported outcomes measures (PROMS). MCID is commonly determined using anchor-based methods, often in combination with distribution-based methods.²⁸ We explored a preliminary MCID for the HAE-C1INH-QoL using SE measurement (SEM) and multiples of SD.²⁸

- SEM estimates the variation in HAE-C1INH-QoL score caused by unreliability and is calculated as $SD \times \sqrt{(1 - R)}$, in which R is the test-retest reliability coefficient.

- We used 0.5 SD of the HAE-C1INH-QoL mean change score between the first survey and the second subset survey (n = 61). A value of 0.5 SD is a commonly used multiple in MCID estimates.²⁸

All analyses were performed in StataIC 15 (StataCorp, College Station, Texas).

Results

Development of a Concept Framework and Item Generation

The item generation phase led to the identification of 41 items that were likely relevant to US patients with HAE-C1INH. Each item and its origin are summarized in Table 1. These cover different recall periods, either the last 7 days, the last year, or in general, depending on the likely frequency of occurrence of the problems described.

Pilot Study

The preliminary HAE-C1INH-QoL 41-item questionnaire was pilot tested from August 9 through September 2, 2019, with 10 patients who self-reported an HAE-C1INH diagnosis type 1 or 2. All patients completed the online preliminary version and provided reflective notes online after answering each item. Their mean age was 52.25 years; most (87.5%) were female, and 62.5% stated that they were employed at the time. Eight participated in an individual, anonymous, in-depth interview. Two interviews did not take place because of scheduling challenges. We used the reflective notes and interview feedback to refine and reword both the item and answer options, which led to an updated 41-item instrument.

Item Reduction and Factor Analysis

Patients in the HAEA membership database were invited by email to evaluate item frequency and importance for all the updated 41 items in the HAE-C1INH-QoL instrument from September 9 to November 26, 2021. The evaluation process was administered using the online survey platform SurveyMonkey (SVMK Inc, San Mateo, California), and participation was voluntary. Participants signed an online consent form and were compensated financially. The time

delay between the pilot study and the item reduction stage was longer than anticipated because of the limitations imposed by the severe acute respiratory syndrome coronavirus 2 pandemic. The initial response rate was 11.1% (625/5646). A total of 529 patients completed the survey, and the final analysis cohort comprised 415 (7.4%) patients who self-reported a diagnosis of HAE type 1 or 2. The 114 excluded respondents comprised 91 who reported they had HAE with normal C1INH, 9 with acquired AE, and 14 who gave clinically inconsistent responses. The demographic, socioeconomic, and clinical characteristics of the sample are shown in Table 2. Most (75%) patients were female, 35% were aged between 18 and 40 years, and 84% received prophylactic treatment. The cohort was geographically diverse, covering 48 (96%) US states. Respondents reported an average of 1.5 attacks during the last month and an average general HAE severity of 5.2. (Table 3).

Participants were required to give item frequency and importance responses for each of the 41 items. Five items with a mean impact score of < 1.5 were excluded (Table 1), leaving 36 items. The driver of exclusion for these items was low frequency (range, 0.232-0.319 compared with 0.391-0.799 for included items). Factor analysis identified 5 factors (domains) with an eigenvalue ≥ 1 . Thirty-one of the 36 items were assigned to the domains based on a factor loading of ≥ 0.5 . The remaining 5 items, all with factor loadings < 0.5, were removed (Table 1). The 31 items were assigned across the 5 domains (eFig 3), defined as follows:

- **Activities:** items related to daily routines, engagements and activities, traveling, and energy.
- **Worries:** items related to worries about HAE and the adverse effects of HAE medicines.
- **Access:** items related to access to and availability of HAE medication.
- **Feelings:** items related to mood and feelings.
- **Embarrassment:** items related to the feelings of shame associated with HAE attacks.

The retained items exhibited low cross-loadings between factors, suggesting the 5 domains represent distinct and separate concepts. The final 31-item HAE-C1INH-QoL instrument can be found in eTable 3.

Table 2
The Demographic, Socioeconomic, and Clinical Characteristics of Patients Included in the Main Study

Characteristics	No. of respondents	Share of respondents, ^a %
Sex	Female	310
	Male	102
	Other	3
Age	18-29	71
	30-39	64
	40-49	89
	50-59	94
	60-69	70
	≥ 70	27
	Education	Associate degree or lower
	Bachelor's degree or higher	223
	Other ^b	5
Employment	Working	239
	Student or stay-at-home parent	48
	Unemployed	54
	Retired or other ^b	74
Treatment received	Prophylactic	349
	Not prophylactic	63
	Do not know	3
Attack free	No. attacks last months	199
	No. attacks last 3 months	154

NOTE. Showing patient, treatment, and attack characteristics (N = 415).

^aSum not equal to 100% because of rounding.

^bFor both education and employment, other is self-reported by respondents if none of the other categories described them.

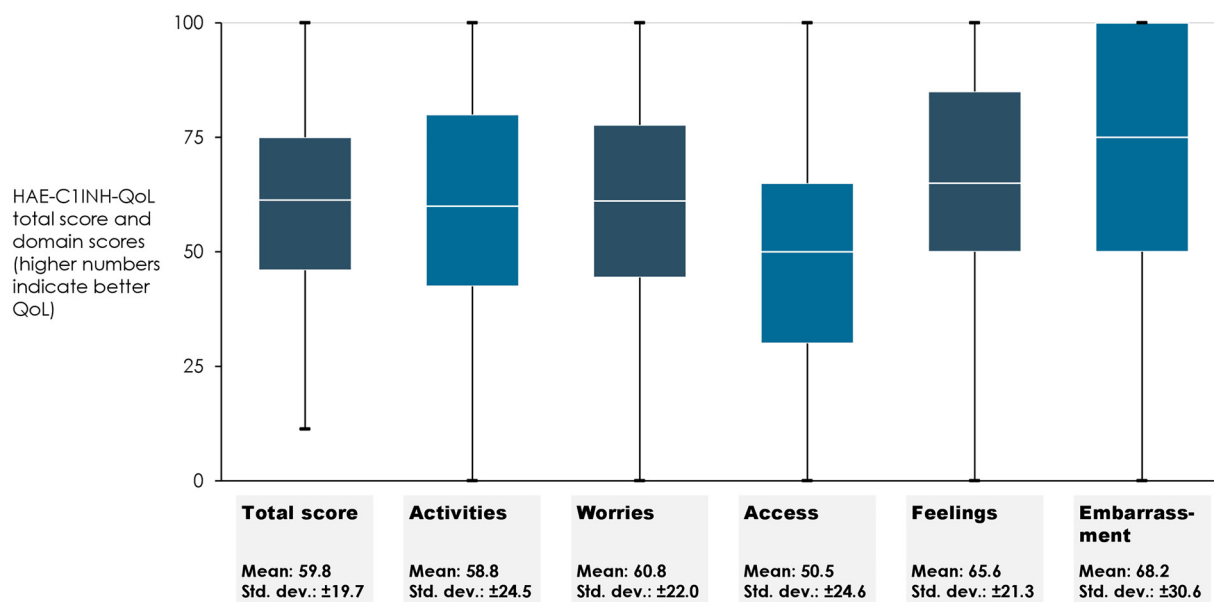


Figure 1. Distribution of final HAE-C1INH-QoL total and domains scores. Box and whisker plots show the distribution of HAE-C1INH-QoL scores in the sample, including the median, 25th and 75th percentiles, and minimum and maximum scores. HAE-C1INH-QoL, hereditary angioedema due to deficiency in C1 inhibitor quality of life tool; QoL, quality of life.

Main Study: Full Instrument and Domain Scores

Figure 1 shows the mean and SDs of the HAE-C1INH-QoL scores for each domain and an overall score. Higher HAE-C1INH-QoL scores indicate better QoL or lower impairment. The mean total HAE-C1INH-QoL score was 59.8 (SD, 19.7). The domain of access was most affected (mean score \pm SD, 50.5 \pm 24.6), followed by the domains of activities and worries. The domains of feelings and embarrassment exhibited higher scores, implying that QoL was less adversely affected in these domains. The broad distributions of the total HAE-C1INH-QoL scores and each domain score suggest that the instrument can differentiate between patients with differences in QoL (Fig 1). Reviewing potential floor or ceiling effects (eTable 4), we see no floor effects, but there was a ceiling effect in the embarrassment domain (30.4% had a score of 100).

Concept Validation

Four different assessments showed that the HAE-C1INH-QoL instrument is a valid and reliable measure of QoL in patients with HAE.

Internal Consistency

Calculation of Cronbach's alpha showed that the HAE-C1INH-QoL is internally consistent in the range of 0.87 to 0.94 across the different domains and 0.96 for the full instrument (Table 4).

Convergent Validity

All correlations were negative, as expected, and ranged between -0.362 and -0.821 for the HAE-C1INH-QoL (Table 5). There were

differences found between the HAE-C1INH-QoL and the AE-QoL. Food was the AE-QoL domain that exhibited the lowest correlation with the HAE-C1INH-QoL domains, and the HAE-C1INH-QoL access domain showed the lowest correlation with the AE-QoL domains (Table 5). Eight items in the HAE-C1INH-QoL had low correlations with all AE-QoL items and domains (Table 6). Correlations ≥ -0.5 were considered indicative of items in the HAE-C1INH-QoL that were not strongly described in the AE-QoL.

Discriminant Validity

Attack frequency and HAE severity were both negatively associated with the HAE-C1INH-QoL total score, meaning that the higher the attack frequency or HAE severity, the lower the HAE-C1INH-QoL score. An analysis of variance trend test across the 3 attack groups (eFig 1) and 5 severity groups (eFig 2) showed that the null hypothesis of no difference in means could be rejected at the 0.1% level using both attack frequency (F value = 53.87; $df_1 = 2$; $df_2 = 407$; $P < .0001$) and severity (F value = 21.04; $df_1 = 4$; $df_2 = 404$; $P < .0001$), thereby supporting known-group validity.

Test-Retest Reliability

The intraclass correlation coefficients between the total and domain scores of the first and second assessments were between 0.766 and 0.880 across the different domains and 0.880 for the full instrument, showing that the HAE-C1INH-QoL can yield stable test scores over a short time period (3-6 weeks).

Table 3
Characteristics of Average Number of Attacks and their Severity of Patients Included in the Main Study

Characteristics	Mean \pm SD	Median	IQR (min-max)	No. of respondents
No. of attacks last months	1.5 \pm 2.3	1	0-13	411
No. of attacks last 3 months	3.5 \pm 5.8	1	0-45	410
Severity of HAE (in general) ^a	5.2 \pm 2.7	5	0-10	409
Severity of most recent attack ^a	4.2 \pm 2.6	4	0-10	403

Abbreviations: HAE, hereditary angioedema; max, maximum; min, minimum.

^aSeverity of HAE and severity of most recent attack are both measured on a scale from 0 to 10.

Table 4
Internal Consistency as Measured by Cronbach's Alpha

Domain	Question	Alpha
Activities	Your mental energy	0.942
	Your sleep	
	Your physical energy	
	Your ability to travel	
	Your job, schoolwork, or other commitments	
	Getting things done at home	
	Doing activities for fun	
	Enjoying life	
	Exercise	
Worries	Being active	0.888
	That doctors/nurses taking care of you do not understand HAE	
	Lack of understanding of HAE from people around you	
	Passing HAE onto your children	
	Your actions or behavior triggering an attack	
	That your HAE attacks will get worse in the future	
	Experiencing pain from HAE attacks	
	Serious HAE attack for which you would need to go to the emergency room	
	Dying during an HAE attack	
Access	HAE treatment will have adverse effects	0.870
	Having access to your HAE medications in case you need to treat an attack (carrying medication)	
	Lack of access to medication during an attack (treatment)	
	Being able to afford the cost of medication	
	Health care payer denying you treatment	
Feelings	That manufacturers will no longer make medications that you need	0.872
	Your mood	
	Feeling anxious or fearful	
	Feeling depressed	
	How you feel about yourself	
Embarrassment	Feeling isolated or lonely	0.889
	That others will look at you when you are experiencing excessive swelling	
	Willingness to go out in public	
HAE-C1INH-QoL		0.957

Abbreviations: HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

NOTE. N = 415. A value of 0.957 may reflect the length of the questionnaire or suggest that items are redundant.

Multiple Linear Regression

We used multiple linear regression to identify drivers of the HAE-C1INH-QoL total and domain scores and to sense-check the instrument's applicability (eTable 5). The HAE-C1INH-QoL score and individual domain scores were each regressed on the number of attacks in the last month, being attack-free in the last month, self-rated disease severity, age, sex, and education. Attack frequency and attack severity were statistically significant factors that influenced the total and domain scores. Higher HAE-C1INH-QoL scores were seen for patients who were attack-free, who experienced fewer attacks, and/or who had a low attack severity ($P < .001$). In addition, sex and age were statistically significant determinants of both the total HAE-C1INH-QoL score and the worries, feelings, and embarrassment domains ($P < .01$). Higher HAE-C1INH-QoL total scores were seen among men and older patients. In contrast, we did not see a statistical significance of being attack-free in the access domain scores ($P > .05$). Patients who were attack free did not show higher access domain scores, whereas these patients do show higher scores in the 4 other

domains. We interpret this score as illustrating that attack-free patients anticipate challenges with access because of a general knowledge among patients with HAE of past medicine shortages and the relatively high level of insurance delays and denials for reimbursement of HAE medicines.

Exploratory Analysis: Minimal Clinically Important Difference

Different MCID calculation methods lead to different MCID estimates,²⁹ which we saw in our preliminary calculations. Using the test-retest reliability coefficient of 0.88, the SEM approach gave an MCID of 6.84 (point estimate). The 0.5 SD provides an MCID estimate of 4.95 based on an HAE-C1INH-QoL mean change score of -4.14 ($n = 61$) and an SD of 9.89.

Discussion

The HAE-C1INH-QoL consists of 31 items that are used to assess QoL across 5 domains, namely activities, worries, access, feelings,

Table 5
Convergent Validity Domains

HAE-C1INH-QoL: total score and domains	AE-QoL: total score and domains				
	Total score	Functioning	Fatigue/ mood	Fears/shame	Food
Total score	−0.821	−0.705	−0.734	−0.750	−0.546
Activities	−0.714	−0.634	−0.697	−0.586	−0.490
Worries	−0.769	−0.642	−0.640	−0.753	−0.520
Access	−0.566	−0.487	−0.471	−0.546	−0.377
Feelings	−0.616	−0.513	−0.617	−0.535	−0.362
Embarrassment	−0.660	−0.572	−0.468	−0.699	−0.435

Abbreviations: AE-QoL, angioedema quality of life; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

NOTE. Pearson pairwise correlations. All correlations are significant at the 0.1% level (P values all $< .0001$). N = 413 (2 respondents missing AE-QoL total and/or domain scores).

Table 6
Convergent Validity Items

No.	Domain	HAE-C1INH-QoL item	Largest correlation across AE-QoL items ^a	Largest correlation across AE-QoL domains ^b
1	Feelings	Your mood	–0.635	–0.535
2	Feelings	Feeling anxious or fearful	–0.583	–0.528
3	Feelings	Feeling depressed	–0.741	–0.587
4	Activities	Your mental energy	–0.606	–0.597
5	Feelings	How you feel about yourself ^c	–0.419 ^c	–0.345 ^c
6	Worries	That doctors/nurses taking care of you do not understand HAE ^c	–0.440 ^c	–0.483 ^c
7	Worries	Lack of understanding of HAE from people around you	–0.502	–0.552
8	Feelings	Feeling isolated or lonely	–0.617	–0.507
9	Worries	Passing HAE onto your children ^c	–0.343 ^c	–0.369 ^c
10	Activities	Your sleep	–0.638	–0.641
11	Activities	Your physical energy	–0.613	–0.621
12	Activities	Your ability to travel	–0.512	–0.521
13	Activities	Your job, schoolwork, or other commitments	–0.561	–0.550
14	Activities	Getting things done at home	–0.583	–0.581
15	Activities	Doing activities for fun	–0.615	–0.576
16	Activities	Enjoying life	–0.605	–0.562
17	Activities	Exercise ^d	–0.493 ^d	–0.510
18	Activities	Being active	–0.587	–0.587
19	Worries	Your actions or behavior triggering an attack	–0.594	–0.616
20	Embarrassment	That others will look at you when you are experiencing excessive swelling	–0.748	–0.680
21	Embarrassment	Willingness to go out in public	–0.681	–0.649
22	Worries	That your HAE attacks will get worse in the future	–0.627	–0.630
23	Worries	Experiencing pain from HAE attacks	–0.612	–0.625
24	Worries	Serious HAE attack for which you would need to go to the emergency room	–0.585	–0.625
25	Worries	Dying during an HAE attack	–0.571	–0.619
26	Worries	HAE treatment will have adverse effects ^e	–0.665	–0.480 ^c
27	Access	Having access to your HAE medications in case you need to treat an attack (carrying medication) ^c	–0.441 ^c	–0.499 ^c
28	Access	Lack of access to medication during an attack (treatment)	–0.557	–0.598
29	Access	Being able to afford the cost of medication ^c	–0.371 ^c	–0.376 ^c
30	Access	Health care payer denying you treatment ^c	–0.379 ^c	–0.379 ^c
31	Access	That manufacturers will no longer make medications that you need ^c	–0.367 ^c	–0.392 ^c

Abbreviations: AE-QoL, angioedema quality of life; HAE, hereditary angioedema; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life. NOTE. Pearson pairwise correlations.

^aThe largest correlation for item i of the HAE-C1INH-QoL across all j items of the AE-QoL is $item_corr_i = \max(\text{corr}(item_i, item_j)) \forall j = 1, \dots, 17$.

^bThe largest correlation for item i of the HAE-C1INH-QoL across all k domains of the AE-QoL is $domain_corr_i = \max(\text{corr}(item_i, domain_k)) \forall k = 1, \dots, 4$.

^cHAE-C1INH-QoL items have nonstrong correlations (> -0.5) with any AE-QoL items and domains.

^dHAE-C1INH-QoL items have nonstrong correlations (> -0.5) with any AE-QoL items.

^eHAE-C1INH-QoL items have nonstrong correlations (> -0.5) with any AE-QoL domains.

and embarrassment. It is the first HAE-QoL tool that was validated in the United States and that uses a scale with highly informative labels. The availability of multiple treatment options, including novel agents for long-term prophylaxis, has transformed the treatment landscape for US patients with HAE and heightens the importance of measuring how various treatments affect clinically meaningful outcomes. The HAE-C1INH-QoL is the first HAE-QoL tool validated in the United States. When compared with the AE-QoL, the HAE-C1INH-QoL is better suited to reflect the QoL experienced by US patients with HAE.

Strengths and Limitations of the Study/Research

In addition to the disease and population-specific benefits described above, our approach to concept development and validation has multiple strengths. The concept framework was discussed with HAE experts and evaluated by patients with HAE in a small pilot study, allowing for one-on-one feedback on item phrasing and comprehension. We developed and validated the instrument in a patient cohort that was substantially larger than reported for the AE-QoL,¹² the HAE-QoL,¹³ and the HAEA-QoLv2.⁶ The validation cohort was geographically diverse, representing patients in 48 of the 50 states in the United States. Although a high proportion of patients reported prophylaxis use, patients in our study experienced a wide range of attack frequencies (eFig 1 and Table 6) and disease severities (eFig 2 and Table 6). Overall, we believe our study generally reflects current HAE treatment patterns in the United States.

We followed US Food and Drug Administration guidelines¹⁴ for developing domains related to patient-reported outcomes. Four different assessment analyses showed that the HAE-C1INH-QoL instrument (1) is a valid and reliable measure of QoL among patients with HAE-C1INH and (2) can yield stable test scores over a short time period. Cronbach's alpha measured the extent to which all the individual domains in the questionnaire measured the same concept or construct. Our Cronbach's alpha values of between 0.87 and 0.94 for individual domains and 0.96 for the full instrument show that the HAE-C1INH-QoL instrument is internally consistent.

Convergent validity analysis showed that the HAE-C1INH-QoL total score and 5 domain scores were related to the AE-QoL score and domain scores. We also calculated the correlations (range, –1 to 1) between the HAE-C1INH-QoL items and the AE-QoL items and domains. The AE-QoL food domain correlation score was low. The HAE-C1INH-QoL does not include food-related items; they were not highlighted during the conceptual framework and item generation phase.⁶ Our assessment was that food was not relevant to US patients with HAE, likely because of the absence of commonly recognized food triggers for HAE when compared with those causing mast cell-mediated AE attacks. Eight items included in the final HAE-C1INH-QoL instrument were not well described by the AE-QoL, including how patients feel about themselves, about passing HAE onto their children, and 3 of 5 items in the access to therapy domain. Therefore, the HAE-C1INH-QoL items are more relevant and important to US patients with HAE than those in the AE-QoL. Accordingly, we believe

that the HAE-C1INH-QoL will more accurately assess the burden of disease for US patients with HAE.

The development and validation of the HAE-C1INH-QoL includes certain limitations. The patients with HAE who were involved in the pilot study and the item reduction stage were self-selected, self-reported their HAE diagnosis, and were subject to several potential biases, including recall and social desirability biases.^{30–32} Groupings for attack frequency were determined after a review of the results, because no standard groupings were found in the literature. The US Food and Drug Administration's guidance for industry¹⁴ for PROMs state that the rationale and the appropriateness of the recall period for an instrument should be evaluated. The choice of recall period may be influenced by multiple factors, such as the instrument's purpose and intended use, the variability, duration, frequency, and intensity of the concept being measured, the disease characteristics, and the treatment being tested.¹⁴ We used a short, 7-day recall period for items frequently experienced by patients and a longer, 1-year recall period for other less frequently experienced items. Some items, such as making important life decisions, could not be captured meaningfully in a specific timeframe and were therefore formulated without a prespecified recall period. When developing QoL tools, floor and ceiling effects may be seen. Using the impact factor method, we sought to mitigate these effects in the item reduction phase. A ceiling effect was seen in the embarrassment domain (30.4% had a score of 100) when benchmarked against Terwee (15%).²¹ This high proportion of patients with a domain score of 100 may be associated with a high use of prophylaxis among the respondents. Our preliminary work estimated MCID values of 6.84 and 4.95 using different distribution criterion-based approaches. Although helpful indicators, Revicki et al³³ recommended using an anchor-based method to produce a primary recommendation for the MCID and using distribution-based methods to provide the supporting evidence for that MCID. A more extensive assessment that uses both the anchor and distribution-based approaches is needed before we can make a final recommendation on the HAE-C1INH-QoL MCID value.

Although men and women have a similar HAE prevalence, as in most surveys of patients with HAE, women were overrepresented in our sample. A survey response rate of 11.1% is low; however, a final analysis cohort of 415 aligns with response numbers in other surveys of US patients with HAE^{3,5,34} or registry reporting.³⁵ Despite these limitations, however, we believe that the large number of patients with HAE involved supports the accuracy of our findings.

Translation and validation of the HAE-C1INH-QoL in Spanish and validation in a pediatric and/or adolescent population would expand the availability of this tool in the United States. The HAE-C1INH-QoL instrument is simple to self-administer, takes approximately 15 minutes to complete, and can be used as part of a comprehensive management plan for HAE in which consistent, validated measures of QoL impact are necessary.

Unanswered Questions and Future Research

Guidelines for developing PROMs in the United States¹⁴ and subsequent attempts at standardization have contributed substantially to assessing the impact of care on patients affected by chronic diseases such as HAE. Although the HAE-C1INH-QoL instrument further contributes to these outcomes, a validated short-form version and a full MCID assessment using anchor and distribution-based methods would be important next steps. In addition, in using novel informative labels, we sought to ensure a broad representation of respondents in our questions and responses, which may have led to some ambiguity in the wording. Further research is needed to better understand the impact of highly informative label wording in comparison with more traditional questionnaire designs.

In conclusion, the HAE-C1INH-QoL fulfills the US HAE guideline recommendation for a disease-specific tool that evaluates QoL as part of a comprehensive HAE management plan. The instrument has been shown to be a valid and reliable measure of QoL in US patients with HAE-C1INH.

Acknowledgments

We thank the US Hereditary Angioedema Association members for participating in the item generation, development, and validation of the new US quality of life instrument for hereditary angioedema due to C1 inhibitor deficiency. We also thank Prof Pelle Guldborg Hansen for input on questionnaire techniques to inform the highly informative label approach and Dr Lynn Hamilton for editorial support. We also thank Laura Virtanen, Mariana Cardoso, and Martha Lahann for valuable research assistance.

Disclosures

A.J.C., C.N.S., and D.C. report working for the US Hereditary Angioedema Association. They have no personal conflicts of interest to declare in relation to this work. C.J. reports being a partner in and N.S. reports being an employee of Copenhagen Economics. S.C.C. reports serving as a consultant for KalVista Pharmaceuticals, Inc and BioCryst Pharmaceuticals, Inc. M.A.R. reports being a research investigator for BioCryst Pharmaceuticals, Inc, BioMarin Pharmaceuticals, Inc, CSL Behring, Ionis Pharmaceuticals, Inc, KalVista Pharmaceuticals, Inc, Pharvaris N.V., and Takeda Pharmaceutical Company Ltd and serving as a consultant for Astria Therapeutics, Inc, BioCryst Pharmaceuticals, Inc, BioMarin Pharmaceuticals, Inc, CSL Behring, Cycle Pharmaceuticals, Grifols, S.A., Intellia Therapeutics Inc, KalVista Pharmaceuticals, Inc, Pfizer Inc, Pharming Group N.V., Pharvaris N.V., and Takeda Pharmaceutical Company Ltd. B.L.Z. reports serving as a consultant for BioCryst Pharmaceuticals, Inc, CSL Behring, and Takeda Pharmaceutical Company Ltd; serving on the data safety monitoring board for BioMarin Pharmaceuticals, Inc; and having a laboratory service agreement with Ionis Pharmaceuticals, Inc. P.J.B. reports serving on the advisory board of or as a consultant for and receiving a grant or research support from BioCryst Pharmaceuticals, Inc, CSL Behring, KalVista Pharmaceuticals, Inc, Novartis AG, Regeneron Pharmaceuticals, Inc, and Takeda Pharmaceutical Company Ltd.

Funding

The US Hereditary Angioedema Association funded this project. The organization received financial support from various sources, including its members and the public. The Hereditary Angioedema Association also accepted grants for disease education and awareness from Astria Therapeutics, Inc, BioCryst Pharmaceuticals, Inc, BioMarin Pharmaceuticals, Inc, CSL Behring, Intellia Therapeutics, Ionis Pharmaceuticals, Inc, KalVista Pharmaceuticals, Inc, Pharming Group N.V., Pharvaris N.V., and Takeda Pharmaceutical Company Ltd.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2024.07.018>.

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Supplementary Data

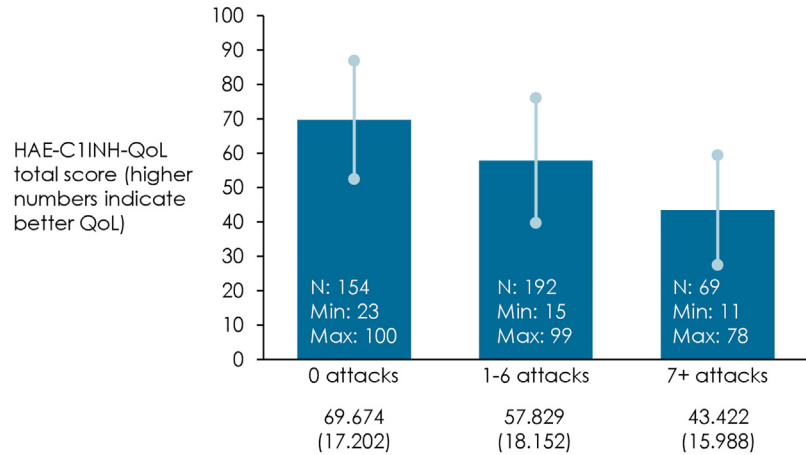


Figure 1. Discriminant validity – HAE attacks. Mean HAE-C1INH-QoL score by 3-month attack frequency (\pm SD indicated by lines). HAE, hereditary angioedema; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life; max, maximum; min, minimum.

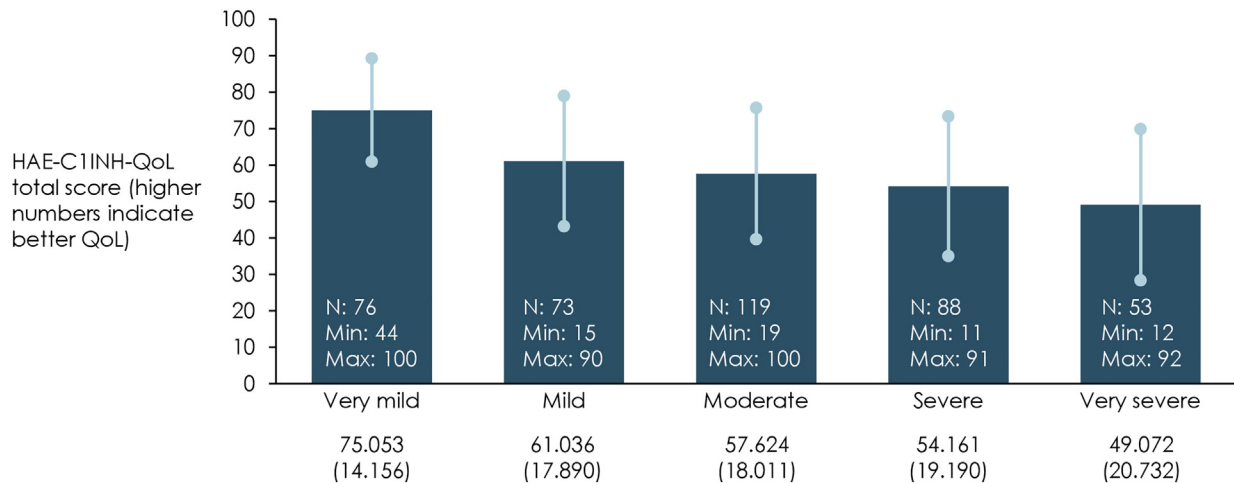


Figure 2. Discriminant validity – severity of HAE. Mean HAE-C1INH-QoL score by HAE severity (\pm SD indicated by lines). Severity is of HAE and is measured on a scale from 0 to 10 with 0 to 2 indicating very mild, 3 to 4 indicating mild, 5 to 6 indicating moderate, 7 to 8 indicating severe, and 9 to 10 indicating very severe. HAE, hereditary angioedema; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life; max, maximum; min, minimum.

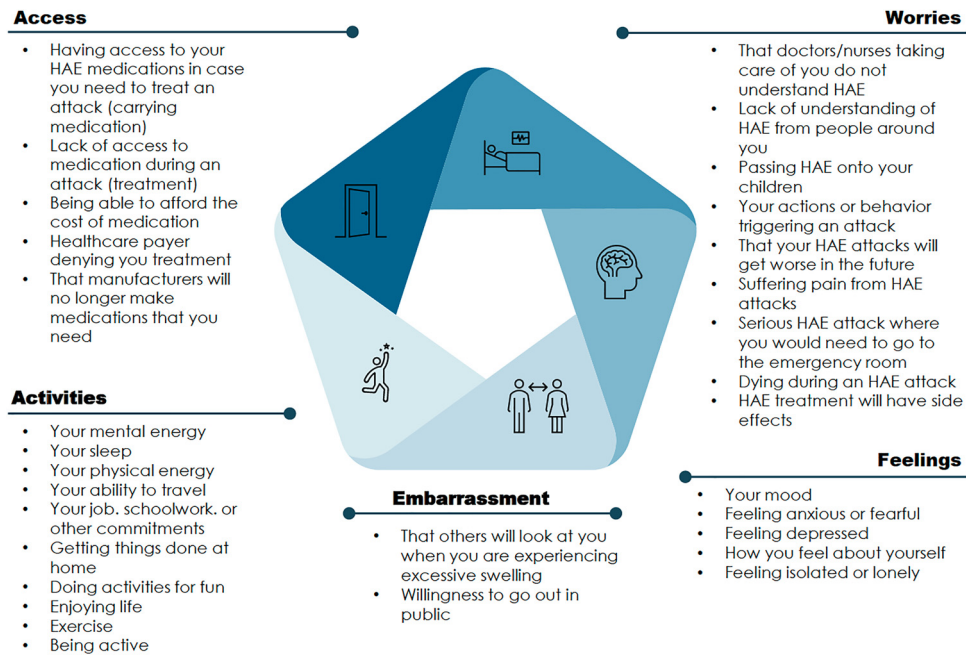


Figure 3. Domains and items in the HAE-C1INH-QoL instrument. HAE, hereditary angioedema; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

eTable 1
Scoring Guidelines

The following methodology is used for calculating the HAE-C1INH-QoL domain and total scores:

- 1) Each item answer option (scenario) is given a raw score ranging from 0 to 4, where higher numbers imply better quality of life. 0 is assigned to answer option 1, 1 is assigned to answer option 2, and so forth.
- 2) The raw domain scores are obtained by calculating the mean of the items scores within each domain.
- 3) The raw total score is obtained by calculating the mean of *all* item scores.
- 4) The raw domain and total scores are standardized into percentage scores by dividing the scores with the number of non-missing items in the domain and in total, respectively. The domain and the total scores are percentage scores (ranging from 0 to 100) and indicate the location of the raw scores in relation to the maximum possible score.

Abbreviation: HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

NOTE. You can access an Excel sheet to support calculating scores in the [Supplementary information](#).

eTable 2
Handling Missing Replies

The following guidelines for scoring of the HAE-C1INH-QoL domain and total scores should be used:

- 1) The domain total score is divided by the number of non-missing items if no more than 25% of items within the domain are missing (at most 2 items in the Activities and Worries domains, at most 1 item in the Feelings and Access domains, and no items in the Embarrassment domain).
- 2) The total HAE-C1INH-QoL score should only be calculated if none of the domain scores are missing (i.e., no more than 25% of the items within each domain are missing).

Abbreviation: HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

eTable 3
Final HAE-C11NH-QoL tool

HAE-C11NH-QoL questions and scenarios

In the following questions, you are asked to choose one scenario that best describes you out of five possible scenarios. There are 31 questions in total.

1. Your mood: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. My mood has generally been very bad. I have had negative feelings and thoughts most of the time and I have struggled to feel positive about anything.
2. My mood has generally been fairly bad. I have had frequent negative feelings or thoughts and occasionally felt positive about anything.
3. My mood has been both good and bad. I have had equally many negative and positive feelings.
4. My mood has generally been fairly good. I have had mostly positive feelings or thoughts.
5. My mood has generally been very good. On most or all of the days, I have had many positive feelings or thoughts.

2. Feeling anxious or fearful: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. I have felt very anxious and fearful. I have constantly worried about the smallest things.
2. I have frequently felt anxious and fearful. I have often worried about the smallest things.
3. I have occasionally felt anxious and fearful, but also had days without any worries.
4. I have rarely felt anxious and fearful. I have only worried occasionally.
5. I have not felt anxious or fearful at all. I have generally not been worried.

3. Feeling depressed: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. For most or all of the past 7 days, I have generally felt depressed and/or hopeless. I have had little or no interest in doing things.
2. During the past 7 days, I have often felt depressed and/or hopeless. I have had little interest in doing things.
3. During the past 7 days, there have been some moments in which I have felt depressed and/or hopeless. I have had some interest in doing things.
4. During the past 7 days, I have felt good. Only once or twice have I felt somewhat depressed and/or hopeless. I have had interest in doing things.
5. During the past 7 days, I have felt very good. I have not felt depressed and/or hopeless at any moment. I have had great interest in doing things.

4. Your mental energy: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. My mental energy has been very low. I find that I frequently have trouble focusing on or grasping even simple tasks, and I often felt fatigued.
2. My mental energy has generally been fairly low. I have had some difficulty focusing on simple tasks, and I sometimes felt fatigued.
3. My mental energy has been both high and low. I have carried out most tasks, while others had to wait because they felt overwhelming, and only occasionally did I feel fatigued.
4. I have had sufficient mental energy. I have carried out almost all tasks, though some better than others, and I rarely felt fatigued.
5. I have had plenty of mental energy. My mind has felt fully energized and no task has been too much to carry out, and I never felt fatigued.

5. How you feel about yourself: Of the following 5 scenarios, which scenario best describes you:

1. I strongly believe that I am inferior to other people. I constantly worry about what other people think of me and I am extremely sensitive to criticism.
2. I often believe I am inferior to other people. I worry a lot about what other people think of me and I am sensitive to criticism.
3. Sometimes I get the feeling that I am inferior to other people. I tend to worry about what other people think of me and I am somewhat sensitive to criticism.
4. I seldom get the feeling that I am inferior to other people. Only occasionally do I worry about what other people think of me. I am not very sensitive to criticism.
5. I do not believe I am inferior to other people. I never worry about what other people think of me and I am not sensitive to criticism.

6. That doctors/nurses taking care of you do not understand HAE: Of the following 5 scenarios, which scenario best describes you during the past year:

1. I have experienced many situations in which I have been very worried about the possibility that I may not be treated appropriately by doctors and nurses because they do not understand HAE.
2. I have experienced some situations in which I have been worried about the possibility that I may not be treated appropriately by doctors and nurses because they do not understand HAE.
3. I have experienced occasional situations in which I have been somewhat worried about the possibility that I may not be treated appropriately by doctors and nurses because they don't understand HAE.
4. I have experienced a few situations in which I have been slightly worried that I may not be treated appropriately by doctors and nurses because they don't understand HAE.
5. I have never experienced a situation in which I was worried that I may not be treated appropriately by doctors and nurses because they don't understand HAE. This is not something I worry about.

7. Lack of understanding of HAE from people around you: Of the following 5 scenarios, which scenario best describes you during the past year:

1. During the past year, I have constantly worried that people around me (excluding medical staff) do not understand HAE and this lack of knowledge about HAE concerns me a lot.
2. During the past year, I have frequently worried that people around me (excluding medical staff) do not understand HAE and this lack of knowledge about HAE is something that concerns me.
3. During the past year, I have occasionally worried that people around me (excluding medical staff) do not understand HAE and this lack of knowledge about HAE is something that concerns me a little.
4. Once or twice during the past year, I have worried that people around me (excluding medical staff) do not understand HAE but this lack of knowledge about HAE is generally not something that concerns me.
5. During the past year I have not worried that people around me (excluding medical staff) do not understand HAE and lack of knowledge about HAE is not something that concerns me.

8. Feeling isolated or lonely: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. I have generally felt very lonely. During most or all of the days, I have wished that I had more people who cared for me.
2. I have generally felt fairly lonely. During most of the days I have had moments in which I have wished that I had more people who cared for me.
3. I have occasionally felt lonely. There have been moments in which I have wished that I had more people who cared for me.
4. I have almost never felt lonely. I have very rarely wished that I had more people who cared for me.
5. I have never felt lonely. I have not at all wished that I had more people who cared for me.

9. Passing HAE onto your children: Of the following 5 scenarios, which scenario best describes you during the past year:

1. During the past year, I have constantly worried about passing HAE onto my current or future child/children or felt bad that I have already done so, and this concerns me a lot.
2. During the past year, I have worried about passing HAE onto my current or future child/children or felt bad that I have already done so, and this concerns me.
3. During the past year, I have occasionally worried about passing HAE onto my current or future child/children or felt bad that I have already done so, and this concerns me slightly.
4. Once or twice during the past year, I have worried about passing HAE onto my current or future child/children or felt bad that I have already done so, but this is generally not something that concerns me.
5. During the past year, I have not worried about passing HAE onto my current or future child/children or felt bad that I have already done so, and this is not something that concerns me at all.

(continued)

10. Your sleep: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. I have barely slept. I have struggled to fall asleep or stay asleep without interruptions on most or all of the nights.
2. I have not slept well. I have struggled to fall asleep or stay asleep without interruptions on a number of nights.
3. My sleep has been both good and bad. I had an equal number of good nights in which I could fall asleep and slept well and bad nights in which I struggled to fall asleep and slept with many interruptions.
4. I have slept fairly well. I fell asleep quite easily and if I woke up during the night, I had no trouble falling back to sleep.
5. I have slept very well. I did not have problems falling asleep and was not bothered by interrupted sleep.

11. Your physical energy: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. I have generally felt very tired. On most or all of the days, low energy levels have stopped me from carrying out many or all of my planned activities and tasks.
2. I have generally felt fairly tired. On some of the days, low energy levels have stopped me from carrying out some of my planned activities and tasks.
3. I have generally felt both energized and tired. I have completed most of my planned activities and tasks, but low energy levels mean that some of them are incomplete.
4. I have generally felt fairly energized. I have had enough energy to do all of the activities and tasks that I had to do, but I felt tired occasionally.
5. I have generally felt very energized. I have had plenty of energy to do all of the activities and tasks that I had to do.

12. Your ability to travel: Of the following 5 scenarios, which scenario best describes you during the last 7 days:

1. My physical or mental condition would have made it extremely difficult for me to travel on a long flight, train ride and/or road trip.
2. My physical or mental condition would most likely have prevented me from travelling on a long flight, train ride and/or road trip.
3. My physical or mental condition would have played a role in considering if I could travel on a long flight, train ride and/or road trip.
4. My physical or mental condition most likely would not have played any role in considering if I could travel on a long flight, train ride and/or road trip.
5. My physical or mental condition would not in any way have limited me in travelling on a long flight, train ride and/or road trip.

13. Your job, schoolwork, or other commitments: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. For most or all of the days in the last work week, it has been extremely difficult for me to attend and perform my best at my job, schoolwork, or other commitments.
2. For many days in the last work week, it has been difficult for me to attend and perform my best at my job, schoolwork, or other commitments.
3. For some of the days in the last work week, I have occasionally had trouble attending and performing my best at my job, schoolwork, or other commitments.
4. For most of the days in the last work week, I have not had any problems attending and performing my best at my job, schoolwork, or other commitments.
5. During the last work week, I have not had any problems attending and performing my best at my job, schoolwork, or other commitments.

14. Getting things done at home: Of the following 5 scenarios, which scenario best describes you during the last 7 days:

1. For most or all of the past 7 days, my physical and/or mental condition has made it extremely difficult for me to complete daily tasks at home.
2. For the past 7 days, my physical and/or mental condition has made it quite difficult for me to complete daily tasks at home.
3. For the past 7 days, my physical and/or mental condition has sometimes played a role in doing daily tasks at home.
4. For the past 7 days, my physical and/or mental condition has almost never limited me in doing daily tasks at home.
5. For all of the past 7 days, my physical and/or mental condition has not in any way limited me in doing daily tasks at home.

15. Doing activities for fun: Of the following 5 scenarios, which scenario best describes you during the last 7 days:

1. My physical and/or mental condition has made it extremely difficult for me to participate in activities for fun.
2. My physical and/or mental condition has occasionally affected my participation in activities for fun.
3. My physical and/or mental condition has sometimes affected my participation in activities for fun.
4. My physical and/or mental condition has rarely affected my participation in activities for fun.
5. My physical and/or mental condition has never affected my participation in activities for fun.

16. Enjoying life: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. For most or all of the past 7 days, my physical and/or mental condition has made it extremely difficult for me to enjoy life. I have found it almost impossible to engage in activities that make me happy.
2. For the past 7 days, my physical and/or mental condition has made it difficult for me to enjoy life. I have had trouble engaging in activities that make me happy.
3. For the past 7 days, my physical and/or mental condition has influenced my enjoyment of life. On some occasions my condition made it difficult for me to participate in activities that make me happy.
4. For the past 7 days, my physical and/or mental condition has not had any major influence on my enjoyment of life. I have almost never had trouble engaging in activities that make me happy.
5. For all of the past 7 days, my physical and/or mental condition has not in any way prevented me from enjoying life. I have not had any trouble engaging in activities that make me happy.

17. Exercise: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. I have generally found it very difficult to incorporate my desired amount of exercise into my lifestyle. I have not at all been able to exercise as much as I would like to.
2. I have generally found it somewhat difficult to incorporate my desired amount of exercise into my lifestyle. I have not been able to exercise as much as I would like to.
3. I have found it both easy and difficult to incorporate my desired amount of exercise into my lifestyle. I have been somewhat able to exercise but I would like to exercise more.
4. I have generally found it quite easy to incorporate my desired amount of exercise into my lifestyle. I have been able to exercise almost as much as I would like to.
5. I have generally found it very easy to incorporate my desired amount of exercise into my lifestyle. I have been fully able to exercise as much as I would like to.

18. Being active: Of the following 5 scenarios, which scenario best describes you during the past 7 days:

1. For most or all of the past 7 days, my physical or mental condition has completely prevented me from being active like others my age.
2. For the past 7 days, my physical or mental condition has often prevented me from being active like others my age.
3. For the past 7 days, my physical or mental condition has sometimes prevented me from being active like others my age.
4. For the past 7 days, my physical or mental condition has rarely prevented me from being active like others my age.
5. For the past 7 days, my physical or mental condition has never prevented me from being active like others my age.

19. Your actions or behavior: Of the following 5 scenarios, which scenario best describes you during the past year:

1. I have worried, nearly every day, that my own actions or behaviors may trigger an HAE attack, (eg.), stressing too much at work, in schoolwork, or with other commitments.
2. I have frequently worried that my own actions or behaviors may trigger an HAE attack, (eg.), stressing too much at work, in schoolwork, or with other commitments.
3. I have sometimes worried that my own actions or behaviors may trigger an HAE attack, (eg.), stressing too much at work, in schoolwork, or with other commitments.
4. I have rarely worried that my own actions or behaviors may trigger an HAE attack, (eg.), stressing too much at work, in schoolwork, or with other commitments.
5. I have never worried that my own actions or behaviors may trigger an HAE attack, (eg.), stressing too much at work, in schoolwork, or with other commitments.

20. That others will look at you when you are experiencing excessive swelling: Of the following 5 scenarios, which scenario best describes you during the past year:

1. I have felt extremely embarrassed about the possibility of other people seeing me while I am swelling.
2. I have frequently felt embarrassed about the possibility of other people seeing me while I am swelling.
3. I have occasionally felt embarrassed about the possibility of other people seeing me while I am swelling.

4. I have rarely felt embarrassed about the possibility of other people seeing me while I am swelling.
5. I have never felt embarrassed about the possibility of other people seeing me while I am swelling.
- 21. Willingness to go out in public: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have been unable and/or very reluctant to go out in public when I was experiencing swelling, and I only spend time in public areas if strictly necessary.
 2. I have had severe difficulties and/or been somewhat reluctant to go out in public when I was experiencing swelling, and I frequently chose not to go out in public.
 3. I have occasionally been unable and/or reluctant to go out in public when I was experiencing swelling, and I sometimes chose not to do so.
 4. I have rarely been unable to and/or reluctant to go out in public when I was experiencing swelling, and I rarely avoided doing so.
 5. I have never been unable or reluctant to go out in public when I was experiencing swelling, and never avoided doing so.
- 22. That your HAE attacks will get worse in the future: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. During the past year, I have thought, nearly every day, about the possibility that my HAE could become worse in the future and it worries me a lot.
 2. During the past year, I have frequently thought about the possibility that my HAE could become worse in the future, and it worries me.
 3. During the past year, I have occasionally thought about the possibility that my HAE could become worse in the future, and it worries me slightly.
 4. Once or twice during the past year, I have thought about the possibility that my HAE could become worse in the future, but it is generally not something that worries me.
 5. During the past year, I have not thought about the possibility that my HAE could become worse in the future and thinking about it now, it is not something that worries me at all.
- 23. Suffering pain from HAE attacks: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have thought, nearly every day, about the pain that I might experience during HAE attacks, and it worries me a lot.
 2. I have frequently thought about the pain that I might experience during HAE attacks, and it worries me.
 3. I have occasionally thought about the pain that I might experience during HAE attacks, and it worries me slightly.
 4. I have rarely thought about the pain that I might experience during HAE attacks, but it is generally not something that worries me.
 5. I have not thought about the pain that I might experience during HAE attacks, and it is not something that worries me at all.
- 24. Serious HAE attack in which you would need to go to the emergency room: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have thought, nearly every day, about the possibility of a serious HAE attack in which I would need to go to the emergency room, and it worries me a lot.
 2. I have frequently thought about the possibility of a serious HAE attack in which I would need to go to the emergency room, and it worries me.
 3. I have occasionally thought about the possibility of a serious HAE attack in which I would need to go to the emergency room, and it worries me slightly.
 4. I have rarely thought about the possibility of a serious HAE attack in which I would need to go to the emergency room, but it is not something that worries me.
 5. I have not thought about the possibility of a serious HAE attack in which I would need to go to the emergency room, and it is not something that worries me at all.
- 25. Dying during an HAE attack: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. During the past year, I have thought, nearly every day, about the fact that I could die during a laryngeal HAE attack. When I think about it, it worries me a lot.
 2. During the past year, I have frequently thought about the fact that I could die during a laryngeal HAE attack. When I think about it, it worries me.
 3. During the past year, I have occasionally thought about the fact that I could die during a laryngeal HAE attack. When I think about it, it worries me slightly.
 4. Once or twice during the past year, I have thought about the fact that I could die during a laryngeal HAE attack. It is generally not something that worries me.
 5. During the past year, I have not thought about the fact that I could die during a laryngeal HAE attack. It is not something that worries me at all.
- 26. HAE treatment will have adverse effects: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have thought, nearly every day, about the potential adverse effects from my HAE treatments (both now and in the future) and it worries me a lot.
 2. I have frequently thought about the potential adverse effects from my HAE treatments (both now and in the future) and it worries me.
 3. I have occasionally thought about the potential adverse effects from my HAE treatments (both now and in the future) and it worries me slightly.
 4. I have rarely thought about the potential adverse effects from my HAE treatments (both now and in the future) but it is generally not something that worries me.
 5. I have not thought about the potential adverse effects from my HAE treatments (both now and in the future) and it is not something that worries me at all.
- 27. Having access to your HAE medications in case you need to treat an attack: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have thought, nearly every day, about potential difficulties in having access to my HAE medications and it worries me a lot.
 2. I have frequently thought about potential difficulties in having access to my HAE medications and it worries me.
 3. I have occasionally thought about potential difficulties in having access to my HAE medications and it worries me slightly.
 4. I have rarely thought about potential difficulties in having access to my HAE medications, but it is generally not something that worries me.
 5. I have not thought about potential difficulties in having access to my HAE medications and it is not something that worries me at all.
- 28. Lack of access to medication during an attack: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have thought, nearly every day, about possible situations in which neither I nor anyone else would be able to give me my medicine during an HAE attack for physical reasons or because the medicine was not easily available, and it worries me a lot.
 2. I have frequently thought about possible situations in which neither I nor anyone else would be able to give me my medicine during an HAE attack for physical reasons or because the medicine was not easily available, and it worries me.
 3. I have occasionally thought about possible situations in which neither I nor anyone else would be able to give me my medicine during an HAE attack for physical reasons or because the medicine was not easily available, and it worries me slightly.
 4. I have rarely thought about possible situations in which neither I nor anyone else would be able to give me my medicine during an HAE attack for physical reasons or because the medicine was not easily available, but it is generally not something that worries me.
 5. I have not thought about possible situations in which neither I nor anyone else would be able to give me my medicine during an HAE attack for physical reasons or because the medicine was not easily available, and it is not something that worries me.
- 29. Being able to afford the cost of medication: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have frequently thought about being able to afford the medication that I have been prescribed both now and in the future, and it worries me a lot.
 2. I have often thought about being able to afford the medication that I have been prescribed both now and in the future, and it worries me.
 3. I have occasionally thought about being able to afford the medication that I have been prescribed both now and in the future, and it worries me slightly.
 4. I have rarely thought about being able to afford the medication that I have been prescribed both now and in the future, but it is generally not something that worries me.
 5. I have never or almost never thought about being able to afford the medication that I have been prescribed both now and in the future, and it is not something that worries me.
- 30. Healthcare payer denying you treatment: Of the following 5 scenarios, which scenario best describes you during the past year:**
1. I have frequently thought about the risk of my healthcare payer ((eg.), insurance company or public healthcare system) denying me treatment and it worries me a lot.
 2. I have often thought about the risk of my healthcare payer ((eg.), insurance company or public healthcare system) denying me treatment and it worries me.
 3. I have occasionally thought about the risk of my healthcare payer ((eg.), insurance company or public healthcare system) denying me treatment and it worries me slightly.
 4. I have rarely thought about the risk of my healthcare payer ((eg.), insurance company or public healthcare system) denying me treatment and it is not something that generally worries me.
 5. I have never thought about the risk of my healthcare payer ((eg.), insurance company or public healthcare system) denying me treatment and it is not something that worries me.

(continued)

31. That manufacturers will no longer make medications that you need: Of the following 5 scenarios, which scenario best describes you during the past year:

1. I have very often thought about the possibility that manufacturers will stop making the medication that I need, and it worries me a lot.
2. I have frequently thought about the possibility that manufacturers will stop making the medication that I need, and it worries me.
3. I have occasionally thought about the possibility that manufacturers will stop making the medication that I need, and it worries me slightly.
4. I have rarely thought about the possibility that manufacturers will stop making the medication that I need but it is generally not something that worries me.
5. I have not thought about the possibility that manufacturers will stop making the medication that I need, and it is not something that worries me at all.

Abbreviations: HAE, hereditary angioedema; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

eTable 4
Proportion of Patients Reporting 0 and 100 Domain Scores

0 and 100 scores by Domain	n (N = 415)	Proportion, %
Activities		
0 domain score	2	0.5
100 domain score	12	2.9
Worries		
0 domain score	1	0.2
100 domain score	10	2.4
Access		
0 domain score	16	3.9
100 domain score	15	3.6
Feelings		
0 domain score	3	0.7
100 domain score	24	5.8
Embarrassment		
0 domain score	19	4.6
100 domain score	126	30.4

eTable 5
Multiple Linear Regression Results for the HAE-C1INH-QoL

Domain	(1) HAE-C1INH-QoL	(2) Activities	(3) Worries	(4) Access	(5) Feelings	(6) Embarrassment
Attacks	−2.099 (0.458) [.0000]	−2.516 (0.597) [.0000]	−2.291 (0.524) [.0000]	−1.451 (0.652) [.0267]	−1.320 (0.533) [.0137]	−2.724 (0.781) [.0005]
Attack-free	6.334 (2.105) [.0028]	7.909 (2.745) [.0042]	5.430 (2.410) [.0248]	3.849 (2.999) [.2000]	5.990 (2.450) [.0149]	9.608 (3.588) [.0077]
Severity of HAE^a						
Mild (3–4)	−8.597 (2.708) [.0016]	−11.682 (3.532) [.0010]	−6.616 (3.101) [.0335]	−9.004 (3.858) [.0201]	−7.860 (3.153) [.0131]	−2.920 (4.616) [.5274]
Moderate (5–6)	−11.359 (2.453) [.0000]	−12.332 (3.199) [.0001]	−9.429 (2.808) [.0009]	−13.792 (3.494) [.0001]	−11.102 (2.855) [.0001]	−9.750 (4.181) [.0202]
Severe (7–8)	−14.980 (2.590) [.0000]	−14.691 (3.378) [.0000]	−13.557 (2.966) [.0000]	−19.443 (3.690) [.0000]	−12.744 (3.016) [.0000]	−17.260 (4.415) [.0001]
Very severe (9–10)	−19.900 (2.995) [.0000]	−19.996 (3.906) [.0000]	−18.749 (3.429) [.0000]	−26.017 (4.267) [.0000]	−16.298 (3.487) [.0000]	−18.318 (5.105) [.0004]
Age	0.180 (0.053) [.0007]	0.096 (0.069) [.1623]	0.298 (0.060) [.0000]	0.018 (0.075) [.8077]	0.292 (0.061) [.0000]	0.191 (0.090) [.0338]
Male^b	4.668 (1.926) [.0158]	4.245 (2.512) [.0918]	6.171 (2.205) [.0054]	1.333 (2.744) [.6275]	5.446 (2.242) [.0156]	6.419 (3.283) [.0512]
Bachelor's degree or higher^c	4.479 (1.618) [.0059]	6.922 (2.111) [.0011]	3.275 (1.853) [.0780]	0.153 (2.306) [.9471]	5.684 (1.884) [.0027]	5.488 (2.759) [.0474]
Constant	58.384 (3.640) [.0000]	60.937 (4.748) [.0000]	53.347 (4.168) [.0000]	62.631 (5.186) [.0000]	56.028 (4.238) [.0000]	63.563 (6.205) [.0000]
No. adjusted R²	397 0.370	397 0.297	397 0.330	397 0.176	397 0.270	397 0.239

Abbreviations: HAE, hereditary angioedema; HAE-C1INH-QoL, hereditary angioedema due to C1 inhibitor deficiency quality of life.

NOTE. Average treatment effects estimates. SD is provided in parentheses. P values from t statistics are provided in brackets. Respondents with other sex (n = 3) or other education (n = 5) were omitted because of a few observations.

^aGeneral HAE severity. Baseline severity was very mild (severity 0–2).

^bBaseline sex was female.

^cBaseline education was associate degree or less.