



Time Trade-Off Utilities for Hereditary Angioedema Health and Caregiver States

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Abstract

Background Hereditary angioedema (HAE) is an inherited chronic rare disease characterised by recurrent swelling attacks that are associated with significant physical and psychological burden. There is limited understanding of the effect of attack location on this burden and of caregiver burden.

Objective Our objective was to capture the relative burden of HAE health and caregiver states, including different attack locations, through a time trade-off (TTO) analysis involving participants from the general public.

Methods Qualitative interviews were undertaken to inform vignette development for the TTO study, including vignettes for abdominal, facial, hand and laryngeal attack health states, and an attack-free and caregiver state. Members of the general public in England rated vignettes in TTO interviews, which included a visual analogue scale (VAS) component. For the development of the health state vignettes, qualitative interviews with 15 patients, 5 caregivers and 1 clinical expert were performed. TTO analysis was based on vignette valuation completed by 100 members of the general public.

Results The TTO values were as follows: attack-free, 0.783 (standard deviation [SD] 0.316); hand: 0.582 (SD 0.380); facial: 0.483 (SD 0.448); abdominal: 0.345 (SD 0.458); and laryngeal: 0.128 (SD 0.529). The caregiver rating was 0.762 (SD 0.303). V^* scores were similar and consistent with TTO values.

Conclusion TTO utility values demonstrate that HAE places a significant burden on patients, which is influenced by attack location, and on caregivers. These utility weights can provide important information on quality of life for future economic evaluations of treatments.

Key Points for Decision Makers

A time trade-off analysis to estimate utility weights for hereditary angioedema (HAE) health states showed that this disorder has a significant negative impact on quality of life.

The location of the body affected by HAE influences the extent to which quality of life is affected.

HAE also has a negative impact on the lives of caregivers while they are caring for a person having an HAE attack.

1 Introduction

Hereditary angioedema (HAE) is characterised by recurrent attacks of localised swelling in the skin and/or mucosa, affecting the extremities, face, gastrointestinal tract and/or larynx [1]. HAE is rare, occurring in approximately 1 in 50,000 to 1 in 67,000 people, and the majority of cases are caused by autosomal dominant mutations in *SERPING1* [2, 3]. Symptoms often present in childhood or adolescence and worsen during puberty; there is no cure for HAE and attacks occur throughout a patient's lifetime [1]. Attacks are often unpredictable [1, 4], and frequency and severity can vary widely [1, 5]. Because of the physical nature of swelling, even a mild attack may cause transient discomfort, pain and disfigurement [1, 2, 6]. Abdominal attacks may be very painful and, because of non-specific symptoms (such as nausea, vomiting and abdominal swelling), can lead to misdiagnoses and unnecessary procedures in undiagnosed patients [6]. Laryngeal swelling can be fatal because of obstruction of the airways,

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and more than 50% of people with HAE have experienced at least one laryngeal attack [1, 6]. Although prophylactic and on-demand treatments are available, these may not be suitable for all patients because of adverse effects and routes of administration [7]. On-demand treatments require that people with HAE and their caregivers are trained on the urgent administration of these (often injectable) drugs, and this can be associated with a further burden to the patient and their family [8].

Given the chronic, recurrent nature of HAE attacks and the potential for severe symptoms, insights into patients' and caregivers' quality of life (QoL) are important to better guide clinical decision making and resource allocation. Understanding of the impact of HAE on QoL is based on studies using generic and disease-specific assessments and on real-world surveys. Generic assessments showed that patients with HAE have reduced QoL scores compared with population norms, with negative impacts across physical and mental health domains, and employment and education [9–11]. Anxiety and/or depression were also common [10]. Disease-specific QoL assessments, such as the Angioedema Quality of Life (AE-QoL) questionnaire [12] and Hereditary Angioedema Quality of Life (HAE-QoL) tool [13], have revealed effects in fear/shame, perceived control of disease and fatigue/mood domains [14, 15]. Both generic and disease-specific QoL scores were associated with attack rate [10, 16].

Further data on the impact of HAE have been collated via the Hereditary Angioedema Burden of Illness Study (HAE-BOIS), a cross-sectional real-world survey of people with HAE over the age of 12 years [8, 17, 18]. Five major QoL themes were identified: unnecessary treatments and procedures; symptom triggers; attack impacts; caregiver impacts; and long-term impacts [8]. Attacks have a negative impact on daily activities, and associations between QoL and attack severity, frequency and pain severity were found [17, 19]. Clinically meaningful anxiety or depression was reported for 38 and 14% of respondents, respectively [19], with the greatest anxiety caused by the potential for children to inherit HAE [19]. Anxiety associated with HAE extends into long-term planning, with further concerns about travelling and about progressing career or education opportunities. HAE-BOIS included five adolescents and young adults under the age of 25 years, who also felt that participation in physical activities was affected and had anxieties about the future [8]. The need for training in the use of acute treatments was highlighted [8], with both patients and caregivers being required to learn to administer urgent treatment.

The caregivers' perspective has been studied to a more limited extent than that of patients, but their burden

also extends into adapting social plans and carrying out increased daily activities, with significant negative effects on managing family life, consistent with studies of people with HAE [8, 20].

The EQ-5D tool is often recommended as a tool to measure disease burden and provide utility weights for health technology assessments (HTAs) [21], and it is the preferred measure for health-related QoL (HRQoL) assessments undertaken by the National Institute for Health and Care Excellence (NICE) [22]. HAE-BOIS results have been used to estimate EQ-5D utility scores, with mean scores when attack-free estimated as 0.72, during an attack as 0.44, and for attacks causing severe pain as 0.08 [23].

Utility weights can also be generated through the time trade-off (TTO) method using vignette descriptions of health states [24]. The general public typically rates the vignettes to provide the societal perspective in the valuation task, and the TTO method allows for utility weights to be estimated for health states where these values are difficult to obtain, such as during temporary, acute events [25]. HAE attacks fall into this category of events as it could be difficult to access patients with HAE during an attack because of the variable and unpredictable nature of attacks. Furthermore, the impact of attack location on patient HRQoL and the impact of HAE attacks on caregiver HRQoL have not been estimated and are a source of heterogeneity. Therefore, in the present study, we used the TTO approach to understand the impact of attack location and the impact of HAE on caregivers' QoL.

The objective of this study was to estimate utility weights for HAE patient and caregiver health states using the TTO method, including an attack-free state, attacks at different locations and a single caregiver state during an HAE attack, to improve understanding of the burden of HAE.

2 Methods

This study was reviewed and approved by the Western Institutional Review Board (WIRB; 1 June 2020) and was conducted in three stages:

- Part I: Qualitative interviews to describe burden and HRQoL across patients and caregivers (conducted June and July 2020).
- Part II: Patient and caregiver vignette development, informed by the results of Part I and incorporating attack location for patient states (conducted September 2020).
- Part III: TTO interviews using the vignettes developed in Part II and participants from the general public to estimate utility weights (conducted October 2020).

2.1 Part I: Qualitative Interviews on Patient and Caregiver Burden

People with HAE and caregivers were recruited through the patient organisation HAE UK using a short advertisement placed on the HAE UK website and social media, or invitation letters. Potential participants were asked to complete a screener questionnaire to ensure the basic inclusion criteria were met:

- a diagnosis of HAE and/or being a caregiver to someone with a diagnosis of HAE
- over 12 years of age
- living in the UK
- willing and able to consent to take part in an audio-recorded interview (or verbal assent combined with parental assent for minors aged under 18 years).

Informed consent was obtained prior to completion of a background questionnaire and participation in qualitative interviews. Background questionnaires (including the AE-QoL questionnaire) collected data on sociodemographics and clinical details. Patient data were self-reported, and patient-related responses from caregivers were proxy-reported. Data were analysed using descriptive statistics.

Qualitative interviews were supported by a semi-structured guide as shown in Online Resource 1, which was developed based on previous studies of the burden of HAE in people with the disease and caregivers [8, 20, 26, 27]. Data were collected on patient background, symptoms and treatment, and the impact on daily life, emotional well-being and physical appearance during attacks and attack-free periods, during adolescence, and on caregivers.

Interviews were conducted via telephone or an online video/voice call using Zoom and lasted between 60 and 90 min. Interviews were recorded, fully transcribed and de-identified for analysis purposes. All adolescent patients chose to be interviewed without their parents present. All participants received a £30 e-voucher from an online retailer as compensation for their time.

Interview transcripts were analysed using content analysis supported by MAXQDA software. The analysis was conducted by the experienced qualitative researchers who had conducted the interviews. Two team members independently coded one adult patient transcript, one caregiver transcript and one patient/caregiver transcript, resulting in 3 of 20 transcripts being double-coded. After the transcripts had been coded twice, the coding was compared and, where there was disagreement, a process of reconciliation took place and all codes were compared, discussed and reconciled wherever differences occurred. When sufficient agreement between the two coders was established, one coder analysed the remaining transcripts.

2.2 Part II: Vignette Development

Draft vignettes for five HAE health states and one caregiver health state, as provided in Online Resource 2, were developed based on the findings of the qualitative interviews:

- HAE adult patient: attack-free (i.e. currently not experiencing any swelling)
- HAE adult patient: abdominal attack (i.e. currently experiencing swelling in the abdomen)
- HAE adult patient: facial attack (i.e. currently experiencing swelling in the face)
- HAE adult patient: hand attack (i.e. currently experiencing swelling in a hand)
- HAE adult patient: laryngeal attack (i.e. currently experiencing swelling in the throat)
- HAE caregiver: person they care for is experiencing an attack.

Vignettes were refined through interviews with two people with HAE and two caregivers who had participated in Part I of the study and had agreed to be recontacted. Patients and caregivers were recruited based on experiences of different attack locations, in order to allow them to provide feedback on a range of HAE health state vignettes. A clinician with expertise in the management and treatment of HAE also provided feedback. All interviews were conducted via online video/voice call using Zoom and were based on semi-structured guides with a line-by-line assessment of draft vignettes (see Online Resource 3 for interview guides). Interviews were summarised, detailing the feedback on the descriptions; vignettes were revised on an iterative basis and reviewed in further interviews. Patient and caregiver vignettes were compared where appropriate to ensure consistency.

2.3 Part III: Time Trade-Off (TTO) Valuation of Vignettes

In the valuation interviews, participants were first asked to rate each state (plus the dead state) using the visual analogue scale (VAS) anchored between best imaginable health and worst imaginable health. The VAS task was used to familiarise participants with both the content of the health states and the concept of valuing health. The TTO interviews essentially employed the composite TTO approach [28]. In this method, the conventional TTO approach with a 10-year time horizon was used for states better than dead, and states worse than dead were assessed using the lead-time approach. The TTO method did not replicate the EuroQol Group's approach [29] because the visual presentation of the TTO materials was not exactly the same and the iteration method for eliciting values used the ping-pong approach (detailed later in this section).

Participants were 100 members of the general public aged over 18 years, recruited by interviewers through informal networks using quota-based convenience sampling, including snowballing, to match the general public in terms of age, sex and ethnicity. The sample size was informed by samples in other published TTO studies [30–33]. Informed consent was obtained and background sociodemographic questionnaires were completed prior to interview. Participants received £30 as compensation for their time. Sociodemographic data were analysed using descriptive statistics.

Interviews were conducted according to a script (see Online Resource 4 for interview script) using video calls (Skype or Zoom), and participants were requested to print the vignettes prior to interview or have the vignettes open on a separate screen to the one that the online video call was conducted on. This enabled the interviewer to maintain eye contact via the videoconference software and to display the paper VAS and wooden TTO board alongside themselves on the screen. All interviewers were trained in the TTO methodology. Each participant was assigned to one of four versions of the vignettes, with versions counterbalancing order effects. The VAS component was conducted first, with two generic HAE-unrelated practice vignettes, and then patient or caregiver vignettes and ‘dead’ from Part II of this study were presented one by one. The VAS ratings for each vignette were rescaled such that the value for the dead state was fixed at zero and all other values varied between 100 and the worst health state. The following formula was used to rescale the data (Eq. 1) [34]:

$$V' = \left(\frac{V - V_{\text{Dead}}}{100 - V_{\text{Dead}}} \right) \times 100, \quad (1)$$

where V' is the rescaled VAS value, V is the original VAS value and V_{Dead} is the value given to the dead state. After rescaling, the V' data were summarised descriptively.

Following the VAS exercise, the TTO interview was conducted for the patient and caregiver vignettes developed in Part II of the study. We used a composite TTO method [28], incorporating a standard TTO for health states considered to be better than dead and a lead-time TTO for health states worse than dead, as used for valuation of EQ-5D health states [35]. The ping-pong method was used to minimise bias in participants’ responses, whereby the amount of time in full health was alternated between high and low values, modified in 6-month increments. Thus, time in full health varied from 10 to 0 years, and then to 9.5 years and then 6 months and so on, to avoid framing effects influencing participants’ responses. Time in full health was varied until the participant was considered indifferent between the two choices or had ‘switched’ their preference from one state to the other. If the participant considered 5 years in full health to be the same as 10 years in the health state, then the state

was given a value of 0.5. If the switch in their preference occurred between 5 years and 5 years and 6 months, then a value of 0.525 was entered.

If participants stated that 0 years in full health was preferable to 10 years in the health state, then the state was considered as worse than dead; they were asked to confirm that they believed that this was the case. The interviewer then switched to a lead-time TTO exercise, which asked participants whether they would prefer to live for 10 years in full health followed by 10 years in a health state, or to live for 10 years in full health. They then completed the lead-time TTO procedure for states worse than dead. TTO data were scored according to the point of indifference or the average of the two values when the ‘switch’ had occurred. TTO data were summarised descriptively.

3 Results

3.1 Part I: Qualitative Interviews on Patient and Caregiver Burden

The study population consisted of 15 patients (of whom 6 were also a caregiver to someone with HAE and 2 were adolescents) and 5 caregivers who did not have HAE themselves. The majority of participants were female ($n = 12$ [80%] among patients and $n = 4$ [80%] among caregivers), and the mean age was 41.9 years (range 15–56 years) for patients and 37.6 years (range 32–44 years) for caregivers. The majority of adult patients had achieved secondary or degree-level qualifications ($n = 10$; 77%), as had caregivers ($n = 4$; 80%), and most adult patients ($n = 8$; 62%) and caregivers ($n = 4$; 80%) were employed full- or part-time. All patients except 1 had a parent, sibling and/or child with HAE. All caregivers and patients who cared for someone else with HAE cared for a single person with HAE, except for 1 caregiver who cared for 2 people with HAE.

All participants who had HAE completed the AE-QoL questionnaire. The mean total score for all participants was 59.4 (standard deviation [SD] 21.9), with the highest domain scores for fear/shame (mean 65.8; SD 23.9), followed by fatigue/mood (mean 64.5; SD 25.9), functioning (mean 51.2; SD 23.7) and nutrition (mean 43.4; SD 30.9).

The results of the content analysis of the qualitative interviews that informed the vignette content specific to each health or caregiver state are summarised in Table 1. HAE has a substantial impact across multiple aspects of the daily lives of people with HAE, extending beyond the period of the attack and managing treatments, into employment, education, family and social elements of life. Most participants reported low mood/depression, and being distressed/upset and/or anxious when having an attack, although some

reported minimal impact on their emotions. Fatigue (both before and after attacks) and sleep problems were commonly reported, independent of the location of the attack. Most patients described themselves as being reluctant to attend social events while having an attack, because of either the severe pain experienced or the impact of external swellings on their physical appearance.

Negative impacts also applied to caregivers and included the need for providing caregiving activities (such as help with treatment administration) and providing practical and emotional care more generally during an attack, and disruption to daily activities and employment. Caregivers also experienced an emotional impact of having a loved one with HAE during both attacks and attack-free periods, and negative impacts on social activities as a result of providing care.

3.2 Part II: Vignette Development

Draft vignettes were informed by the results of the qualitative interviews in Part I of this study and revised following further interviews with two people with HAE, two caregivers and one clinician with experience of HAE. Participants' feedback is shown in Online Resources 5 and 6 and suggested the draft vignettes were fair and balanced, and

participants suggested some revisions to refine and simplify the vignettes prior to their finalisation (see Online Resource 7 for final vignettes). These revisions were focused on adequate generalisation across patients' experiences because of the variability of the condition, the need for lifestyle changes, the psychological impact of (the possibility of) a laryngeal attack, and treatment and management of HAE.

3.3 Part III: TTO Analyses of Vignettes

Demographics of participants in the TTO valuation interviews are shown in Table 2. The English sample characteristics were broadly similar to the UK census data in terms of age, sex and ethnicity.

V' and TTO ratings for each patient or caregiver state are shown in Table 3. The lowest mean V' was for laryngeal attacks and the highest mean was for the attack-free state, with all mean V' ratings of attack states lower than the mean rating of the attack-free state. TTO scores show a similar ordering of states to V' scores, with the lowest score for a laryngeal attack and the highest for the attack-free state. For both V' and TTO, the second lowest scores were for abdominal attacks, followed by facial and then hand attacks. For both V' and TTO, the mean values of the caregiver state

Table 1 Summary of qualitative findings informing health state vignettes

State	Qualitative patient and caregiver burden findings
Attack-free state	No impacts on physical functioning were reported when patients were attack-free HAE impacts on daily activities were described as minimal or small, and included the need to plan ahead and remembering to take HAE medication when going out. Some reported scarring and bruising from injections Some reported being mindful of potential triggers when performing daily activities and choosing social and leisure activities (e.g. avoiding strenuous activities/sports and/or repetitive movements, sticking to a routine, avoiding stress)
Abdominal attack state	Abdominal attacks typically had a negative impact on patients' ability to move because of severe or extreme pain and were often associated with gastrointestinal issues, such as nausea, diarrhoea, vomiting and/or constipation Painful abdominal swellings could affect all aspects of daily life and were typically described as debilitating Abdominal attacks were among the most emotionally impactful attacks
Facial attack state	Swollen eyelids were reported to limit patients' vision as a result of one or both eyes closing Some described facial swelling as drawing unwanted attention from other people Facial attacks were among the most emotionally impactful attacks
Hand attack state	Hand and arm swellings could affect the ability to grasp, lift and/or carry objects, or in severe cases could result in not being able to use the hand(s)/arm(s) at all Some described hand swellings as drawing unwanted attention from other people
Laryngeal attack state	Throat attacks had the most impact emotionally of all attack locations Throat attacks were most likely to result in patients going to hospital
Caregiver state while caring for someone having an HAE attack	Caregivers commonly described helping with treatment administration and arranging healthcare during an attack. Some reported stress and anxiety related to poor veins and timely administration of the treatment Patients and caregivers also reported caregiver help with housework, childcare, emotional support and sometimes self-care (e.g. washing, dressing) Severe attacks had a great impact on caregivers' daily activities, such as leaving work early and taking on more housework and childcare duties Caregivers typically reported emotional impacts on themselves as a result of seeing the person they care for in pain and/or distress, with throat and abdominal attacks being the most emotionally impactful

during attacks were lower than those of the attack-free state of a person with HAE. This suggests consistency in how participants valued the health states.

If participants rated the attack-free state as worse than an attack state during TTO valuations, this was considered inconsistent. Of 400 TTO ratings of patient (abdominal, facial, hand and laryngeal) attack states, this happened 12 times (3% of ratings), most commonly with the hand

attack ($n = 9$). The inconsistent ratings were retained in the overall analysis and reflect measurement error. The frequency of TTO ratings worse than dead (i.e. below 0) was as follows: attack-free ($n = 2$; 2%), abdominal attack ($n = 9$; 9%), facial attack ($n = 6$; 6%), hand attack ($n = 3$; 3%), laryngeal attack ($n = 17$; 17%), and caregiver during an attack ($n = 1$; 1%).

Table 2 Demographics of participants of TTO valuation interviews

Characteristic	English general public sample for TTO valuation [$n = 100$] Mean (SD)	UK population Median
Age, years	42.0 (17.8)	40.4
	<i>n</i> (%)	%
Sex		
Male	51 (51)	49 ^a
Female	49 (49)	51 ^a
Ethnicity		
White	83 (83)	85 ^b
Asian	6 (6)	8 ^b
Black	5 (5)	3 ^b
Mixed	4 (4)	2 ^b
Other	2 (2)	2 ^b
Long-term condition ^c		
Yes	45 (45)	38 ^d
Informal carer ^e		
Yes	10 (10)	6 ^f

SD standard deviation, *TTO* time trade-off, *ONS* Office for National Statistics

^aData from the UK ONS—estimates of the population for the UK, England and Wales, Scotland and Northern Ireland, 2020 (<http://www.ons.gov.uk>)

^bUK ONS—population characteristics research tables, December 2019

^cIncluding anxiety (8%), arthritis (4%), cancer (2%), depression (3%), diabetes (2%), digestive disorders (1%), heart disease (3%), hypertension (5%), respiratory conditions (3%) and ‘other’ conditions (6%); percentages do not add up to 45% as some participants reported multiple long-term conditions

^dUK ONS—people with long-term health conditions, UK, January to December 2019

^eIncluding carer to a partner (2%), child (2%), parent or sibling (4%), other relative (1%) and friend (1%)

^fUK National Statistics—Family Resources Survey: financial year 2018/2019 (www.gov.uk/search/research-and-statistics)

Table 3 V' and TTO ratings of health states for patients and caregiver

Health state	V'		TTO	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Patient state 1: attack-free state	68.5 (14.9)	65.6–71.5	0.783 (0.316)	0.720–0.846
Patient state 2: abdominal attack state	33.6 (15.7)	30.5–36.7	0.345 (0.458)	0.254–0.436
Patient state 3: facial attack state	41.7 (16.7)	38.4–45.0	0.483 (0.448)	0.394–0.572
Patient state 4: hand attack state	43.1 (18.6)	39.4–46.8	0.582 (0.380)	0.507–0.657
Patient state 5: laryngeal attack state	24.6 (15.2)	21.5–27.6	0.128 (0.529)	0.023–0.233
Caregiver state while caring for someone having an HAE attack	59.9 (18.3)	56.3–63.5	0.762 (0.303)	0.701–0.822

CI confidence interval, *HAE* hereditary angioedema, *SD* standard deviation, *TTO* time trade-off, V' visual analogue scale data

4 Discussion

This study highlights the substantial physical and emotional burden of HAE through TTO valuation interviews of HAE disease and caregiver state vignettes with the general public. Disease and caregiver vignettes were informed by qualitative interviews with people with HAE and caregivers. The content analysis of the qualitative interviews describes the burden of HAE during an attack and when attack-free. This burden affects multiple aspects of the lives of the person with HAE and their family, confirming findings from HAE-BOIS and other QoL studies of people with HAE [8–11, 19]. Both the physical and emotional burden are the result of a disease that is variable between patients and in terms of the type, severity and unpredictability of attacks for a single patient. The unpredictability of attacks can cause anxiety over when the next attack might occur, its severity and location, and the extent of treatment required. During attacks, the physical impact and effects on daily activities are associated with severity and location, highlighting the need to understand the potential heterogeneity of the burden. The qualitative interviews also highlight the burden on caregivers and patients who also care for someone else with HAE, which also affects their emotional well-being and disrupts daily activities.

We present data from TTO valuation interviews of HAE patient and caregiver states with participants from the general population. The TTO utility weights demonstrate the burden of HAE attacks and the less severe burden when patients are attack-free, and are broadly consistent with estimates from HAE-BOIS. The between-attack utility score for HAE-BOIS was 0.72, compared with 0.783 in our study, and the acute attack score for HAE-BOIS was 0.08–0.61 (depending on pain severity), compared with 0.128–0.582 (depending on attack location) in our study [23]. These results show the substantial burden of laryngeal and abdominal attacks in comparison with attacks affecting the extremities. The attack-free state TTO value (0.78) was lower than the estimated EQ-5D population norm for the UK (0.86) [36] and is similar to values for type I diabetes mellitus (0.79) [37] and partially controlled or uncontrolled asthma (0.72) [38]. The abdominal attack weight (0.35) is only slightly higher than that for acute stroke (0.31) [39], and the mean facial attack weight (0.48) is similar to that for ischaemic heart disease with moderate/severe angina (0.45) [40].

Our study further extends knowledge of the burden of HAE by also examining a caregiver state; the TTO scores indicated that the caregiver state has a lower utility than the attack-free patient state, supporting the burden described by caregivers during the qualitative interviews. The TTO caregiver weight (0.76) is close to that reported for caregivers

of people with multiple sclerosis (0.74) [41] and lower than that for caregivers of people with Alzheimer's disease (0.86–0.82) [42]. Our caregiver vignette does not describe attack location and, as with the patient vignettes, there is the potential for there to be variation between supporting a patient through, for example, a laryngeal attack compared with an attack affecting the extremities. It would also be worth examining the caregiver state in the attack-free period to further clarify understanding of anxieties and of changes to family and lifestyle routines.

Our findings should be interpreted in the context of a number of study limitations. First, the TTO method is a difficult task that produces measurement error, logical inconsistencies and irrational responses, which is an obvious limitation in this study [43]. Other methods exist, such as standard gamble (which probably produces just as many errors) and discrete choice experiments. At present, decision makers seem to prefer TTO and therefore this method was employed in this study. A degree of uncertainty around the estimated utility values should be acknowledged. The 95% confidence intervals overlap across a number of health states, as a result of the study sample size and degree of variability in valuations given by participants. Second, although the vignettes were developed using patient, caregiver and clinician feedback, vignette descriptions may not fully convey the impact on HRQoL to members of the general public, who may find it difficult to imagine having a condition with the characteristics of HAE. Third, health state vignettes in TTO valuations are designed to depict a 'typical' experience for a patient or caregiver and represent a simplification of individuals' experiences. This is of particular relevance in the context of HAE, as it is known to be a very heterogeneous condition. The EuroQoL Group has developed online methods of data collection for valuation research with a fixed iteration procedure between states (as opposed to the ping-pong approach used here) [29]. The iteration procedure may well have contributed to spikes in the data distribution (at -1 , -0.5 , 0 , etc.) seen in some EQ-5D studies [44]. In the present study, the ping-pong approach was used to avoid these data issues, although it is possible that it produces its own framing effects. Finally, TTO valuations conducted via video calls have not been formally validated or compared against face-to-face TTO valuations, although a TTO published in 2020 suggests they yield similar results [45]. The online interviews in this study were designed to minimise differences in the online versus the standard face-to-face TTO interviewing procedures. The findings suggest good validity, as states were consistently ordered across the VAS and TTO exercises and were in line with the severity of attack locations as reported by patients and caregivers in the qualitative interviews.

5 Conclusions

The vignette methodology is increasingly being used to estimate utility weights for rare diseases, such as HAE, where observational research is challenging. Although we did not include details of attack frequency (which is a known contributor to disease burden [10, 16]) in the vignettes, we extend previous studies by examining attack locations and caregiver utility weights. A key aspect of HTAs is the societal perspective on disease states; by conducting TTO valuation interviews, we have shown that the general public have valued HAE patient and caregiver states as involving substantial decreases in QoL, consistent with the results of our qualitative interviews with people living with HAE and their caregivers. The results of this study provide estimated utility weights that could be used as a basis for future HTAs in the evolving HAE treatment landscape.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s41669-021-00302-6>.

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Declarations

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Conflict of interest Siu Hing Lo is an employee of Acaster Lloyd Consulting Ltd. Andrew Lloyd is an employee and shareholder of Acaster Lloyd Consulting Ltd. Acaster Lloyd Consulting Ltd were commissioned by BioCryst Pharmaceuticals, Inc., the study sponsor, to conduct the study. Shuayb Elkhalfifa has previously received consulting fees from BioCryst Pharmaceuticals, Inc. that were not related to this manuscript. Zlatko Sisic is an employee and shareholder of BioCryst Pharmaceuticals, Inc. Floortje E. van Nooten was an employee and shareholder of BioCryst Pharmaceuticals, Inc. during the conduct of this study.

Ethics approval This study was reviewed and approved by the WIRB (1 June 2020). The procedures used in this study adhere to the Declaration of Helsinki.

Consent Informed consent was collected prior to participation in this study (or verbal assent combined with parental assent for minors aged under 18 years).

Availability of data and material The datasets generated and analysed within this study are not publicly available due to restrictions imposed within the informed consent provided by participants.

Code availability Not applicable.

Author contributions Siu Hing Lo and Andrew Lloyd made substantial contributions to the conception and design of the study, and the acquisition, analysis and interpretation of data. Shuayb Elkhalfifa made

substantial contributions to the analysis and interpretation of data. Floortje van Nooten made substantial contributions to the conception and design of the study, and to the analysis and interpretation of data. Zlatko Sisic made substantial contributions to the interpretation of data. All authors drafted or revised the work critically, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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