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ORIGINAL RESEARCH ARTICLE

A Model-Based Economic Evaluation of Hypothetical Treatments for Amyotrophic Lateral Sclerosis in the UK: Implications for Pricing of New and Emerging Health Technologies

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a devastating disease which leads to loss of muscle function and paralysis. Historically, clinical drug development has been unsuccessful, but promising disease-modifying therapies (DMTs) may be on the horizon.

Objectives The aims of this study were to estimate survival, quality-adjusted life-years (QALYs) and costs under current care, and to explore the conditions under which new therapies might be considered cost effective.

Methods We developed a health economic model to evaluate the cost effectiveness of future ALS treatments from a UK National Health Service and Personal Social Services perspective over a lifetime horizon using data from the ALS-CarE study. Costs were valued at 2021/22 prices. Two hypothetical interventions were evaluated: a DMT which delays progression and mortality, and a symptomatic therapy which improves utility only. Sensitivity analysis was conducted to identify key drivers of cost effectiveness.

Results Starting from King's stage 2, patients receiving current care accrue an estimated 2.27 life-years, 0.75 QALYs and lifetime costs of £68,047. Assuming a 50% reduction in progression rates and a UK-converted estimate of the price of edaravone, the incremental cost-effectiveness ratio for a new DMT versus current care is likely to exceed £735,000 per QALY gained. Symptomatic therapies may be more likely to achieve acceptable levels of cost effectiveness.

Conclusions Regardless of efficacy, DMTs may struggle to demonstrate cost effectiveness, even at a low price. The cost effectiveness of DMTs is likely to be strongly influenced by drug price, the magnitude and durability of relative treatment effects, treatment starting/stopping rules and any additional utility benefits over current care.

1 Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disease of the nervous system, characterised by a progressive loss of muscle function, paralysis and death [1]. ALS is one of the most devastating diseases in neurology and accounts for around 11,000 deaths in Europe each year [2]. The incidence rate of ALS in Europe is estimated at 2.6 per 100,000 individuals, with a peak age of onset between 50 and 70 years [3]. Life expectancy is short and over 70% of patients with ALS die within 3 years of their first symptom [3]. The clinical management of progressive neurodegenerative disease is provided in a multidisciplinary setting with early access to symptomatic care. There is compelling evidence that patient-oriented care pathways that are responsive to the complex physical, communication, cognitive and psychosocial needs of ALS patients and their carers improves both quality of life and survival [4, 5].

Pharmacological treatments for ALS include disease-modifying therapies (DMTs) and symptomatic treatments. Currently, only one DMT—riluzole—has been recommended for the treatment of ALS in Europe. Riluzole was first approved in the United States (US) and Europe in the 1990s, after clinical trials demonstrated that this treatment

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Key Points for Decision Makers

Historically, clinical drug development in amyotrophic lateral sclerosis (ALS) has been largely unsuccessful. As such, there are few recent economic evaluations of treatments for ALS.

Our analysis draws together population-based real-world data which is used to generate estimates of health outcomes and costs for patients living with ALS.

Our analysis suggests that the cost effectiveness of disease-modifying therapies for ALS is likely to be strongly influenced by the price of the technology, the magnitude and durability of relative treatment effects, when treatment is started and stopped and any additional potential gains in health-related quality of life over and above current care.

produces modest improvements in disease progression and survival [6, 7]. Despite substantial efforts to develop more effective treatments, in the 20 years following the approval of this medicine, the majority of human clinical trials of potential treatments for ALS have failed to demonstrate significant efficacy [8]. Newer DMTs, including edaravone and tofersen (BIIB067), have indicated potential benefits for some people with ALS [9, 10]. Both of these products have been granted marketing authorisations for treating ALS in the US, but as yet, neither product holds a full license for use in Europe. The recent phase III ADORE trial of an investigational formulation of oral edaravone (ClinicalTrials.gov identifier: NCT05178810) did not meet key primary or secondary endpoints. The manufacturer of the proprietary formulations of edaravone (Radicava IV® and Radicava ORS®) subsequently stated that ADORE did not evaluate the approved formulation of oral edaravone and that the findings of this trial do not affect the commercial availability of Radicava ORS in the US [11].

The limited success of drug development in ALS means that there have been few recent comparative economic analyses of treatments for ALS, as well as limited research reporting on the expected lifetime outcomes and health care costs for contemporary cohorts of patients living with ALS. A 2017 review of published economic studies in motor neurone disease (MND) by Moore et al. [12] found that amongst the 13 identified economic evaluations, most were evaluations of riluzole and only two economic evaluations of ALS therapies had been published since 2010. The review also highlighted that most existing economic analyses of ALS therapies were subject to problems relating to lack of data, uncertainty around the disease course and the use of inappropriate economic modelling frameworks. More recent research has focussed on developing methodological standards for the economic evaluation of ALS therapies [13].

Considerable research efforts have also been made to address issues relating to lack of data. Population-based ALS registers capture all incident cases in Ireland, the Netherlands, the UK, Italy, Sweden and Germany. These datasets contain detailed clinical, epidemiologic and survival data. The ALS-CarE research programme—a cross-national Joint Programme in Neurodegeneration Disease (JPND)-funded project—was initiated in 2014 [14]. This programme utilised data from European ALS registers and national ALS services to generate a patient-oriented care pathway for European ALS patients that is sensitive to phenotype, cognitive status, rate of progression and long-term prognosis. The data collected in ALS-CarE include a wealth of information on outcomes and costs of people with ALS over the course of their disease.

The aims of this paper are twofold. First, we aimed to develop a baseline model to generate up-to-date estimates of expected survival, quality-adjusted life-years (QALYs) gained and disease management costs in ALS from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) in England, informed by data from ALS-CarE [15]. Second, we aimed to extend this analysis into a comparative health economic model that can evaluate the cost effectiveness of new and emerging treatments for ALS, including DMTs and symptomatic interventions.

2 Methods

2.1 The ALS-CarE Study

The overall objective of the ALS-CarE programme was to design, estimate the costs, and measure the benefits of a multifaceted care programme that can be standardised across Europe, and adapted for use in other neurodegenerative conditions. Participants were recruited through the clinical principal investigators at five participating national specialist ALS sites in the UK, Ireland, Italy, Germany, and the Netherlands. Investigators verified patient eligibility and obtained written informed consent. Inclusion criteria required patients to have possible, probable, laboratory supported probable or definite ALS, according to the El Escorial criteria, and provision of written informed consent. Patients were approached regardless of cognitive status, unless impaired to the extent that they could not complete an informed consent

process. The aim was to consecutively recruit up to one hundred patients at each of the participating sites, with longitudinal follow-up for 24 months. The sample size was based on numbers of incident and prevalent cases attending each clinic per year.

The ALS-CarE project spanned clinical, epidemiological and health services research. Contacts with the health system and all health-related expenses were collected to determine the clinical pathway of ALS patients. The study population included two cohorts of consecutively enrolled patients: (a) newly diagnosed patients enrolled at the time of diagnosis and (b) a cross-sectional patient cohort enrolled at different stages of the disease. The type and frequency of clinical visits and evaluations were performed as per routine clinical practice. Data collection within ALS-CarE took place during 2016–2018 and included clinical assessments and disease progression metrics, including staging information based on the King's and Milan-Torino (MiToS) staging systems and the ALS Functional Rating Scale Revised (ALSFRS-R), which were recorded each time a patient attended an ALS or MND centre associated with the expert neurologists at each study site. Data on socioeconomic status and resource use were collected at up to five in-home interviews with patients or their caregivers at 4- to 6-month intervals over the course of the study. Qualitative and survey analyses of data collected from patients and caregivers in ALS-CarE have been published elsewhere [16–18].

2.2 Health Economic Model Scope

We developed a cohort-level state transition model to estimate the expected survival, QALYs, costs and cost effectiveness associated with future treatments for ALS. Economic model development was approached in two phases: (1) the development of a baseline model to estimate expected health outcomes and costs of current care (including riluzole) for people with ALS, based on the ALS-CarE dataset [15], and (2) adaptation of the baseline model to evaluate the cost effectiveness of hypothetical future treatments for ALS. The economic model estimates health outcomes and costs of competing health care interventions for ALS from the perspective of the NHS and PSS in England over a 37-year time horizon (up to a maximum patient age of 100 years). The base case model considers only health impacts on people with ALS; effects on caregivers were considered in sensitivity analyses. Health outcomes and costs were discounted at a rate of 3.5% per annum [19]. Costs were valued at 2021/22 prices in GBP Sterling (£). The analysis was informed by a health economics analysis plan which evolved over the course of the study (see Appendix in the electronic supplementary material [ESM]).

2.3 Health Economic Model Structure

The economic model structure and its accompanying assumptions were informed by systematic reviews of ALS models (Moore et al. [12] and our own systematic review), other more recent ALS models [13, 20, 21] and clinical input from the ALS-CarE study investigators. The model structure was based on King's staging classification (Fig. 1). Whilst ALS-CarE also collected data on MiToS stage, King's classification was preferred because more data were available throughout the disease course and this staging system has been used in other recent models of ALS therapies [13, 20, 21]. The King's staging classification includes five overall stages which describe the number of clinical regions involved (Stages 1–3) and the onset of significant nutritional or respiratory failure (Stages 4a and 4b, respectively), ultimately leading to death (Stage 5) [22]. The model assumes that the disease course of ALS is exclusively progressive; regression to improved health states is not permitted. This assumption is consistent with other recent ALS models [13, 20, 21]. Disease progression and mortality are modelled using monthly cycles. The model uses longitudinal data on stage and mortality from patients in ALS-CarE [15] to estimate rates of disease progression and death under current care. Each alive health state was assigned a level of health-related quality of life (HRQoL) and a monthly management cost, which were also estimated using data from ALS-CarE [15]. As the patient's disease progresses, they transition through the King's stages, accumulate QALYs and accrue disease management costs.

The baseline model employs the following structural assumptions:

- Based on clinical advice, all patients enter the model in King's stage 2. This assumption was made because ALS-CarE adopted a cross-sectional design, whereas the economic analyses focus on the earliest point at which ALS patients might receive treatment, whereby greater absolute health gains may be realised. Alternative assumptions regarding initial disease stage are explored in sensitivity analyses.
- King's stages 4a and 4b were combined into a single health state. This reflects how staging data were recorded in the ALS-CarE dataset.
- Mortality risks, HRQoL and disease management costs are dependent on King's stage. This is consistent with previous models of ALS therapies [13, 20, 21].
- During each model cycle, patients can transition from any alive health state to any other health state further along in the sequence. Patients cannot regress to an improved health state (e.g., a patient with King's stage 3 at time t_0 cannot revert to King's stage 2 at time t_0+t_n). This assumption was based on input from the ALS-CarE

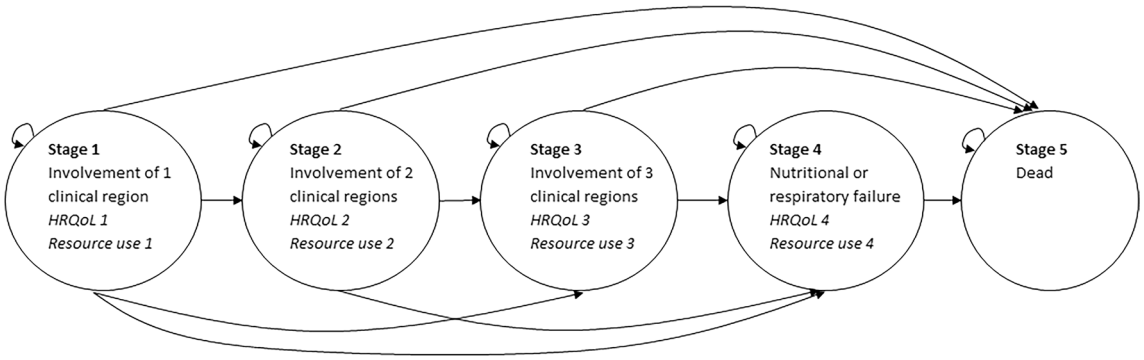

Fig. 1 Model structure based on King's staging classification. *HRQoL* health-related quality of life

investigators and is consistent with other ALS models [13, 20, 21].

- Except for age-specific mortality risks, progression rates are constant over time. This assumption is consistent with other ALS models [13, 20, 21].

The relative effects of health care interventions for ALS are modelled through two potential mechanisms: (1) by slowing the rate of disease progression and mortality relative to current care, and (2) through the inclusion of beneficial HRQoL effects in each King's stage over and above the equivalent utility values for patients receiving current care. These treatment effects and costs may be applied indefinitely or for a finite number of model cycles, either in some or all of the model health states.

2.4 Evidence Used to Inform the Baseline Model Parameters Under Current Care

The baseline model includes four groups of parameters: (1) patient characteristics; (2) transition probabilities; (3) health state utility values and (4) resource costs (Table 1). Most of these parameters were informed by ALS-CarE [15], except for unit costs which were taken from external sources. The ALS-CarE datasets for stage, mortality, patient EuroQol 5-Dimensions 5-Level (EQ-5D-5L) responses and resource use were combined and linked for each study site (Ireland, Sheffield [UK], Germany, the Netherlands, Milan [Italy] and Turin [Italy]) across up to five timepoints.

Within ALS-CarE [15], the date of the patient/caregiver interviews which collected data on EQ-5D-5L and resource use did not always coincide with the date of the patient's clinical staging assessments. Within our analysis, the EQ-5D-5L and resource use analyses were restricted to only include records for which a clinical stage value could be attributed. This was defined as any EQ-5D-5L or resource use assessment undertaken within 2 months of a clinical staging assessment. This 2-month threshold was selected to maximise the amount of usable data whilst also ensuring that utility and cost estimates reasonably reflect each specific stage. This interval is generally consistent with UK and European clinical practice, whereby patients are typically seen every 2–3 months.

2.4.1 Patient Characteristics

Patient age and sex were estimated from ALS-CarE [15], based on the patient's first clinical visit in the study. Mean age was 63 years and 39% of the population was female (ESM, Table S1). These parameters are used in the baseline model to determine patient age at model entry and to inform all-cause mortality risks.

2.4.2 Transition Probabilities for King's Stage Progression and Death Under Current Care

We fitted a continuous-time homogenous multistate model to a combined ALS-CarE dataset including clinical stage and death; this is an extension of competing risks analysis which also captures transitions to intermediate health states [23]. Patients in ALS-CarE who had a clinical stage value without a contemporaneous stage date, or vice versa, were excluded. Patients with only a single staging record were also excluded, as multiple records are required to provide information on transition rates between King's stages. The final dataset included 707 usable records across 204 patients. The multistate model was fitted to the processed ALS-CarE dataset using the *msm* package in R [24]. The *pmatrix* function was used to generate monthly probabilities of transitioning between the stage-specific health states. The goodness-of-fit of the multistate model was examined using the *prevalence* function and a Pearson's Chi-square test. Uncertainty around predicted progression and mortality rates was handled by bootstrapping the transition intensities

Table 1 Model parameters

Parameter	Value	Distribution	Source
Patient characteristics			ALS-CarE [15]
Starting age	63.36 y	Fixed	
Proportion female	38.69%	Fixed	
Transition probability, point estimate (95% CI bootstrapped)[a]			ALS-CarE [15]
Stage 1 to Stage 1	0.873 (0.814–0.921)		
Stage 1 to Stage 2	0.111 (0.046–0.166)		
Stage 1 to Stage 3	0.010 (0.002–0.047)		
Stage 1 to Stage 4	0.005 (0.001–0.030)		
Stage 1 to Stage 5	0.001 (0.001–0.003)		
Stage 2 to Stage 2	0.904 (0.878–0.931)		
Stage 2 to Stage 3	0.056 (0.031–0.083)		
Stage 2 to Stage 4	0.028 (0.006–0.049)		
Stage 2 to Stage 5	0.012 (0.002–0.027)		
Stage 3 to Stage 3	0.917 (0.893–0.938)		
Stage 3 to Stage 4	0.056 (0.034–0.082)		
Stage 3 to Stage 5	0.027 (0.011–0.043)		
Stage 4 to Stage 4	0.929 (0.916–0.941)		
Stage 4 to Stage 5	0.071 (0.059–0.084)		
Baseline utility, mean (SE)			ALS-CarE [15]
Stage 1	0.60 (0.03)	Beta	
Stage 2	0.47 (0.03)	Beta	
Stage 3	0.38 (0.04)	Beta	
Stage 4	0.19 (0.03)	Beta	
Treatment effect, mean (SE)			
RRR for DMT	0.50 (0.05[b])	Normal	Assumption
Utility gain for symptomatic therapy	0.10 (0.01[b])	Normal	Assumption
Cost			
Medical cost[c]			ALS-CarE [15]
Stage 1	£1046.95 per month	Gamma[d]	
Stage 2	£1868.07 per month	Gamma[d]	
Stage 3	£1685.53 per month	Gamma[d]	
Stage 4	£3374.47 per month	Gamma[d]	
End of life care	One-off £8705.50	Fixed	
New treatment cost			
Hypothetical DMT	£9500 per month	Fixed	Assumption
Hypothetical symptomatic therapy	One-off £10,000	Fixed	Assumption

CI confidence interval, *DMT* disease modifying therapy, *RRR* relative risk reduction, *SE* standard error

[a]Bootstrapped estimates used for probabilistic model

[b]SE assumed to be 10% of mean value

[c]Aggregated costs, calculated from usage of resources and unit costs. Details shown in ESM, Table S3

[d]Assuming gamma distributions for resource use. Unit costs were fixed when calculating aggregated costs

using the *boot.msm* function across 5000 iterations. The economic model includes a structural constraint which ensures that the monthly risk of death in ALS patients is at least as high as the all-cause death risk in the UK general population, based on UK life tables [25]. The estimated monthly transition probabilities from the multistate model, together with bootstrapped 95% confidence intervals (CIs), are shown in Table 1. The model trace suggests a rapid progression through the health states (ESM, Fig. S1). The prevalence plots and Chi-square test indicate that the multistate model provides a generally good fit to the data (ESM, Fig. S2).

2.4.3 Health-Related Quality of Life by King's Stage Under Current Care

In ALS-CarE [15], patient HRQoL was measured using the EQ-5D-5L questionnaire. In line with current recommendations from the National Institute for Health and Care Excellence (NICE), the EQ-5D-5L data were mapped to the 3-level version [19, 26]. Records were only included if the patient had both a complete EQ-5D response and a date of assessment, and the patient also had a King's staging value within 2 months of their EQ-5D-5L assessment (either before or after). The final dataset comprised 415 records of mapped EQ-5D-3L and linked clinical stage from 204 patients. Mean utility values by King's stage are summarised in Table 1. The data indicate that EQ-5D-3L declines with advancing disease stage (from mean utility values of 0.60 for King's stage 1 to 0.19 for King's stage 4). We also fitted a mixed-effect linear regression model to the mapped EQ-5D-3L data to better account for multiple observations from the same patients; this model was fitted using the *lme4* package in R. The regression model suggests a narrower spread of utility values (from 0.54 for King's stage 1 to 0.23 for King's stage 4; ESM, Table S2). The base case analysis uses raw mean values; the regression-based estimates are explored in sensitivity analyses. Within the economic model, utility values were adjusted for age using UK general population EQ-5D-3L estimates [27].

ALS-CarE also included data collection on caregiver HRQoL including the Zarit Burden Interview and the Quality of Life in Life-Threatening Illness–Family Carer Version (QOLLTI-F). However, these are not preference-based measures and cannot be used to derive utility values. Instead, the inclusion of caregiver disutility was explored in sensitivity analysis, using an approach similar to that reported by Thakore et al. [13]. In this analysis, caregiver disutility was assumed to be equal to half of the patient's disutility in each King's stage relative to age-specific UK general population EQ-5D-3L. A bereavement-related QALY loss of 0.05 was also applied at the point of patient death, based on Song et al. [28].

2.4.4 Baseline Resource Costs by King's Stage Under Current Care

The ALS-CarE patient/caregiver interviews included data collection on nine categories of resource use: (1) general practitioner (GP)/primary care visits and community care; (2) social care; (3) palliative care; (4) counselling services; (5) hospital visits; (6) Accident and Emergency (A&E) visits; (7) overnight hospital stays; (8) aids and appliances and (9) pharmacological medications and nutritional/vitamin supplements. Within the analysis, resource use records were included only if the patient had a King's stage value within 2 months of their resource use interview date (either before or after). The final dataset comprised 453 records of resource use and matched stage from 204 patients, although slightly fewer data were available on medications ($N = 429$). Unit costs were obtained from the Personal Social Services Research Unit (PSSRU), NHS Reference Costs 2020/21, the British National Formulary (BNF) and other NHS cost sources (e.g., the NHS Business Service Authority [BSA]) [29–32]. Where cost items were not available from these sources, assumptions were made based on commercial prices from internet sources (including Amazon, Boots Pharmacy, Lloyds Pharmacy and other providers). The costs of aids and appliances were annuitised using a rate of 3.5% per annum and an assumed product lifetime of 5 years. Within the economic model, costs were estimated based on the frequency of use of each resource type per month. The analysis suggests that monthly disease management costs generally increase with more advanced disease, ranging from £1047 in King's stage 1 to £3374 in King's stage 4. Further details on the resource use estimates and unit costs are provided in the ESM, Table S3.

We explored the impact of including lost productivity and household costs borne by patients in an exploratory sensitivity analysis. Lost productivity was estimated for patients in each state based on the reported employment status of ALS-CarE patients at the first study time point using the human capital approach [33]. Within the model, we assumed a retirement age of 65 years. Household costs were estimated within the linked ALS-CarE cohort based on the sum of self-reported costs of extra treatment, patient access to treatment, modifications and complementary/alternative medicines. Costs by health state are shown in the ESM, Table S4.

2.5 Evaluating the Relative Cost Effectiveness of New ALS Treatments Versus Current Care

In general terms, a new intervention for ALS may be considered clinically valuable if it slows the rate of disease progression and death and/or if it improves HRQoL by reducing symptom burden. Within the economic model, the potential cost effectiveness of two hypothetical treatments for ALS was evaluated in comparison to current care:

- Intervention 1: a hypothetical DMT which delays disease progression and death

  The first intervention is a hypothetical DMT which slows disease progression and extends survival. Relative treatment effects were modelled using a relative risk reduction (RRR) which was applied monotonically across all King's stages. An RRR of 0.50 was assumed, based on clinical advice from one of the ALS-CarE study investigators (CM) about what might reflect an effective

treatment for ALS. This RRR is twice the magnitude of the RRR applied in the Canadian Agency for Drugs and Technologies in Health (CADTH) assessment of edaravone [21]. The value of the RRR is tested fully in sensitivity analyses. For illustrative purposes, the cost of the DMT in the base case was based on the acquisition cost of edaravone in Canada converted to GBP Sterling using Purchasing Price Parities (PPPs) (cost = £9500 per month) [21]. This cost was assumed to include all costs associated with drug acquisition, administration, monitoring and managing adverse events (AEs). In the base case analysis, the DMT was assumed to be given to patients in all alive health states (up to King's Stage 4, inclusive) and the effects and costs of the intervention were assumed to apply whilst the patient remains on treatment. Waning or loss of treatment effect was not considered in the base case analysis.

- Intervention 2: a hypothetical symptomatic intervention to improve patient HRQoL

  The second intervention is a hypothetical symptomatic therapy which improves HRQoL without delaying progression or death (e.g., talking therapies, orthoses or other assistive devices). This analysis assumes that the intervention generates an additional utility gain of 0.10 in each alive health state. A once-only intervention cost of £10,000 was applied in the first model cycle.

2.6 Model Evaluation Methods

Estimates of mean survival, QALYs and costs for the baseline model and incremental cost-effectiveness outcomes for intervention type were generated using both the probabilistic and deterministic versions of the model. The deterministic model applies point estimates of parameters, whereas the probabilistic model uses Monte Carlo sampling across 5000 iterations to generate distributions of expected lifetime health outcomes and costs for each treatment group. Uncertainty around the transition probabilities was handled using bootstrapping within the multistate model estimation, whereas uncertainty around utility and resource use parameters was characterised using beta distributions and gamma distributions, respectively. Model results are presented as mean incremental cost-effectiveness ratios (ICERs), tornado diagrams, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) for each intervention versus current care. Deterministic sensitivity analyses (DSAs) were undertaken to identify key drivers of cost effectiveness. These included alternative scenarios relating to the magnitude and duration of treatment effects; treatment initiation and stopping rules; intervention costs; transition probabilities; utility values; disease management costs; the inclusion of caregiver QALY losses and indirect costs. In addition, threshold analyses were undertaken for both the DMT and the symptomatic therapy evaluations to explore the circumstances under which these treatments might achieve acceptable levels of cost effectiveness.

In 2022, NICE published an updated Methods Manual which allows for the inclusion of QALY weighting based on the severity of the condition [19]. To account for severity, we estimated the absolute and proportional QALY shortfall under current care using the York QALY Shortfall Calculator [34]. The severity weight was used to determine the appropriate range of willingness-to-pay (WTP) thresholds for decision making.

The economic model was programmed in Microsoft Excel® and is fully replicable from the information reported here. The executable model is available from the authors upon request.

2.7 Model Verification and Validation

Several measures were taken to ensure the credibility of the model. These included the use of clinical input to inform the model structure and assumptions; review of the model methods and results by clinical and methodological experts; double-programming of the deterministic model; scrutiny of model code and formulae to verify their accuracy; checking the goodness-of-fit of the fitted multistate model; black-box testing of the economic model and cross-validation of the model inputs and predictions against other relevant economic analyses in ALS [13, 20, 21, 35].

3 Results

3.1 Baseline Estimates of Survival, QALYs and Costs Under Current Care

Estimates of health outcomes and costs under current care for patients with King's stages 1–3 are presented in Table 2. Starting at King's stage 2, the probabilistic version of the model suggests that under current care, ALS patients have a mean survival duration of 2.27 years (Table 2). The probability of remaining alive at 3 years and 5 years is estimated to be around 0.27 and 0.07, respectively. The model suggests that under current care, patients will accrue 0.75 discounted QALYs at a mean discounted cost to the NHS and PSS of £68,047. The deterministic model yielded similar results to the probabilistic model. A breakdown of undiscounted lifetime costs by resource use category and stage is provided in the ESM, Table S5.

Based on the characteristics of the ALS-CarE population (mean age = 63 years, probability female = 39%) and a mean QALY estimate of 0.75, the absolute QALY shortfall is estimated to be 10.88 QALYs whereas the proportional QALY shortfall is estimated to be 93.55%. This suggests a severity modifier of 1.2, which corresponds to a maximum cost-effectiveness threshold of £36,000 per QALY gained.

3.2 Relative Cost Effectiveness of a Hypothetical DMT Versus Current Care

The probabilistic version of the economic model suggests that the hypothetical DMT is expected to generate 0.74 additional QALYs at an additional cost of £543,024; the corresponding ICER is £735,898 per QALY gained (Table 3). The CEACs suggest that the probability that the DMT is cost effective at WTP thresholds below £36,000 per QALY gained is approximately zero (ESM, Fig. S5). The DSAs consistently suggest ICERs which are well above £36,000 per QALY gained across all scenarios considered (Table 4), and that the ICER is sensitive to the RRR and DMT price. Of particular note, the model suggests that the DMT would not be considered cost effective even at zero price; this is because the DMT is assumed to extend survival, but the additional survival time is associated with low utility and high background costs. However, the ICER remains very high even when all disease management costs are excluded. The DSAs also highlight that including caregiver QALY losses increases the ICER.

The threshold analyses (Fig. 2A and ESM, Table S6) suggest that it is likely to be challenging for a DMT to achieve an acceptable level of cost effectiveness. These analyses indicate that the cost effectiveness of a hypothetical DMT may be more favourable if the DMT is more effective in delaying progression than is assumed in the base-case analysis; treatment is initiated at earlier disease stages; hard treatment stopping rules are applied once patients reach particular King's stages; the price of the DMT is lower than that assumed in the base case analysis, and/or the DMT offers additional HRQoL benefits over and above those for current care within each King's stage. To achieve an ICER which is below or approaching an acceptable cost-effectiveness threshold, the joint consideration of all of these factors may be required. The threshold analyses indicate that even if background costs are excluded, the ICER for the DMT remains high in almost all scenarios unless its price is <£1000 per month.

We note that the previous economic analysis of edaravone by the CADTH assumed an RRR on progression of 0.25 [21], which is considerably less favourable than the treatment effect assumed in our base case analysis. Based on a converted UK price of £9500 per month, our model suggests an ICER for edaravone versus current care of £1.46 million per QALY gained. This is substantially higher than typical UK cost-effectiveness thresholds.

Table 3 Base case cost-effectiveness results (probabilistic model)

	Intervention	Usual care	Incremental
Hypothetical disease-modifying therapy versus current care assumed RRR = 0.50			
LYGs[a]	4.80	2.27	2.53
QALYs	1.49	0.75	0.74
Costs	£611,070	£68,047	£543,024
ICER			£735,898
Hypothetical symptomatic therapy versus current care assumed utility gain = 0.10			
LYGs[a]	2.27	2.27	0.00
QALYs	0.96	0.75	0.21
Costs	£78,047	£68,047	£10,000
ICER			£46,958

ICER incremental cost-effectiveness ratio, *LYG* life-year gained, *QALY* quality-adjusted life-year

[a]Undiscounted

3.3 Relative Cost-Effectiveness of a Hypothetical Symptomatic Therapy Versus Current Care

The probabilistic model suggests that the symptomatic therapy is expected to generate 0.21 additional QALYs at an additional cost of £10,000; the corresponding ICER is £46,958 per QALY gained (Table 3). The CEACs indicate that the probability that the symptomatic therapy is cost

Table 2 Baseline estimates of mean survival, QALYs and costs under current care for ALS

Outcome	Patients start in King's Stage 1		Patients start in King's Stage 2		Patients start in King's Stage 3	
	Deterministic	Probabilistic	Deterministic	Probabilistic	Deterministic	Probabilistic
Overall survival (years)[a]	2.79	2.8	2.23	2.27	1.76	1.78
Time in stage 1 (years)[a]	0.62	0.65				
Time in stage 2 (years)[a]	0.76	0.73	0.83	0.87		
Time in stage 3 (years)[a]	0.60	0.61	0.59	0.60	0.97	0.98
Time in stage 4 (years)[a]	0.81	0.82	0.81	0.80	0.79	0.80
Lifetime QALYs	1.05	1.06	0.73	0.75	0.49	0.50
Lifetime NHS/PSS costs	£72,744	£72,598	£67,616	£68,047	£57,163	£57,557

NHS National Health Service, *PSS* Personal Social Services, *QALY* quality-adjusted life-year

[a]Undiscounted

Table 4 Deterministic sensitivity analysis results

Scenario no.	Scenario description	Inc. LYGs[a]	Inc. QALYs	Inc. costs	ICER
Case study 1: Hypothetical DMT versus current care					
–	Base case	2.27	0.67	£515,429	£767,478
1	Efficacy increased to 75%	6.79	1.81	£970,846	£534,928
2	Efficacy decreased to 25%	0.76	0.23	£338,651	£1,458,840
3	Efficacy lost at 5 years	1.72	0.57	£456,142	£803,238
4	Efficacy lost at 2 years	0.90	0.34	£356,837	£1,048,390
5	Treatment stops at King's stage 3	1.46	0.55	£333,481	£607,006
6	Treatment stops at King's stage 2	0.87	0.36	£204,637	£562,037
7	Patients start treatment in King's stage 1	2.82	0.95	£621,878	£655,079
8	Patients start treatment in King's stage 3	1.80	0.46	£416,616	£902,820
9	Drug cost halved	2.27	0.67	£283,976	£422,842
10	Drug cost doubled	2.27	0.67	£978,336	£1,456,749
11	Drug given at zero price	2.27	0.67	£52,522	£78,206
12	Additional utility gain of 0.10 for DMT-treated patients	2.27	1.07	£515,429	£482,059
13	Utility values from mixed-effect linear regression fitted to ALS-CarE data	2.27	0.67	£515,429	£764,876
14	Utility values estimated using 5-level EQ-5D Devlin value set	2.27	0.97	£515,429	£532,809
15	Transition probabilities from Thakore et al.	3.25	0.78	£708,222	£907,816
16	Utility values from Moore et al.	2.27	1.03	£515,429	£499,212
17	Costs by King's stage increased by 25%	2.27	0.67	£528,703	£787,242
18	Costs by King's stage reduced by 25%	2.27	0.67	£502,155	£747,713
19	Costs by King's stage from Moore et al.	2.27	0.67	£479,408	£713,842
20	Costs by King's stage excluded	2.27	0.67	£462,334	£688,418
21	Inclusion of caregiver disutility	2.27	0.23	£462,334	£1,977,887
22	Inclusion of indirect costs	2.27	0.67	£542,654	£808,015
Case study 2: Hypothetical symptomatic therapy versus current care					
–	Base case	0.00	0.21	£10,000	£47,636
1	Utility gain increased to 0.15	0.00	0.31	£10,000	£31,758
2	Utility gain decreased to 0.05	0.00	0.10	£10,000	£95,273
3	Efficacy lost at 5 years	0.00	0.20	£10,000	£49,223
4	Efficacy lost at 2 years	0.00	0.15	£10,000	£68,626
5	All patients start in King's stage 1	0.00	0.26	£10,000	£38,411
6	All patients start in King's stage 3	0.00	0.17	£10,000	£59,845
7	No utility gain in King's stage 4	0.00	0.14	£10,000	£73,460
8	Intervention cost halved	0.00	0.21	£5000	£23,818
9	Intervention cost doubled	0.00	0.21	£20,000	£95,273
10	Intervention cost = £833 applied for 12 months	0.00	0.21	£8893	£42,364
11	Utility values from linear mixed effects model	0.00	0.21	£10,000	£47,636
12	Utility values from Moore et al.	0.00	0.21	£10,000	£47,636
13	Utility values estimated using 5-level EQ-5D Devlin value set	0.00	0.21	£10,000	£47,636
14	Costs by King's stage increased by 25%	0.00	0.21	£10,000	£47,636
15	Costs by King's stage reduced by 25%	0.00	0.21	£10,000	£47,636
16	Costs by King's stage from Moore et al.	0.00	0.21	£10,000	£47,636
17	Costs by King's stage excluded	0.00	0.21	£10,000	£47,636
18	Inclusion of caregiver disutility	0.00	0.32	£10,000	£31,704
19	Inclusion of indirect costs	0.00	0.21	£10,000	£47,636

DMT disease-modifying therapy, *ICER* incremental cost-effectiveness ratio, *Inc.* incremental, *LYG* life-year gained, *QALY* quality-adjusted life-year

[a]Undiscounted

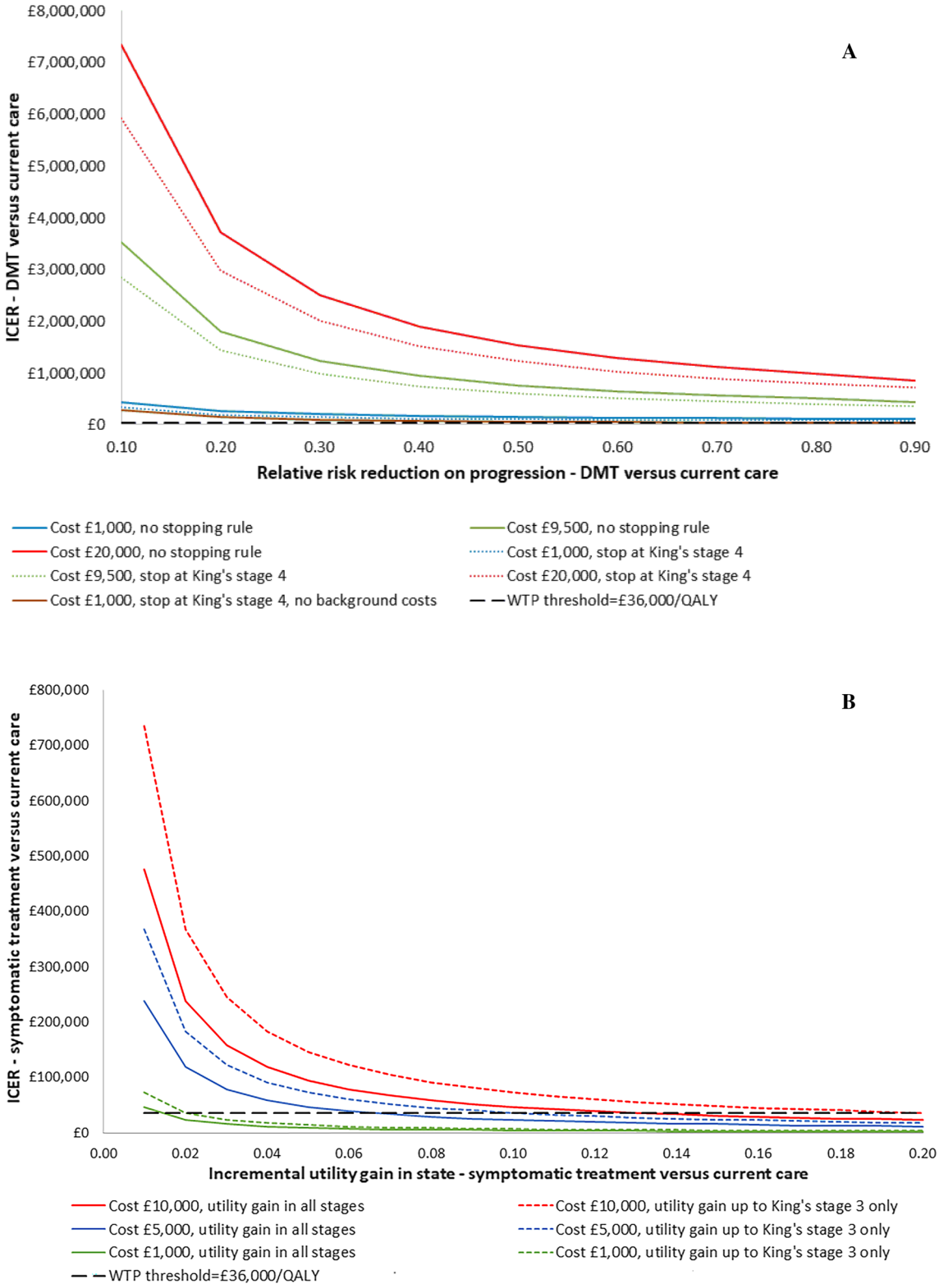

Fig. 2 Threshold analysis around treatment benefit for the hypothetical DMT and the symptomatic therapy. **A** Threshold analysis of RRR for DMT versus current care; **B** threshold analysis of additional utility gain in health state for symptomatic therapy. *DMT* disease-modifying therapy, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *WTP* willingness to pay

effective at WTP thresholds below £36,000 per QALY gained is <0.02 (ESM, Fig. S8). The DSAs (Table 4) indicate that the cost effectiveness of a symptomatic therapy may be more favourable if the additional utility gain in each state is higher than that assumed in the base case analysis; treatment is initiated at an earlier disease stage; caregiver disutilities are included, and/or the intervention cost is lower than that assumed in the base case analysis. However, the ICER will be less favourable if the utility gain attributable to the intervention persists only over earlier King's stages (Fig. 2B). The inclusion of alternative patient utility values in each King's stage, alternative costs in each King's stage, and indirect costs have no impact on the ICER because the intervention is not assumed to influence disease progression or mortality.

4 Discussion

Few economic evaluations of ALS therapies have been published in the last 2 decades [12], which likely reflects a historical lack of success in clinical drug development in ALS (a summary of model-based economic evaluations of ALS therapies is provided in the ESM, Table S7). Older economic analyses in ALS have been subject to limitations in methods and data, and most have been restricted to economic evaluations of riluzole, a therapy which has been routinely used in clinical practice for more than 2 decades. More recent model-based analyses conducted by CADTH and the Institute for Clinical and Economic Review (ICER) have focussed on newer drug therapies, including edaravone and AMX0035 [20, 21]. In April 2024, the manufacturer of AMX0035 indicated their intention to withdraw this product from the market following negative findings from the PHOENIX trial [20]. These economic analyses have both been undertaken in a North American setting and have relied on analyses of PRO-ACT [36], a pooled, open access, clinical trials database which includes mostly data from randomised controlled trials, as a means of estimating progression and mortality rates, with separate sources used to estimate health utility values and resource use. PRO-ACT may not fully reflect outcomes seen in current clinical practice, as data are drawn from restrictive populations reflecting the inclusion criteria of trials [36]. With the exception of the CADTH and ICER analyses of edaravone and AMX0035 [20, 21], no other model-based economic analyses of these ALS therapies have been published. The most recent published economic evaluation of ALS therapies conducted in a UK setting is >20 years old [37].

Our analysis attempts to address two aims: firstly, to provide up-to-date estimates of expected health outcomes and costs for a contemporary cohort of ALS patients receiving current care in Europe based on appropriate methods, and secondly, to use this information within a health economic model to explore the circumstances under which new and emerging therapies for ALS might be considered economically attractive. Our baseline model suggests that under current care, patients with ALS diagnosed at King's stage 2 have an expected survival of 2.27 years, accrue 0.75 discounted QALYs and incur expected discounted lifetime costs of £68,047. Our comparative economic analyses indicate that even if a new DMT can demonstrate substantial treatment effects on disease progression and mortality, it will only be able to achieve an ICER which is below or approaching a potentially acceptable threshold if its price is low. The consideration of some combination of early treatment initiation and hard stopping rules, and the demonstration of additional HRQoL benefits over and above current care, might also be required to support an economic case for the reimbursement of such therapies. These factors, their clinical rationale and the evidence to support them, should be considered by pharmaceutical companies intending to make future submissions for reimbursement of DMTs for ALS. Our analyses indicate that symptomatic therapies may be more likely to achieve acceptable levels of cost effectiveness, although this conclusion will depend on the acquisition cost of the intervention and the magnitude and duration of its effect on HRQoL.

Overall, our economic analysis suggests a potentially bleak outlook for future DMTs for ALS. Our baseline model suggests a maximum acceptable cost-effectiveness threshold of £36,000 per QALY gained, whereas our comparative economic analyses suggest the potential for DMTs to not be cost effective at zero price. There is currently no clear solution to this problem [38, 39]. Some commentators have advocated the exclusion of unrelated medical costs, or all background costs, from the economic analysis. This approach is permitted as a non-reference case analysis within NICE's Methods Manual [19]. However, this would fail to fully account for the opportunity costs associated with the DMT. Alternatively, there may be a reasonable ethical argument that society might place additional value, over and above that captured within the decision modifier, on a new effective treatment for people with ALS. However, even if a maximum cost-effectiveness threshold of £50,000 per QALY gained was deemed acceptable, achieving an ICER below this threshold would likely require the DMT to be highly effective, early treatment initiation, hard stopping rules and a low drug price.

The economic model described here is structurally similar to other recent economic models of ALS therapies [13, 20, 21]. These models also include health states defined by King's staging, and each assumes a progressive disease course, with worsening HRQoL and increasing costs at advanced stages of the disease. Our estimates of predicted overall survival using the ALS-CarE dataset are lower than

those estimated from previous models but remain in line with clinical expectations. Our estimates of patient utility by King's stage are broadly consistent with other published estimates when based on the UK EQ-5D-5L value set [35]. Our estimates of disease management costs by King's stage are markedly higher than other UK estimates [35]; the reasons for these differences are not fully clear. However, our modelled lifetime costs for current care are similar to UK-equivalent estimates obtained from other economic models developed in Canadian and US health care settings [13, 20, 21]. Further detail on comparisons of utility values, costs and predicted survival across studies is provided in the ESM (Tables S8–S10 and Fig. S9).

Our economic analysis has several strengths. The ALS-CarE dataset [15] reflects health outcomes and resource use in a cohort of > 200 ALS population-based patients. The estimates of disease progression, survival, QALYs and resource use are all based on this same overall dataset, linked by the date of clinical visits and EQ-5D and resource use interviews. In line with previous methodological guidance provided by Thakore et al. [13], transition rates under current care have been estimated using multistate modelling which jointly estimates all transition rates under a competing risks framework [23, 24], and represents a substantial improvement over earlier models in ALS. Overall, our analysis is consistent with the NICE Reference Case [19] and considers the implications of including a severity modifier on the cost effectiveness of ALS treatments. The baseline model for current care is reproducible and may be used as the basis for modelling current care in future economic analyses of ALS therapies. Our sensitivity analyses are extensive and highlight the factors which are likely to be most influential in determining the economic attractiveness of future ALS therapies.

Our analyses are also subject to limitations. Whilst the ALS-CarE population might better reflect outcomes for ALS patients treated in current practice compared with alternative sources such as PRO-ACT [36], the sample size used to estimate transition probabilities, EQ-5D-3L and costs in ALS-CarE is fairly small ($N = 204$). In addition, because the clinical visits to determine stage did not always coincide with the dates on which EQ-5D and resource use interviews were held, we had to link the data, assuming a tolerance of 2 months. This may have led to some inaccuracy. In addition, although we have explored the potential impact of including caregiver effects, the lack of relevant data means that this analysis is necessarily based on assumptions. Perhaps most importantly, because there are currently no new licensed DMTs available in Europe, our exploratory analyses are indicative at best and our results should be interpreted carefully. However, the model is flexible and can be easily adapted to reflect the specific characteristics of future interventions as and when they become available.

5 Conclusions

Our analysis indicates that DMTs will likely struggle to demonstrate cost effectiveness, regardless of their efficacy. Achieving ICERs which are below or approaching acceptable cost-effectiveness thresholds will likely require a combination of a low drug price, substantial treatment effects, early treatment initiation and hard stopping rules at key points in the disease process. The exclusion of background disease management costs and the inclusion of severity weighting may be relevant for consideration by decision makers. However, it may be easier to demonstrate economic value for other types of symptomatic treatments for ALS.

Two key areas of further research may be warranted. Firstly, larger, longer-term observational data collection on clinical stage, mortality and health utility, such as the PRECISION ALS project [40], may allow for a better characterisation of health outcomes amongst ALS patients in a real-world setting. Secondly, full economic analyses of emerging ALS therapies (e.g., tofersen and others) will be required if these products are granted marketing authorisation in England and Europe. These analyses could be undertaken using the model described here, with sensitivity analyses based on alternative sources [13, 20, 21], or vice versa. Future economic analyses should include a detailed exploration of the magnitude and durability of relative treatment effects, treatment starting and stopping rules, as well as price considerations to ensure that the technology represents good value for money for health services.

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Declarations

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Conflict of interest None of the authors have any conflicts of interest to declare.

Availability of data and material The individual patient data from ALS-CarE cannot be made publicly available for reasons of privacy and confidentiality. However, access to de-identified datasets can be made available on request to Mr Mark Heverin mark.heverin@tcd.ie. The economic model is fully replicable from the information reported in this paper. The executable model is available from the authors upon request.

Ethics approval All European study sites obtained ethical approval from their own Institutional Review Boards to allow them to collect information locally. This approval took account of the international

collaborative nature of the study and how the data were to be analysed by the ALS-CarE consortium.

Informed consent Not applicable.

Author contributions Paul Tappenden, Orla Hardiman, Miriam Galvin, Chris McDermott conceptualised and designed the study. All authors contributed to the development and analysis. All authors contributed to writing the manuscript. All authors read and approved the final version. The ALS-CarE Study Group consortia provided support over the course of the study, including in data collection, cleaning and analysis.

References

1. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. Nat Rev Dis Primers. 2017;3:17071.
2. GBD 2016 Motor Neuron Disease Collaborators. Global, regional, and national burden of motor neuron diseases 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1083–97.
3. Hardiman O, Al-Chalabi A, Brayne C, Beghi E, van den Berg LH, Chio A, et al. The changing picture of amyotrophic lateral sclerosis: lessons from European registers. J Neurol Neurosurg Psychiatry. 2017;88(7):557–63.
4. Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy C, et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg Psychiatry. 2015;86(5):496–501.
5. Aridegbe T, Kandler R, Walters SJ, Walsh T, Shaw PJ, McDermott CJ. The natural history of motor neuron disease: assessing the impact of specialist care. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(1):13–9.
6. European Medicines Agency. Rilutek (riluzole) 50mg film-coated tablets. London: Summary of product characteristics; 1996.
7. U.S. Food and Drug Administration. Search orphan drug designations and approvals—Riluzole (rilutek) 1993.
8. Petrov D, Mansfield C, Moussy A. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? Front Aging Neurosci. 2017. https://doi.org/10.3389/fnagi.2017.00068.
9. Gao M, Zhu L, Chang J, Cao T, Song L. Safety and efficacy of edaravone in patients with amyotrophic lateral sclerosis: a systematic review and meta-analysis. Clin Drug Investig. 2023;43(1):1–11.
10. Miller TM, Cudkowicz ME, Genge A, Shaw PJ, Sobue G, Bucelli RC, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med. 2022;387(12):1099–110.
11. Mitsubishi Tanabe Pharma America. Company Press Release: Mitsubishi Tanabe Pharma America, Inc. (MTPA) Statement on Ferrer's Phase 3 ADORE Clinical Trial of FNP122 (FAB122). 2024. https://www.mt-pharma-america.com/media/news/press-releases/2024/01/17/mitsubishi-tanabe-pharma-america-inc-mtpa-statement-on-ferrers-phase-3-adore-clinical-trial-of-fnp122-fab122. Accessed 26 Apr 2024.
12. Moore A, Young CA, Hughes DA. Economic studies in motor neurone disease: a systematic methodological review. Pharmacoeconomics. 2017;35(4):397–413.
13. Thakore NJ, Pioro EP, Udeh BL, Lapin BR, Katzan IL. A cost-effectiveness framework for amyotrophic lateral sclerosis, applied to riluzole. Value Health. 2020;23(12):1543–51.
14. clinicaltrials.gov. A programme for amyotrophic lateral sclerosis care in Europe (ALS-CarE). 2015. https://clinicaltrials.gov/study/NCT03081338?term=%22als-care%22&rank=1#publications. Accessed 06 Jan 2024.
15. Hardiman O, Van Den Berg L, Al-Chalabi A, McDermott C, Tappenden P, Chio A, et al. ALS-CARE: a programme for ALS care in Europe. Patient-level data. 2013.
16. Galvin M, Carney S, Corr B, Mays I, Pender N, Hardiman O. Needs of informal caregivers across the caregiving course in amyotrophic lateral sclerosis: a qualitative analysis. BMJ Open. 2018;27(8):e018721.
17. Galvin M, Gavin T, Mays I, Heverin M, Hardiman O. Individual quality of life in spousal ALS patient-caregiver dyads. Health Qual Life Outcomes. 2020. https://doi.org/10.1186/s12955-020-01551-5.
18. Thurn T, Borasio GD, Chiò A, Galvin M, McDermott CJ, Mora G, et al. Physicians' attitudes toward end-of-life decisions in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(1–2):74–81.
19. National Institute for Health and Care Excellence. NICE health technology evaluations: The manual. London. 2022.
20. Makam AN, Nikitin D, Richardson M, Mohammed R, McKenna A, Pearson SD, et al. AMX0035 and oral edaravone for amyotrophic lateral sclerosis. Final report published by the Institute for Clinical and Economic Review (ICER). 2022.
21. CADTH Common Drug Review. Pharmacoeconomic review report: Edaravone Ontario 2019.
22. Fang T, Al Khleifat A, Stahl DR, Lazo La Torre C, Uk-Mnd Lical S, et al. Comparison of the King's and MiToS staging systems for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3–4):227–32.
23. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389–430.
24. Jackson CH. Multistate modelling with R: The msm package. Version 1.7. J Stat Softw. 2011. https://doi.org/10.18637/jss.v038.i08.
25. Office for National Statistics. National life tables: England 2018–2020. London. 2021.
26. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708–15.
27. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. Sheffield, UK. 2022.
28. Song JI, Shin DW, Choi JY, Kang J, Baek YJ, Mo HN, et al. Quality of life and mental health in the bereaved family members of patients with terminal cancer. Psychooncology. 2012;21(11):1158–66.
29. Jones KC, Burns A. Unit costs of health and social care 2021. Kent, UK. 2021.
30. NHS England. National schedule of NHS costs 2020/21. London, UK. 2022.
31. Joint Formulary Committee. British National Formulary (online). London, UK. 2022.
32. NHS Business Services Authority. What are the current costs of NHS treatment in England? 2023. https://faq.nhsbsa.nhs.uk/knowledgebase/article/KA-03997/en-us. Accessed 05 Jan 2023.
33. Weisbrod BA. The valuation of human capital. J Polit Econ. 1961;69(5):425–36.
34. McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. Value Health. 2022;38:901.
35. Moore A, Young CA, Hughes DA. Health utilities and costs for motor neurone disease. Value Health. 2019;22(11):1257–65.

36. Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E, et al. The PRO-ACT database: design, initial analyses, and predictive features. Neurology. 2014;83(19):1719–25.
37. Tavakoli M. Disease progression in amyotrophic lateral sclerosis. Identifying the cost-utility of riluzole by disease stage. Eur J Health Econ. 2002;3(3):156–65.
38. Davis S. Assessing technologies that are not cost-effective at a zero price. Sheffield, UK. 2014.
39. Mladsi D, Barnett CL, Mader G, Russell-Smith TA, Unuigbe A, Bell T. The zero-price conundrum: exploration of scenarios where a clinically effective new drug might not be cost-effective at zero price. Value Health. 2023;26(3):384–91.
40. McFarlane R, Galvin M, Heverin M, Mac Domhnaill É, Murray D, Meldrum D, et al. PRECISION ALS-an integrated pan European patient data platform for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2023;24(5–6):389–93.