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Estimating health state utilities for aromatic L-amino acid decarboxylase deficiency (AADCd) in the United States

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Abstract

Background AADCd is a rare neurometabolic disorder presenting in infancy. Children with AADCd have motor dysfunction and development delays that result in the need for lifelong care; quality of life is greatly impacted. Current characterizations of health-related quality of life and associated health state utilities (HSUs) may be underestimated in AADCd. Accurate characterization of AADCd burden is important when evaluating the benefits of treatment, especially the improvements observed with the recently approved disease-modifying therapy eladocagene exuparvovec. Time-trade-off (TTO) vignette methods may be used to elicit HSUs in AADCd for assessing the value of new treatments. This study aimed to first update previously published health state vignettes, then estimate AADCd HSUs in the United States (US).

Methods Existing vignettes for five AADCd health states were updated based on the review of published literature and clinician/caregiver input. Health states included: "bedridden/no motor function," "head control," "sitting unassisted," "standing with support," "walking with assistance." Online composite TTO interviews were conducted 1:1 with adults from the US general public. Participants ranked health states in order of preference using a visual analog scale, then were presented with health state vignettes to elicit utilities using TTO. Mean TTO scores were calculated for each health state, and regression models were used to estimate disutility associated with use of feeding tube.

Results Following revision of the vignettes, 120 participants completed the TTO task (mean age: 47 years; 50% female; 70% White); characteristics were not significantly different from US population norms in terms of age, sex, race or ethnicity. Six participants who appeared to misunderstand the exercise were excluded. Mean (SD) HSUs were: -0.258 (0.534) for bedridden state, -0.155 (0.569) for head control, 0.452 (0.523) for sitting unassisted, 0.775 (0.242) for standing with support, and 0.796 (0.235) for walking with assistance. The need for a feeding tube was associated with a disutility of 0.07.

Conclusions This study implemented TTO methods to estimate utilities for five health states which reflect the burden and impact of AADCd. The range in values from the most to least severe health state suggests that there is potential for effective treatments to substantially improve quality of life in these patients.

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Introduction

Aromatic L-amino acid decarboxylase deficiency (AADCd) is a neuromuscular disease caused by a mutation in the *dopa decarboxylase* gene [1]. Although prevalence estimates in the United States (US) are 1/42,000–1/90,000 [2–4], there have been less than 400 cases of AADCd reported in the litaerature globally to date, with global prevalence estimates ranging from 1/32,000–1/1,300,000 [5, 6]. Symptoms associated with AADCd usually present within the first few months of life and broadly include movement disorders, autonomic dysfunction, and behavioral problems. Muscle weakness and low muscle tone, impaired motor function, and gastrointestinal and energy-related symptoms are commonly experienced, and the majority of patients have feeding difficulties that could impair oral feeding such that patients require a feeding tube. Moreover, pain, impaired communication, and cognitive dysfunction are also common [7].

While symptom severity and caregiver-reported impacts are heterogeneous, affected children have significant impairments compared to those with normal development [7, 8]. These do not improve over time, resulting in severe developmental delays, failure to achieve developmental milestones and the need for life-long care. AADCd results in substantial burden for patients, their caregivers, and the healthcare system; a review of studies found that functional impairment and other clinical manifestations of AADCd greatly impact quality of life for both patients and caregivers and require significant healthcare resources to manage [9].

The gene therapy eladocagene exuparvovec is the first disease-modifying treatment approved in the European Union, the United Kingdom (UK), and Israel for the treatment of AADCd among patients 18 months of age and older with a severe phenotype [10, 11]. Treatment with eladocagene exuparvovec improves dopamine production and has been shown in trials to result in meaningful and sustained improvement in key motor and cognitive symptoms [12]. However, the demonstration of these benefits to health technology assessment (HTA) agencies requires their estimation on a larger scale via health economic modeling. It is therefore important to have an accurate assessment of disease-specific health-related quality-of-life (HRQoL), followed by the application of appropriate methods to derive estimates of health state utilities (HSUs).

There are multiple challenges in assessing HRQoL in AADCd and in subsequently estimating HSUs. Particularly in diseases that affect young children with severe consequences, it is not possible to directly ask patients to complete health surveys to evaluate their HRQoL. Given disease rarity, it is also not feasible to achieve the sample size necessary to sufficiently characterize HRQoL across all AADCd stages. Finally, the generic instruments typically used in economic evaluation may not fully capture the most salient disease-specific impacts on HRQoL [13]. In these instances, the National Institute for Health and Care Excellence (NICE) recommends alternative methods, including the use of vignettes to derive utility weights [14].

For AADCd, vignettes to describe HRQoL and the subsequent estimation of HSUs in the UK have been published [15, 16]. The vignettes, reported in Hanbury et al. (2021), describe the symptoms and burden of a typical patient with AADCd across five different health states. The health states are congruent with the economic evaluation model and the primary endpoints of the clinical trials and are based on the following motor milestones: 'bedridden/no motor function' (HS1), 'head control' (HS2), 'sitting unassisted' (HS3), 'standing with support' (HS4), and 'walking with assistance' (HS5) [15, 16]. The HSUs derived from this research range from 0.50 to 0.85 and are substantially higher than HSUs reported for other neuromuscular disorders where health states are also based on motor outcomes [16–18]. Indeed, a recent review by NICE suggested that the AADCd HSUs may lack face validity because they do not reflect the severity and true burden of disease [19].

There are limitations regarding the development of these vignettes and the subsequent derivation of HSUs that may have resulted in the underestimation of AADCd burden. The original vignettes describe the symptoms of AADCd, but not the wider quality-of-life impact [15]. Additionally, the vignette descriptions were presented from a parent/carer of a child with AADCd perspective, potentially impacting participants' responses in the valuation task [20, 21]. Regarding health utility estimation, an adaptation of a time trade-off (TTO) interview was employed as the valuation method, where participants were first asked to rate the vignettes and then state the years of life expectancy they would forego. Notably, this was obtained via a single question (rather than the standard iterative, face-to-face process), and is, therefore, a departure from best practices [22]. The TTO methods did not allow for the estimation of utilities below zero. Finally, the overall data quality of the study was potentially compromised; a high proportion of participants (~21%) produced illogical responses in the valuation tasks, suggesting a lack of understanding.

The present study was undertaken to review and update the pre-existing vignettes to address these limitations and subsequently reevaluate AADCd HSUs from the

perspective of the general US public. Objectives include: (1) Updating the vignettes by Hanbury et al. (2021), followed by a detailed review to determine the accuracy of the revised content via interviews with AADCd caregivers and clinical experts; and (2) Valuing the new vignettes by members of the US general public using a standard TTO valuation method.

Methods

Study design

The first phase of this cross-sectional study comprised reviewing and revising previously published health state vignettes describing symptoms associated with varying AADCd severity [15]. This process was undertaken via consultation with medical experts and published literature. Following this, new in-depth interviews with healthcare professionals (HCPs) and caregivers were conducted to review the revised vignette content to ensure accuracy and improve face and content validity. In the second phase, the final health state vignettes were presented to a sample of the US public for assessment using the TTO method. This study was reviewed and declared exempt by an Institutional Review Board (Western Institutional Review Board, WIRB, July 2023). All participants provided informed consent prior to the interviews. The study complied with the tenets of the Declaration of Helsinki.

Health state vignette review

The five previously developed health state vignettes [15] reflect key motor and developmental milestones in AADCd corresponding to the economic model structure developed to evaluate the cost-effectiveness of eladocagene exuparvovec (Table 1) [15]. The key symptoms or features of AADCd described in the vignettes include hypotonia, dystonia, motor impairment and oculogyric crises, functional impairment such as feeding and swallowing difficulties, mental impairment such as delayed cognitive development, irritability and sleeping difficulties as well as autonomic symptoms including abdominal problems and nasal congestion. The vignettes were refined to better describe the impact of AADCd on HRQoL in consultation with medical experts and based on published literature [23, 24]. As a result, four additional domains (daily activities, leisure activities, social interactions, and pain and discomfort) were added to the vignettes. Additionally, the framing of the health state valuation was changed from a parent/carer perspective to a child perspective (i.e., *Imagine a 10-year-old child in a particular health state*), based on current EuroQol Group recommendations [25]. Finally, as patients with full head control may still require a feeding tube, an additional health state was created to capture the disutility of the need for a feeding tube for the economic analysis (HS6: Full head control without feeding tube). This served as the base/reference health state for estimation of a disutility related to the need for a feeding tube.

Table 1 Health states based on economic model

Health state	Health state label	Definition based on motor functioning
1	Bedridden	No motor function
2	Full head control	Patient can sit supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 4 to 7 s.
3	Able to sit unassisted	Patient is required to sit without support and maintain balance while in sitting position for 30 to 59 s.
4	Standing with support	Patient is able to take 2 to 3 alternating steps, either in place or in forward motion, with support around the trunk.
5	Walking with assistance	Patient can walk at 4 to 7 feet with alternating steps, with minimal support.

Qualitative interviews with HCPs and caregivers

Five HCPs with experience managing patients with AADCd in the US, Canada, Italy, and Brazil were recruited for semi-structured 60-minute interviews via online video calls. The HCPs were asked to describe AADCd symptoms and functioning including prevalence, severity, frequency, variability, duration, and impacts and to review and provide feedback on the vignettes. Interviews were also conducted with four AADCd caregivers, who were recruited through a specialist recruitment agency and through a network of US based patient advocacy groups. Among other criteria, caregivers were eligible to take part if they were 18 years of age or above, cared for an individual with AADCd, and had sufficient English language proficiency to take part in the interview. Caregivers were asked to describe the day-to-day experiences of the child they cared for with AADCd, including their symptoms and overall impact of AADCd on the child's quality of life. They were also asked to review the accuracy of vignettes for the health states most relevant to their own experience. When there was a discrepancy between the perspectives of HCPs and caregivers, priority was given to incorporating the feedback from caregivers. All interviews were audio-recorded, transcribed verbatim, and de-identified for analysis.

Health state valuation

Members of the general public from the US were recruited through a specialist recruitment agency. Among other criteria, eligible participants were at least 18 years old and currently living in the US. Recruitment quotas were set to ensure that the sample was representative of the US population demographics based on age, sex, and ethnicity according to the most recent available census data [26].

The composite TTO method, a recognized interview technique for valuing health states, was used in the current study to generate utilities [27]. The composite TTO method integrates the traditional TTO approach for valuing health states considered better-than-dead (BTD) with a lead-time TTO technique for states perceived as worse-than-dead (WTD). This unified procedure enables the assessment of both BTD and WTD health states within a single framework [28]. A target sample size of 100 participants was considered appropriate based on similar studies [29]. The revised vignettes, presented in a random order, were sent to all participants. Interviews lasted approximately 60 min and were conducted via online video call.

During the TTO interviews, participants first ranked the vignettes on a visual analogue scale (VAS) from 0 to 100 (100 represents full health); participants also rated a vignette described as 'dead'. In the second part of the interview, participants were asked to imagine a 10-year-old child in the presented health states. For each, participants were asked to choose whether they preferred a child being in that health state for 10 years followed by being dead, or a child being in full health for (10–X) years. Time in full health was varied iteratively according to a standard TTO script until participants considered the choices to be the same (point of indifference). If participants preferred the state 'dead' instead of living 10 years in a particular health state, this meant they considered the health state as WTD. When this occurred, the lead-time TTO procedure was employed to elicit utilities for the WTD health states. This approach introduces a 'lead-time' in full health preceding both of the alternatives presented [30]. Participants were asked to compare between living (10–X) years in full health and then dying or living 10 years in full health, followed by 10 years in the valued health state and then dying [27, 28]. Depending on responses, X was again varied iteratively until the point of indifference.

Prior to the main valuation study in the US, three health states ('Bedridden', 'Able to sit unassisted' and 'Walking with assistance') were assessed in pilot TTO interviews with a convenience sample of six members of the general public from the UK. The purpose of the pilot was to ensure participants were able to complete the valuation task as well as to test how different framing of health state perspective would impact on the valuation results (i.e., asking participants to complete the valuation imagining a 10-year old child or themselves living in the health state). In the main valuation study, data from the first 20 (approximately) TTO interviews were evaluated to obtain preliminary insight on the utilities; no issues were identified.

Analysis

The VAS ratings for each vignette were rescaled so that the value for the 'Dead' state was fixed at zero and all other values varied between 100 and the worst health state such that:

$$V' = \left(\frac{V - V_{Dead}}{100 - V_{Dead}} \right) * 100$$

Where V' is the rescaled VAS value, V is the original VAS value and V_{Dead} is the value given to the 'Dead' state. Utility scores (h) from the the rescaled VAS and TTO tasks were calculated using the following formula:

$$h = {}^{(x-l)}\Big/_{t}$$

Where x is the amount of time in full health (Life A) at the point of indifference between Life A and Life B (health state being values), l represents the lead time when lead time TTO iteration is used (l= 0 if no lead time) and t is the amount of time spent in Life B (fixed at 10 years). The rescaled VAS and TTO utilities were summarized using descriptive statistics for each health state and by participant characteristics.

To estimate feeding tube disutility, a separate generalized estimating equation (GEE) model was estimated where the dependent variables were the TTO utilities and independent variables were "HS6: Head control + without feeding tube" (reference health state) and "HS2: Head control". This model generated the mean difference in utilities between H6 and H2 along with the 95% confidence interval (CI), representing the disutility associated with feeding tube use. Each GEE model was fitted with an exchangeable correlation structure, with an identity link between the dependent and independent variables; a normal distribution for error terms was assumed.

Descriptive statistics were used to summarize participants' socio-demographic characteristics. All analyses were conducted using R v 4.2.2.

Results

Health state vignettes review and revision

Four pediatric neurologists and a physical therapist were interviewed; all had experience with AADCd patients over a range of age and disease severity, including the 'Bedridden' (HS1) and 'Full head control' (HS2) states. Overall, HCPs confirmed the accuracy of the revised health state descriptions and highlighted a few items to improve the accuracy of the more severe health state descriptions. Specifically, HCPs noted that a gastric tube (vs. a naso-gastric tube) is used for feeding in the 'Bedridden' (HS1) and 'Full head control' (HS2) states. Refinements were also suggested regarding the oculogyric

crises description, including their characterization and frequency, the characterization of motor ability between the more and less severe health states, and descriptions regarding irritability/screaming.

Three of four caregivers interviewed were female (age range: 38–54 years). The children they cared for were 2–5 years old and were in the 'Stand with support' (HS4) or 'Walk with assistance' (HS5) states. One caregiver was able to share their experience moving from the 'Bedridden' (HS1) to 'Walking with assistance' (HS5) state following gene therapy treatment. Overall, caregivers confirmed the accuracy of the descriptions in the 'Stand with support' (HS4) or 'Walk with assistance' (HS5) states and provided some clarifying details. Like HCPs, caregivers suggested changes to the oculogyric crisis descriptions. Caregivers also suggested refinements regarding feeding/swallowing difficulties. Based on feedback from HCPs and caregivers, full head control is needed for oral feeding, although some children will still require a feeding tube to maintain adequate nutrition. In that regard, valuing the feeding tube in relation to HS2 ('Full head control') has face validity. No further changes were made to HS6 ('Full head control without feeding tube').

As caregiver feedback was prioritized, it was incorporated over that provided by the HCPs when any differences were present. Across all health states, HCPs commented that descriptions around pain and discomfort were overstated in the vignettes, while caregivers felt that pain and discomfort were very much part of the children's experience. Therefore, descriptions of pain and discomfort were included in the final vignettes, which are presented in Supplementary Table 1. A summary of initial changes made to the original vignettes is provided in Supplementary Table 2; changes made based on HCP and caregiver interviews are summarized in Supplementary Table 3.

Health state valuation and estimation of utilities

One hundred twenty partipants took part in the TTO interviews. The mean age was 47 years, the majority were White (70%), employed full-time (51%) and had college or university qualifications (82%); 37.5% were either a parent, caregiver, or legal guardian of a child < 18 years (Table 2). The study sample was not significantly different from the US population norms in terms of age, sex, race, or ethnicity (Table 2) [31]. The final analysis included data from 114 of 120 participants; six participants did not appear to understand the TTO tasks and their responses were excluded. Specifically, they rated the worst health state ('Bedridden'; HS1) as better than or equal to the best health state ('Walking with assistance'; HS5), and/or rated the best health state as equal to or worse than dead.

Overall, the TTO utilities were aligned with the VAS health state rankings; participants preferred health states

Table 2 Sample characteristics from valuation interviews

Characteristic	*N* = 120	US population
Age		
Mean (SD)	47.0 (15.9)	47.8 (18.5)[a]
Range	21.0, 78.0	18.0, 100.0[a]
Prefer not to answer	1	
Sex		
Female	60 (50.0%)	50.4%[b]
Race		
White	84 (70.0%)	75.5%[b]
Black or African American	15 (12.5%)	13.6%[b]
Asian or Asian American	7 (5.8%)	6.3%[b]
Mixed Race	7 (5.8%)	3%[b]
Native American and Alaska Native	1 (0.8%)	1.3% [b]
Native Hawaiians and Other Pacific Islander	0 (0%)	0.3% [b]
Other, please specify	6.0 (5.0%)	
Ethnicity		
Hispanic or Latino	24 (20.0%)	19.1% [b]
Not Hispanic or Latino	96 (80.0%)	
Employment status		
Employed or self-employed, full-time	57 (47.5%)	60.0%[c]
Employed or self-employed, part-time	23 (19.2%)	
Homemaker or full-time carer	11 (9.2%)	
Long-term sick leave	1 (0.8%)	
Other (please specify)	5 (4.2%)	
Retired	15 (12.5%)	
Student	4 (3.3%)	
Unemployed or seeking work	4 (3.3%)	
Education level		
No formal qualifications	0 (0%)	10.9[d]
High school qualification	14 (11.7%)	30.1%[d]
Vocational qualification or other trade certificate	5 (4.2%)	
College or university qualifications	98 (81.7%)	59.1%[d]
Other (please specify)	3 (2.5%)	
Parent, caregiver, or legal guardian of a child aged under 18 years		
No	74 (61.7%)	
Yes	45 (37.5%)	
Prefer not to answer	1 (0.8%)	
Presence of long-term condition		
No	55 (45.8%)	
Yes	65 (54.2%)	
Been a carer for a close friend or relative with a long-term illness or condition	69 (57.5%)	
Carer for:		
Your partner	12 (10.0%)	
Your child	11 (9.2%)	
Your parent or sibling	44 (36.7%)	
Other	7 (5.8%)	
EQ-5D		
Mean (SD)	0.809 (0.199)	0.867[e]
Range	0.036, 1.000	

Table 2 (continued)

Characteristic	*N* = 120	US population
95% CI	0.762, 0.857	
Unknown	1	

[a]Calculations based on 2020 data from United States Census Bureau. For calculation purposes, ages 100 + were assumed as 100. (https://www2.census.gov/programs-surveys/popest/tables/2020-2023/national/asrh/nc-est2023-agesex.xlsx) [31]

[b]Figures based on 2020 data from United States Census Bureau https://www.census.gov/ [31]

[c]Figures based on 2022 data of persons 16 years of age and over from U.S. Bureau of Labor Statistics (https://www.bls.gov/cps/aa2022/cpsaat01.htm) [38]

[d]Figures based on 2023 data of population 25 years and older from United States Census Bureau (https://data.census.gov/table/ACSST1Y2023.S1501?q=S1501&g=010XX00US$0400000) [31]

[e]Based on US population norms in A. Szende et al. (eds.), Self-Reported Population Health: An International Perspective based on EQ-5D, 2014 (https://www.ncbi.nlm.nih.gov/books/NBK500364/pdf/Bookshelf_NBK500364.pdf) [39]

Abbreviations: CI, confidence interval; SD, standard deviation; US, United States

with less severe symptoms and better motor ability. Mean TTO utilities ranged between −0.258 and 0.796 (Fig. 1). There was larger variability in the TTO utilities for the more severe health states ('Bedridden', 'Full head control' and 'Able to sit unassisted'; HS1-3) compared to the less severe health states. On average, 'Bedridden' (HS1) and 'Full head control' (HS2) were valued as worse than dead (Table 3). Participants did not significantly differentiate between these two health states, and there was no statistically significant difference in the associated TTO utilities (Table 4). The estimated feeding tube disutility was −0.073 (standard error 0.076) and not significantly different from the reference health state (HS6: 'Full head control without feeding tube'; Table 5).

In analyses of the effect of participants' characteristics on the TTO valuations of the health states, male participants rated the health states differently compared to female participants, all else being constant (Table 6). Of note, male participants assigned a higher utility for the most severe health state ('Bedridden' state) compared to female participants. However, in the less severe health states such as the 'Able to sit unassisted', 'Standing with support' and 'Walking with assistance' state, male participants had lower utilities compared to female participants. No other participants' characteristics influenced the health state valuations.

Discussion

This study first sought to update previously published health state vignettes describing the symptoms and impact of AADCd on HRQoL based on expert HCP and caregiver feedback. Updates ensured that these vignettes robustly and accurately describe the experience of a child living with AADCd with varying motor abilities. The second part of the study comprised TTO interviews to elicit utilities for these health states from the perspective of a US general population. While both VAS and TTO utilities were estimated in this study, TTO utilities

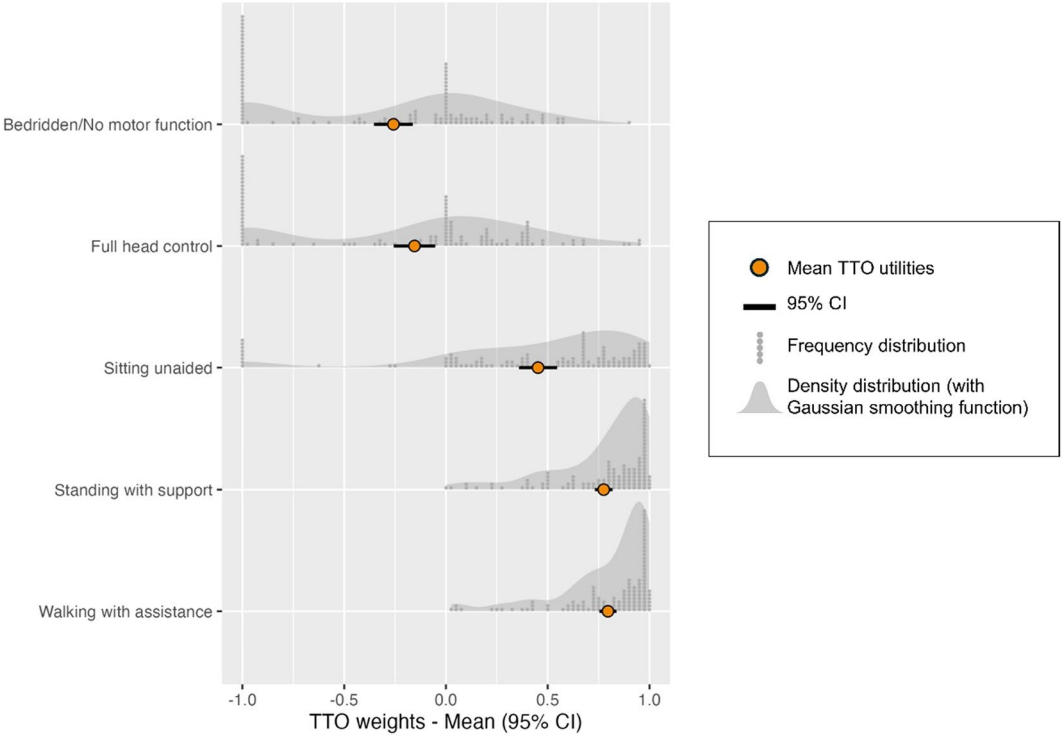

Fig. 1 Mean (95% CI) TTO utilities (*N* = 114) with frequency and density distribution. Abbreviations: CI, confidence interval; TTO, time trade-off

Table 3 VAS and TTO utilities for health state vignettes

Health states		VAS ($N=113$[a, b])	TTO ($N=114$[a])
HS1: Bedridden	**Mean (SD)**	**7.38 (13.1)**	**-0.258 (0.534)**
	95% CI	4.97, 9.79	-0.356, -0.160
HS2: Full head control	**Mean (SD)**	**11.5 (14.3)**	**-0.155 (0.569)**
	95% CI	8.91, 14.2	-0.259, -0.050
HS3: Able to sit unassisted	**Mean (SD)**	**28.0 (18.2)**	**0.452 (0.523)**
	95% CI	24.7, 31.4	0.356, 0.548
HS4: Standing with support	**Mean (SD)**	**40.7 (17.2)**	**0.775 (0.242)**
	95% CI	37.0, 43.3	0.731, 0.819
HS5: Walking with assistance	**Mean (SD)**	**48.1 (18.2)**	**0.796 (0.235)**
	95% CI	44.7, 51.5	0.753, 0.839
HS6: Full head control + without feeding tube	**Mean (SD)**	**11.7 (14.1)**	**-0.081 (0.578)**
	95% CI	9.12, 14.3	-0.187, 0.025

[a]Six participants were excluded as did not understand task

[b]Data from one participant was excluded as they rated dead as 100 on the VAS

Abbreviations: CI, confidence interval; HS, health state; SD, standard deviation; TTO, time trade-off; VAS, visual analog scale

Table 4 TTO utility difference between health states for $N=114$

TTO Utility Difference		*P*-value[a]
HS1-HS2		0.158
Mean (SD)	-0.104 (0.460)	
95% CI	-0.188, -0.019	
HS1-HS3		< 0.001
Mean (SD)	-0.711 (0.589)	
95% CI	-0.819, -0.602	
HS1-HS4		< 0.001
Mean (SD)	-1.033 (0.575)	
95% CI	-1.139, -0.928	
HS1-HS5		< 0.001
Mean (SD)	-1.054 (0.554)	
95% CI	-1.156, -0.952	
HS2-HS3		< 0.001
Mean (SD)	-0.607 (0.587)	
95% CI	-0.715, -0.499	
HS2-HS4		< 0.001
Mean (SD)	-0.930 (0.622)	
95% CI	-1.044, -0.815	
HS2-HS5		< 0.001
Mean (SD)	-0.950 (0.578)	
95% CI	-1.057, -0.844	
HS3-HS4		< 0.001
Mean (SD)	-0.323 (0.514)	
95% CI	-0.417, -0.228	
HS3-HS5		< 0.001
Mean (SD)	-0.343 (0.492)	
95% CI	-0.434, -0.253	
HS4-HS5		0.511
Mean (SD)	-0.021 (0.247)	
95% CI	-0.066, 0.024	

[a]Welch Two Sample t-test

Note: A larger utility difference indicates a larger difference in HRQoL between two health states

Abbreviations: CI, confidence interval; HRQoL, health-related quality of life; HS, health state; SD, standard deviation; TTO, time trade-off

were considered the primary focus. The TTO approach generates utility weights that could be used in economic analyses to measure and compare health gains using different therapies [32]. The VAS task was implemented to introduce and familiarize respondents to the vignettes and health state preferences, after which the health states were valued by the TTO [33].

Utilities elicited here were lower for the more severe health states when compared to a previous study in the UK by Smith et al. [16] However, in that study, the TTO elicitation procedure did not allow health states to be rated as WTD. In the present study, the use of lead-time TTO allowed the utilities of health states considered WTD to span between − 1 and 0. This valuation method is consistent with the valuation work for EQ-5D and better reflects the clinical disease presentation and burden.

The clinical manifestation of AADCd shares some commonalities with other rare genetic neuromuscular diseases with severely impacted motor ability and function, including metachromatic leukodystrophy (MLD) [34]. Findings from this study were consistent with previous studies estimating MLD-associated HRQoL; utilities derived from a TTO study among members of the UK general public ranged from − 0.47 for the most severe health state associated with 'loss of any locomotion as well as any head and trunk control' to 0.71 for the 'Walking without support' health state [35]. These scores are similar to the present study in terms of their range and the extent to which they extend below 0, supporting the face validity of the current findings. While AADCd and MLD share certain features, they are distinct conditions and care should therefore be taken when comparing the associated HSUs.

The health state vignettes were designed to describe the health state of a child; per EuroQol group recommendations, participants were asked to imagine a 10-year-old child in the relevant states in their responses [25]. However, there is no consensus on how best to contextualize health states in children and a number of issues have previously been identified with this approach. These incude significant heterogeneity in how participants envisioned a 10year-old; they may imagine an individual known or unknown to them, as their own child or themselves as a child. Each perspective may therefore introduce framing or other sources of bias [36]. In a study exploring how the assumption of different perspectives impact participants' valuation of health states in a TTO task, participants' views were found to be heterogenous [21]. Some participants were less willing to trade life years for children than for themselves/adults while others indicated that they

Table 5 Feeding tube TTO disutility estimates from the GEE model in relation to HS6

	TTO	
Health state	**Estimate (SE)**	**95% CI**
Intercept (HS6)	-0.081 (0.054)	-0.187, 0.024
Need for feeding tube	**-0.073 (0.076)**	**-0.222, 0.075**

Abbreviations: CI, confidence interval; GEE, generalized estimating equation; HS, health state; SE, standard error; TTO, time trade-off

Note: Health state 6 = Full head control without feeding tube

Table 6 Effect of sociodemographic characteristics on TTO utilities for the health states (*N* = 114)

	TTO			
Health state	**Estimate**	**SE**	**95% CI LL**	**95% CI UL**
Intercept (HS1)	-0.321**	0.118	-0.356	-0.161
HS2	0.150	0.173	-0.039	0.246
HS3	0.892***	0.146	0.574	0.847
HS4	1.166***	0.129	0.926	1.140
HS5	1.190***	0.130	0.947	1.161
Male	0.262**	0.096	-0.356	-0.161
HS2*Male	-0.120	0.146	0.947	1.161
HS3*Male	-0.400**	0.139	-0.356	-0.161
HS4*Male	-0.277**	0.106	-0.039	0.246
HS5*Male	-0.273*	0.108	0.574	0.847
Age 45 above	-0.164	0.100	-0.039	0.246
HS2*Age 45 above	0.0748	0.150	0.926	1.140
HS3*Age 45 above	-0.032	0.138	0.947	1.161
HS4*Age 45 above	0.109	0.110	-0.356	-0.161
HS5*Age 45 above	0.093	0.110	-0.039	0.246
Parent	-0.087	0.105	0.574	0.847
HS2*Parent	0.024	0.156	0.574	0.847
HS3* Parent	0.153	0.140	0.926	1.140
HS4* Parent	0.019	0.117	0.947	1.161
HS5* Parent	0.0280	0.115	-0.356	-0.161
Carer	0.087	0.097	0.926	1.140
HS2*Carer	-0.060	0.145	-0.039	0.246
HS3*Carer	-0.027	0.138	0.574	0.847
HS4*Carer	-0.101	0.108	0.926	1.140
HS5*Carer	-0.100	0.107	0.947	1.161

Abbreviations: CI, confidence interval; HS, health state; LL, lower limit; SE, standard error; TTO, time trade-off; UL, upper limit

Note: A generalized estimating equation (GEE) regression model was estimated to include additional covariates such as age, sex, parental status and carer experience as independent variables to explore whether any of the participants' characteristics had an influence on the health state utilities. These estimates are interpreted relative to the reference group. For sex, the reference group is females; for age, the reference is age 45 years and below; for parental status, the reference is non-parent; and for carer experience, the reference is non-carer

***p-value < 0.001; **p-value < 0.01; *p-value < 0.05

were more prepared to do so if the health state was perceived as severe enough that the child was "suffering".

In terms of other limitations, the vignettes cannot capture the variability between individuals within a particular health state. While the vignette aims to be as comprehensive as possible, lengthy descriptions may make it challenging for participants to consider all aspects of the vignette. Finally, previous research indicates that factors such as being a parent/caregiver may influence number of life-years traded [37]. Pilot testing was conducted to ensure that the perspective employed was the most appropriate and found that the average HSUs were consistent between the two different framings (child vs. adult) despite the aforementioned challenges.

Conclusions

The results of this study demonstrate the importance of robust development of health state vignettes, including the value of obtaining HCP and caregiver feedback to describe the impact of the condition on HRQoL. The study also highlights the importance of using the standard TTO method to elicit utilities that capture the range in burden associated with a disease, especially for diseases with very severe health and quality of life impacts, such as AADCd. As such, the HSUs generated here reflect an accurate representation of the burden and impact of AADCd on HRQoL and can be used in economic evaluations of new treatments in AADCd. The range in values from the most to least severe health state illustrates the devastation of the disease at its most severe, as well as the significant impact on quality of life when a health state is improved, suggestive of the potential for effective treatments to substantially improve HRQoL in these patients.

Abbreviations

AADCd	Aromatic L-amino acid decarboxylase deficiency
CI	Confidence interval
GEE	Generalized estimating equations
HCP	Healthcare professionals
HRQoL	Health-related Quality of Life
HS1	Health state 1 - Bedridden
HS2	Health state 2 - Full head control
HS3	Health state 3 - Able to sit unassisted
HS4	Health state 4 - Standing with support
HS5	Health state 5 - Walking with assistance
HS6	Health state 6 - Full head control + without feeding tube
HSU	Health state utility
HTA	Health technology assessment
MLD	Metachromatic leukodystrophy
NICE	National Institute for Health and Care Excellence
SD	Standard deviation
TTO	Time-trade-off
US	United States
VAS	Visual analogue scale
WIRB	Western Institutional Review Board

Supplementary Information

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Supplementary Material 1

Author contributions

All authors contributed to the study conception and design. Data analysis was performed by GNC and KF. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets produced during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was reviewed and declared exempt by an Institutional Review Board (Western Institutional Review Board, WIRB, July 2023). All participants provided informed consent prior to the interviews. The study complied with the tenets of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
RZ, PC and IT are employees of PTC Therapeutics, Inc. KF, GNC and AL are employees of Acaster Lloyd Consulting Ltd which was contracted by PTC Therapeutics for the conduct of this study. BM received consulting fees from PTC Therapeutics, Inc.

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