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ORIGINAL PAPER

The cost-effectiveness of enzyme replacement therapies versus best supportive care for treating late onset Pompe disease in the UK NHS

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Abstract

Objective To assess the cost-effectiveness of enzyme replacement therapy (ERT) compared with best supportive care (BSC) for late-onset Pompe disease (LOPD) in a UK NHS setting.

Methods A discrete event simulation model was developed using data from a Bayesian network meta-analysis, trials and extension studies, and long-term observational cohorts. Costings were derived from NICE assessments of LOPD treatments. Disease progression was modelled using forced vital capacity (FVC) % predicted and six-minute walk distance (6MWD).

Results ERT was associated with an incremental cost of £3.26 million and 1.64 additional QALYs compared to BSC, yielding an incremental cost-effectiveness ratio (ICER) of £2 million per QALY gained, and generating a net health effect (NHE) exceeding -100 QALYs per treated patient. Scenario analyses confirmed that ERT remained cost-ineffective under all plausible assumptions. Discounts of ~ 92.3% and ~ 89% on the list price of ERT would be required to achieve cost-effectiveness at thresholds of £30,000 and £100,000 per QALY gained, respectively.

Conclusions While ERT provides modest long-term health benefits relative to BSC, it is structurally highly cost-ineffective, generating substantial negative NHE for the NHS population, even under the most optimistic assumptions. These results are primarily driven by very high acquisition costs of ERT. The historic commissioning of ERT without reference to the UK's value-based pricing framework has significantly impacted NHS spending and distorted NICE decision-making. Without reform to the appraisal process, the NHS faces affordability challenges that may hinder access to innovative therapies and result in recommendations that displace more health than they generate.

Keywords Glycogen storage disease type II · Cost–benefit analysis · Enzyme replacement therapy · United Kingdom

JEL classification I1

Introduction

Pompe disease is a rare inherited disorder caused by mutations in the GAA gene, which encodes the lysosomal enzyme acid α-glucosidase (GAA) [1]. The deficiency of this enzyme leads to glycogen accumulation within the lysosomes, particularly in muscle cells, resulting in progressive skeletal, respiratory, and (in infants) cardiac muscle damage [1, 2].

Pompe disease is classified into infantile-onset (IOPD) or late-onset (LOPD) forms. IOPD manifests within the first months of life, and is associated with severe cardiac complications and rapid disease progression [3]. In contrast, LOPD presents after the age of one, but typically well into adulthood, and is characterised by progressive skeletal

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and respiratory muscle weakness with little or no cardiac involvement [3]. The rate of disease progression varies widely according to the individual's degree of enzyme deficiency, but in time leads to significant morbidity, respiratory failure, and early mortality [4–6].

The standard of care in the UK for the treatment of LOPD is enzyme replacement therapy (ERT) [7]. ERT works by replacing deficient GAA enzyme to clear glycogen accumulation, thereby preserving muscle function and improving quality of life [5, 8]. Alglucosidase alfa has been available on the National Health Service (NHS) since 2006, and until recently was the mainstay treatment for LOPD. The National Specialised Commissioning Advisory Group commissioned alglucosidase alfa [9] as part of the Lysosomal Storage Disorders Service [10–12], which provided national funding for diagnosis and treatment across a number of UK centres. As this occurred prior to the establishment of National Institute for Health and Care Excellence (NICE) processes for highly specialised technologies (HST), alglucosidase alfa has never undergone formal assessment by NICE. As a result, the cost-effectiveness of alglucosidase alfa relative to best supportive care (BSC), largely comprising direct support of additional respiratory and mobility needs, remains unknown. Given its high acquisition costs, there is a substantive risk that alglucosidase alfa is not a cost-effective use of NHS resources. This is evidenced by several assessments of cost-effectiveness in other countries, which have estimated very high incremental cost-effectiveness ratios (ICERs). [13–16]

Recently, NICE has recommended two newer ERTs, avalglucosidase alfa and cipaglucosidase alfa (with miglustat), for LOPD through the single technology appraisal (STA) process [17, 18]. In line with standard NICE methods, these appraisals assessed their clinical and cost-effectiveness compared with alglucosidase alfa, the established standard of care, and importantly did not consider BSC without ERT. The absence of a baseline cost-effectiveness assessment for alglucosidase alfa relative to BSC means that comparisons between newer therapies and alglucosidase alfa may generate misleading estimates of their value to the NHS.

This study aims to evaluate the cost-effectiveness of ERT technologies for the treatment of LOPD in comparison with BSC from the perspective of the UK NHS, and to establish an indicative maximum price for ERT treatment given (willingness-to-pay) threshold norms in the UK. This study forms part of a wider evidence synthesis project commissioned by the National Institute for Health and Care Research (NIHR): "The Effectiveness and Cost-Effectiveness of Enzyme Replacement Therapies for the Treatment of Late onset Pompe Disease".

Methods

The de novo model was co-developed with an advisory group comprising UK clinical experts, patients and carers of patients with LOPD, and patient representatives from the Pompe Support Network. The model structure was informed by previous cost-effectiveness analyses identified in a systematic review [13–16], including models considered by NICE in TA821 and 912 [19, 20].

The economic analysis compared the cost-effectiveness of alglucosidase alfa, avalglucosidase alfa, cipaglucosidase alfa plus miglustat, and BSC for the treatment of adult patients with LOPD over a lifetime time horizon in the UK NHS context. A class-level ERT vs. BSC comparison was also conducted, recognising the lack of consistent evidence for superiority of any one ERT over another [21]. Value of information analysis was performed but not detailed here, as there were no scenarios in which ERTs showed a cost-effectiveness probability greater than zero.

Clinical inputs used in the model were informed by a systematic review and Bayesian network meta-analysis (NMA), for which methods and results are reported in full in Corbett et al. [21].

Model structure

The model comprised a de novo, continuous time patient-level simulation built using Visual Basic for Applications in Microsoft Excel. This approach represents each patient's individual experience through a unique sequence of different possible events and processes over their lifetime [22], and captures both first- (stochastic) and second- (parameter) order uncertainty through a two-level sampling superstructure. By simulating each patient's life course under different interventions, their respective costs and benefits can be directly compared.

This approach facilitates the independent, continuous modelling of changes in 6MWD and FVC % predicted scores, allowing for intuitive variation over time. These outcomes, recorded across the key clinical studies for each of the comparators, have been accepted by the NICE Appraisal Committee in TA821 and TA912 as proxies for mobility support needs (6MWD) and respiratory function (FVC %) [17, 18]. While their validity as direct predictors of support requirements is questionable, they are broadly indicative of severity of disease and the support needs of LOPD patients [21].

Modelled support needs are defined by fixed thresholds applied to 6MWD and FVC % predicted score with 13 possible combinations of mobility and respiratory support, each with specific care requirements and mortality implications.

Health related quality of life (HRQoL) is estimated directly from 6MWD using a published regression model [23]. The model was built in alignment with the principles of patient level simulation modelling outlined in NICE DSU Technical Support Document 15 [24]. A schematic of the model structure is presented in Fig. 1.

Simulated patients receive biannual specialist assessments, updating their 6MWD and FVC % scores in line with their current treatment and time since initiation. At each modelled event, discounted costs and quality-adjusted life years (QALYs) accrued since the last event is calculated. If support needs change, time until death is also resampled using state-specific mortality multipliers.

The base-case analysis applies a 60-year time horizon (i.e., lifetime). Costs and benefits are discounted at 3.5% per annum. The analysis adopts a UK NHS and Personal Social Services (PSS) perspective.

Clinical inputs

Population characteristics

The economic model focused on the incident NHS population, which is assumed to be represented by the COMET trial [25, 26], which recruited ERT-naïve patients in a clinical context where ERTs were already available. This study was the only included RCT judged to have an overall low risk of bias [21].

Baseline characteristics for each simulated patient, including age, gender, weight, 6MWD, and predicted FVC%, were drawn from a normal distribution around the means reported in COMET, to propagate the impact of patient heterogeneity through the model. Baseline population characteristics can be found in Table 1 in the supplementary material.

Short-term treatment outcomes

Treatment efficacy between baseline and Week 49/52 (study-dependent) was based on a Bayesian NMA, reported in full in Corbett et al. [21]. Three randomised controlled trials (RCTs) were identified as summarised in the supplementary materials (Table 2). The NMA showed no consistent evidence of a difference in effectiveness between the ERTs over time. Therefore, three approaches to modelling ERT were explored: i) using alglucosidase alfa as a proxy for ERTs as a class; ii) pooling all ERT data in a naïve 'class-effect' Bayesian random effects meta-analysis versus placebo, and iii) modelling ERTs separately based on the one-year NMA results. All efficacy inputs are presented in Table 1. Treatment effects were sampled from a normal distribution using study-derived standard deviations to represent heterogeneity in potential treatment response across the population.

Long-term outcomes

Efficacy outcomes up to Week 104 (i.e. 2 years) were based on long-term, unblinded extension study data for the three RCTs. It was not possible to construct a network at this timepoint, as there was no common comparator across the extension phases. The model therefore adopts two approaches described above to model this period, i.e., alglucosidase alfa as a proxy, and naïve unanchored pooling of extension study outcomes. Sampled change from baseline (CFB) to Week 52 was subtracted from sampled CFB to Week 104 to calculate absolute rates of change during this period.

Beyond Week 104, 6MWD progression on ERTs was based on up to 12 years of follow-up in Semplicini et al. [27], with percentage change converted into metres according to a published algorithm for each patient [28]. A longitudinal survey (n = 189) by van der Meijden et al. reported a HR of 0.36 (95% CI 0.17 to 0.75) for long-term risk of becoming wheelchair dependent on ERT relative to BSC [29]. Interpreting this as the rate of slowed decline of 6MWD yields a multiplication factor of 2.78 (SD 1.16) for BSC progression in 6MWD in patients on BSC, and therefore an average annual rate of decline of 6.39% in predicted 6MWD. It was assumed that patients on BSC could not experience long-term improvement in 6MWD.

Long-term change in % FVC was based on Harlaar et al., which measured FVC for up to 10 years before and after initiation of ERT [30]. Rate of change on BSC is based on mean annual progression prior to initiation of ERT, and rate of change on ERT is based on change between Year 2 and Year 8, to avoid double counting the rebound-effect already accounted for in the trial data whilst maximising the sample size.

Treatment discontinuation

The base-case analysis applied an annual rate of discontinuation on ERT of 1.54%, based on van Kooten et al. [34], where 10.31% (10/97) of living patients discontinued ERT over 7.1 years. The model additionally assumes discontinuation of ERT at the point invasive respiratory support is required, as patients can gain no further benefit from continued treatment in this model framework. A scenario relaxing this assumption is also explored.

Mortality

Long-term data on the mortality impact of ERTs is limited, meaning it is not currently possible to draw inferences about

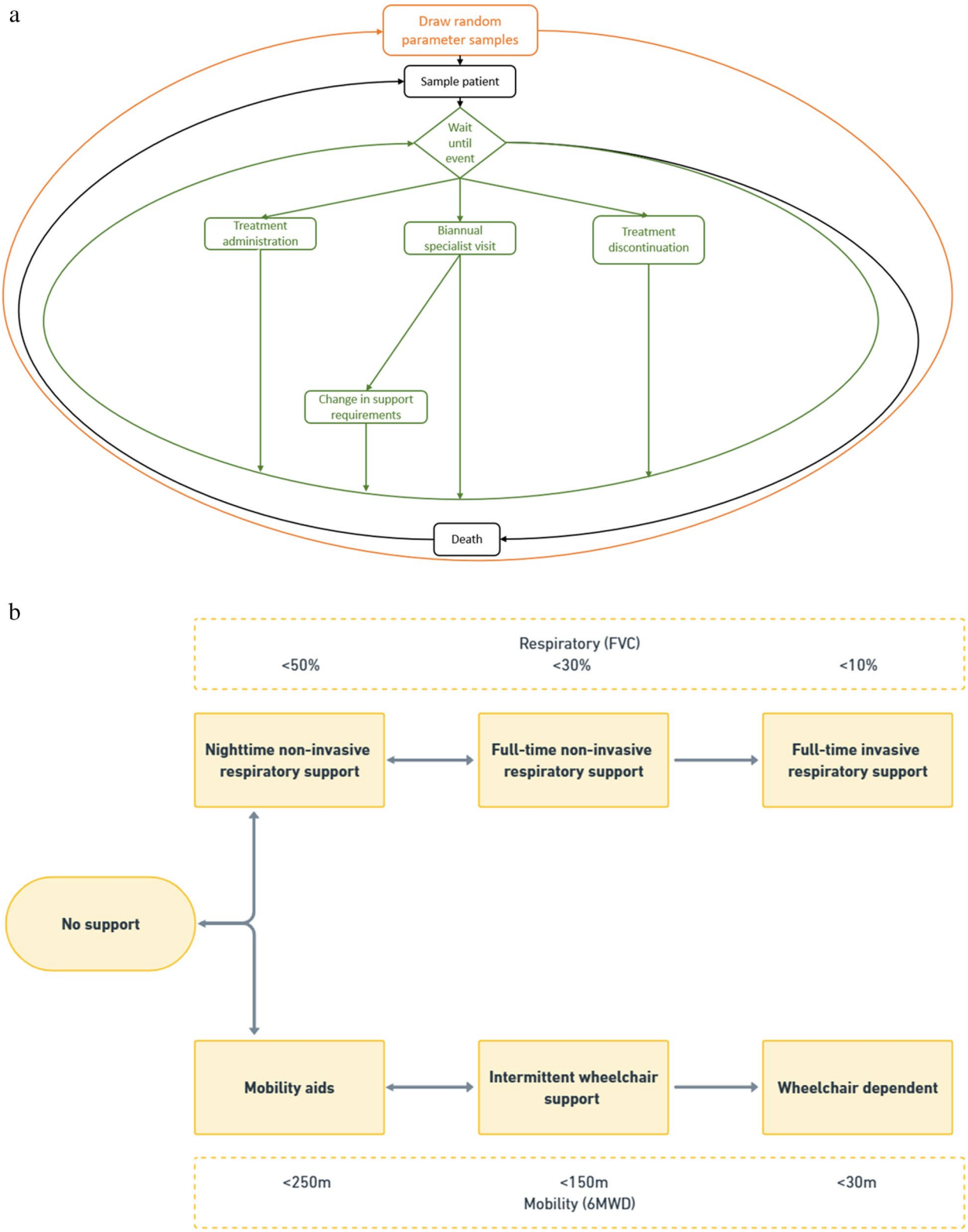

Fig. 1 Model schematic **a**) Discrete-event simulation superstructure; **b**) Modelled progression of support requirements

Table 1 Modelled treatment effectiveness data

Outcome	BSC (SD)	Alglucosidase alfa (SD)	Avalglucosidase alfa (SD)	Cipaglucosidase alfa + miglustat (SD)	Pooled ERT (SD)
Mean change from baseline to 1 year (vs to BSC)					
6MWD (m)	1.22 (7.69)	24.68 (10.62)	53.55 (17.19)	19.29 (18.69)	24.66 (5.6)
FVC % predicted	−1.95 (0.89)	3.58 (3.09)	6.01 (4.41)	3.11 (4.79)	1.69 (1.55)
Source	NMA[21]	NMA[21]	NMA[21]	NMA[21]	
Mean change from baseline to 2 years					
6MWD (m)	−6.39%*	21.3 (78.0)	18.60 (77.8)	38.8 (51.0)	25.01 (74.4)
FVC % predicted	−2.29 (1.33)	0.8 (6.7)	2.65 (6.9)	−4.8 (6.5)	0.57 (6.74)
Source	van der Meijden et al. [29] Harlaar et al.[30]	LOTS [31, 32]	COMET [25, 26]	PROPEL [33]	
Mean annual change beyond 2 years					
6MWD (%)	−6.39*	−2.3 (0.6)	−2.3 (0.6)	−2.3 (0.6)	−2.3 (0.6)
FVC % predicted	−2.29 (1.33)	−1.1 (1.15)	−1.1 (1.15)	−1.1 (1.15)	−1.1 (1.15)
Source	van der Meijden et al. [29] Harlaar et al. [30]	Semplicini et al.[27] Harlaar et al. [30]	Semplicini et al. [27] Harlaar et al.[30]	Semplicini et al. [27] Harlaar et al. [30]	Semplicini et al. [27] Harlaar et al. [30]

* Average based on 2.78 × Semplicini et al. ERT rate

the respective survival benefits from trial data. Baseline mortality rates were based on UK Office for National Statistics (ONS) Life Table data [35]. Gompertz models were independently fitted to mortality data for males and females, which were used to sample time to death at the model outset based on each patient's age and sex. To reflect excess mortality associated with a patient's symptoms, standardised mortality ratios (SMRs) were applied to more severe health states. This approach ascribes a survival advantage to treatments which prevent patients entering the most severe health states for longest. Modelled SMRs are derived from Gungor et al. [36], as summarised in the supplementary materials (Table 3).

Health-related quality of life

Health state utilities were identified through a literature search, but none of the value sets identified fully captured the range of possible health states included in the model. MacCulloch et al. [23] derived regression models from the PROPEL study, describing the relationship between 6MWD, FVC %, and EQ-5D. Due to the collinearity of these outcomes, only 6MWD was a significant independent predictor of HRQoL. We therefore did not consider it appropriate to adopt the composite utilities based on the fitting of separate models to FVC and 6MWD.

Table 2 Effective modelled health state utilities predicted by MacCulloch et al. regression model

Health state	Effective EQ-5D
Mean baseline utility	0.687
Use of mobility aids	0.610
Intermittent mobility support	0.555
Wheelchair dependent, no invasive respiratory support	0.489
Wheelchair and invasive respiratory support dependent	0.286

The base case model therefore uses the MacCulloch et al. regression equation centred on mean 6MWD, allowing a continuous relationship between a patient's current 6MWD and EQ-5D-3L to be estimated, and updated in parallel throughout the model time horizon. Covariate values were sampled from a normal distribution around the published means, with age and sex-specific utility adjustments applied based on Ara and Brazier [37].

To account for the strong aversion to intubation expressed by patient and clinical experts, and additional permanent utility decrement of 0.186 was applied to patients in the full-time invasive respiratory support health state. This value is based on the difference between EQ-5D-5L ratings by the general public of vignettes describing a wheelchair dependent health state and a wheelchair dependent *and* respiratory support-dependent health state, as reported in Hubig et al. [38]. Effective modelled utilities as predicted by the regression equation are illustrated in Table 2. These values broadly resemble those accepted in TA821 [17], which applied a baseline health state utility of 0.652, a utility reflecting wheelchair use of 0.504, declining to 0.397 in those also in receipt of invasive respiratory support. The present analysis thus places a higher value on treatments which slow progression to more severe health states.

Treatment acquisition and administration

Drug acquisition costs for all ERTs were based on their respective unit costs in the British National Formulary [39]. It is important to note that confidential discounts on the list prices of avalglucosidase alfa, cipaglucosidase alfa, and miglustat have been negotiated as part of the NICE appraisal processes. As such, analyses including all comparators assume that treatments are discounted to achieve parity in pricing with alglucosidase alfa at list price. Threshold analysis is also used to identify the level of discount necessary to achieve cost-effectiveness.

The dosing of all ERTs is weight-based, thus the number of vials required per infusion was based on the weight of the sampled patient and the recommended dose per kilogram of body weight. Dosing is based on the respective SmPC for each product [40–43]. ERTs are all infused every two weeks at a dose of 20 mg per kg bodyweight. Miglustat is in the cipaglucosidase alfa arm at a dose of 195 mg for patients weighing ≥ 40 kg to < 50 kg, and 260 mg for patients weighing ≥ 50 kg. The model assumed that vial sharing does not occur. Modelled treatment acquisition costs are presented in Table 3. It was assumed that the first three administrations of ERT would occur in hospital, followed by at-home delivery by a nurse.

Health state resource use

Resource use frequency and cost items was based on those accepted in NICE TA912 of cipaglucosidase alfa with miglustat, with costs updated using the 2023/24 National Cost Collection for the NHS [44]. Other costs were inflated to the 2024 cost year. Health state resource use costs are summarised in Table 4 in the supplementary materials. Health state costs were sampled from a gamma distribution, assuming a standard error of 10% of the mean.

Generation of results and scenario analysis

The base-case analysis considered the lifetime cost-effectiveness of ERTs as a class compared to BSC for treating LOPD. The base case uses the efficacy and list price of alglucosidase alfa as a proxy for ERTs, with threshold analysis used to identify the discount necessary to achieve cost-effectiveness at £30,000 and £100,000 per QALY gained. The analyses presented attempt as a principle to apply inputs most favourable to ERT and can be seen as a generally optimistic interpretation of the evidence available.

Table 3 Treatment acquisition and related costs

Variable	Value	Reference
Alglucosidase alfa (50 mg)	£356.06 per vial	BNF [39]
Avalglucosidase alfa (100 mg)	£783.33 per vial	
Cipaglucosidase alfa (105 mg)	£987.00 per vial	
Miglustat (65 mg capsules)	£700.14 per pack (24 units)	
Treatment administration costs		
Hospital cost per administration	£152.00	NHS Reference Costs 2023–24 [44]
Band 6 nurse cost/hour	£57.00	PSSRU 2023 [45]
Cost of nurse time per administration	£285.00 (£57 × 5 h)	

The base-case analysis included the following data sources and assumptions:

- Clinical equivalence of ERTs based on NMA results for alglucosidase alfa
- Efficacy between Month 12 and 24 based on LOTS extension study
- 60-year (lifetime) time horizon
- Invasive respiratory support associated with disutility of 0.186
- Discontinuation based on van Kooten et al. (1.5% per annum)
- ERT withdrawn when patients become dependent on invasive respiratory support and are wheelchair dependent.

All analyses were run using 4000 probabilistic iterations, each using a cohort of 250 sampled patients (i.e., total 1,000,000 total simulations per intervention). This was more than sufficient to achieve first- and second-order convergence and allowed a large number of different parameter permutations to be propagated through a wide range of patients. Incremental cost-effectiveness ratios (ICERs) and net health benefit (NHB) at willingness-to-pay thresholds of £30,000 and £100,000 were used, the latter value reflecting that a comparison with BSC may hypothetically be made within the HST framework, where higher thresholds may be applicable. The base case is also replicated in a fully incremental analysis of each ERT, based on the results of the NMA and pooled extension study outcomes between Month 12 and 24.

The following scenario analyses were also explored in the results to assess the sensitivity of the model to a range of alternative assumptions and data sources:

- Scenario 1: ERT efficacy up to 1 year based on class effect Bayesian NMA in which evidence from all ERT was pooled and compared (naively) to the placebo (BSC) arm of the LOTs trial.
- Scenario 2: Long-term 6MWD progression on BSC 10 × that of ERT
- Scenario 3: Long-term 6MWD progression on BSC 1.5 × that of ERT
- Scenario 4: Excess mortality only experienced by patients on invasive respiratory support
- Scenario 5: No stopping rule applied for patients on invasive respiratory support
- Scenario 6: Invasive respiratory support required at 30% FVC, full-time non-invasive support at 40% FVC.

The model was validated using detailed patient- and iteration-level outputs of outcomes, disease progression, and event timing to ensure clinical face validity of individual

iterations and long-term outcome projections, and alignment with the model input data. The model was independently validated by a second economic modelling expert (RH) using the TECH-VER checklist. [46] Two UK clinical experts (RL and CLT) confirmed the face validity of clinical and resource input data and the model outcomes.

Results

Results of the base-case analysis are presented in Table 4, and the distribution of simulation results can be found in Fig. 2. ERTs generated 1.64 additional QALYs on average relative to BSC, at an incremental cost of £3,257,645, yielding an ICER of £1,991,975, and a NHB of −107.0 at a threshold of £30,000 per QALY gained, and −30.9 at a threshold of £100,000 per QALY gained, which could be interpreted as representing the QALYs lost from the NHS population for each LOPD patient treated. There was a 0% probability of cost-effectiveness at WTP thresholds of £30,000 and £100,000 per QALY gained.

Whilst commercial in confidence discounts on the list prices of avalglucosidase alfa and cipaglucosidase alfa with miglustat are in place, reducing the acquisition cost of these medicines to the NHS, threshold analysis showed a discount of 89% would be necessary in order for ERT to have a probability of over 50% of being the most cost-effective treatment option at a WTP threshold of £100,000 per QALY gained, while a discount of 92.3% would be needed for cost-effectiveness at a threshold of £30,000.

Table 4 Base-case and scenario analysis results

Intervention	Total			Incremental		ICER	WTP £30,000		WTP £100,000	
	Costs	LYs	QALYs	Costs	QALYs		NHB	CE prob	NHB	CE prob
Base-case analysis										
BSC	£629,668	19.35	5.82							
ERT	£3,887,313	22.12	7.46	£3,257,645	1.64	£1,991,975	−107.0	0.00%	−30.9	0.00%
Base-case analysis (threshold analysis – 92.3% discount off ERT list price)										
BSC	£629,668	19.35	5.82							
ERT	£676,605	22.12	7.46	£46,937	1.64	£28,701	0.1	63.08%	1.2	93.08%
Base-case analysis (threshold analysis – 89.0% discount off ERT list price)										
BSC	£629,668	19.35	5.82							
ERT	£791,397	22.12	7.46	£161,729	1.64	£98,894	−3.8	0.35%	0.02	54.50%
Base-case analysis (separate ERTs—fully incremental)										
BSC	£629,668	19.35	5.82							
Cipa.+mig	£3,864,698	21.61	7.32	£3,235,030	1.50	£2,160,425	−106.3	0.00%	−30.9	0.00%
Alglu	£3,887,313	22.12	7.46	£3,264,969	1.64	£1,991,975	−107.0	0.00%	−30.9	0.00%
Aval	£3,890,404	22.25	7.51	£3,268,495	1.69	£1,931,125	−107.0	0.00%	−30.9	0.00%
Scenario 1: ERT efficacy up to 1 year based on class effect Bayesian NMA, and pooled extension study data from 1 to 2 years										
BSC	£629,668	19.35	5.82							
ERT	£3,868,297	22.03	7.42	£3,238,629	1.60	£2,022,995	−106.4	0.00%	−30.8	0.00%
Scenario 2: Long-term 6MWD progression on BSC 10 × that of ERT										
BSC	£624,572	18.71	4.98							
ERT	£3,886,795	21.70	7.25	£3,262,223	2.27	£1,438,280	−106.5	0.00%	−30.4	0.00%
Scenario 3: Long-term 6MWD progression on BSC 1.5 × that of ERT										
BSC	£632,517	19.73	6.28							
ERT	£3,887,647	22.30	7.53	£3,255,130	1.25	£2,595,392	−107.3	0.00%	−31.3	0.00%
Scenario 4: Excess mortality only experienced by patients on invasive respiratory support										
BSC	£691,631	21.04	6.24							
ERT	£4,184,352	24.61	7.93	£3,492,721	1.69	£2,065,723	−114.7	0.00%	−33.2	0.00%
Scenario 5: No stopping rule applied for patients on invasive respiratory support										
BSC	£629,668	19.35	5.82							
ERT	£4,028,779	22.12	7.46	£3,399,111	1.64	£2,078,478	−111.7	0.00%	−32.4	0.00%
Scenario 6: Inv. respiratory support required at 30% FVC, full-time non-invasive support at 40% FVC										
BSC	£838,468	18.41	5.67							
ERT	£3,699,452	21.14	7.25	£2,860,984	1.58	£1,814,838	−93.8	0.00%	−27.0	0.00%

Alglu. alglucosidase alfa, *aval*. avalglucosidase alfa. cipa.+mig., *BSC* best supportive care, *ce. prob.* probability of cost-effectiveness, cipaglucosidase alfa plus miglustat, *ERT* enzyme replacement therapy, *FVC* forced vital capacity, *ICER* incremental cost-effectiveness ratio, *LYs* life years, *NHB* net health benefit, *NMA* network meta-analysis, *QALY* quality-adjusted life year, *WTP* willingness-to-pay, *6MWD* 6-min walk distance

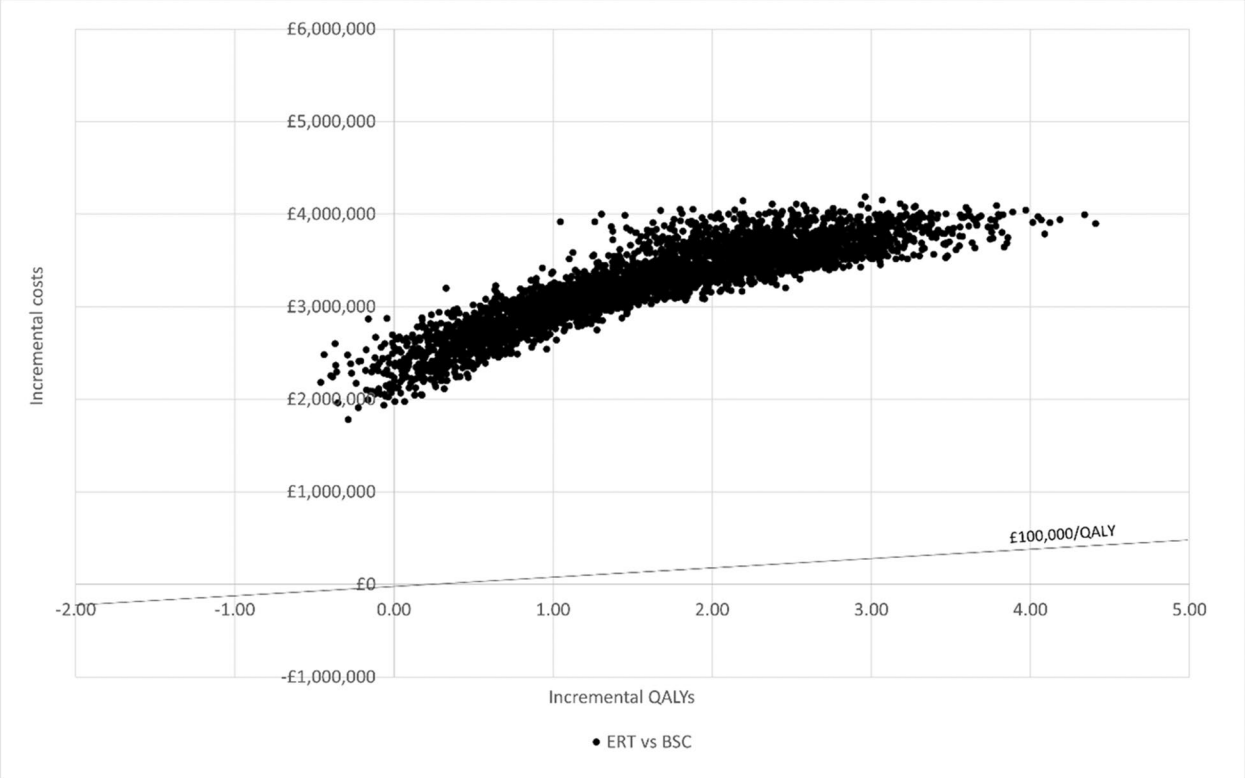

Fig. 2 Base-case cost-effectiveness plane

The results of scenario analysis suggest that there is unlikely to be a combination of alternative assumptions under which ERTs are a cost-effective use of resources. As shown in Table 4, model results demonstrate a degree of sensitivity to certain assumptions and parameter values. However, across all scenarios, ERTs consistently had 0% probability of cost-effectiveness. This is because the exceptionally high treatment acquisition costs cannot be overcome given the total number of available QALYs in this population.

Scenarios 1 and 4, addressing progression rates on ERT, excess mortality, have minimal impact on the ICER. In contrast, Scenarios 2 and 3, which examine the effects of varying assumptions about disease progression on BSC, lead to increased incremental QALY gains associated with ERT; however, ICERs remain significantly above NICE approval thresholds. Scenario 5 shows a large in treatment costs on ERT resulting from the removal of the stopping rule for patients requiring invasive respiratory support. Stopping treatment in such circumstances is a case-by-case decision, and as such may not always occur in practice—it is not a condition of reimbursement or specified in clinical guidelines. Scenario 6 raises the FVC % predicted thresholds for transitioning to full-time non-invasive and invasive respiratory support, substantially increasing BSC costs from £629,668 (base-case) to £838,468 due to earlier and prolonged use of invasive respiratory support. Despite this, the relative impact of scenario analysis on the ICER remains limited due to the high cost of treatment acquisition.

Value of information analysis, including expected value of perfect information (EVPI) and -partially perfect information (EVPPI) was undertaken. As there were no scenarios in which ERT had a probability of cost-effectiveness greater than 0%, there was no value in undertaking further primary research to resolve uncertainty around any of the modelled parameter estimates.

Discussion

This study presents the results of a simulation-based cost-effectiveness analysis integrating data from a Bayesian NMA, trial extension studies, and long-term observational sources to estimate the lifetime costs and benefits of ERT compared with BSC in an incident LOPD population. Our findings indicate that ERT is not cost-effective considering willingness-to-pay norms in the UK.

Our analysis predicted long-term benefits of ERT, including regained function and slowed disease progression, leading to QALY gains from both improved quality of life and extended survival. While slowed disease progression also modestly reduced supportive care costs, these savings were

insufficient to offset annual acquisition costs averaging £250,000 per patient. As a result, the base-case ICER for ERT exceeds £2 million per QALY gained, far in excess of typical NHS cost-effectiveness thresholds, even in the HST programme for rare conditions. Sensitivity and scenario analyses demonstrated that whilst the ICER was influenced by health state definitions and the rate of progression on BSC, even in the most speculatively optimistic scenarios the ICER remained above £1 million per QALY gained. Threshold analysis suggested that ERT prices would need to be reduced by 92.3% and 89% to be considered cost-effective at WTP thresholds of £30,000 and £100,000 per QALY, respectively.

Evaluation of model drivers suggests that structural barriers limit the ability of ERT to generate sufficient QALYs to offset treatment costs. LOPD is often diagnosed later in life, with modern supportive care enabling prolonged survival and independence. The RCT extension studies imply that a patient's initially significant response to a new treatment resulting from a clearance of accumulated glycogen build-up may quickly begin to fade. Long-term observational data also suggests that disease progression continues despite treatment with ERT, further narrowing the potential for significant health benefit relative to BSC. Together, these factors restrict the possible differential in long-term outcomes between ERT and BSC and indicate that even under conservative assumptions regarding BSC efficacy, the available QALY gains are insufficient to offset the high cost of ERT.

These findings have important implications for interpreting NICE's recent appraisals of avalglucosidase alfa and cipaglucosidase alfa with miglustat. Our results suggest that ERTs generate substantial negative net health effects for the broader NHS population. Moreover, they highlight potential limitations in NICE's appraisal processes.

By assessing the cost-effectiveness of new technologies against the established standard of care (SoC), the STA process implicitly assumes the baseline intervention was itself cost-effective against the previous SoC in a chain reaching back to a 'do nothing' approach. In this way, each successive generation of treatment should iteratively generate health benefits versus the last and mean that treating a patient is objectively the correct decision both for patients themselves, and the wider health care system. However, when a profoundly cost-ineffective SoC is used as a baseline, NICE's approach to HTA can entrench inefficiency and risk creating a ratcheting effect on expenditure in a given indication with each new generation of treatment.

Such situations are inevitable under NICE's approach to decision making when technologies have been commissioned outside of the agreed value framework. Current processes lack mechanisms to resolve the potential ramifications in terms of both budget impact, and the fair valuation of innovative technologies in future. With numerous potentially curative gene therapies for LOPD currently in development [47–52], this issue must be confronted to ensure patient access to the next generation of effective treatments.

Limitations and recommendations for future research

The limitations of this economic analysis primarily reflect the constraints of the available evidence. The focus on FVC % predicted and 6MWD in existing studies and historic HTA may overlook the broader benefits of ERT. Additionally, the systematic review and meta-analysis used to support the model raised concerns about the reliability of treatment effect estimates derived from the RCTs, which had small sample sizes (i.e. subject to influence by outliers). There is likewise a lack of robust long-term evidence on the durability of treatment effects over the long term.

Uncertainty remains surrounding several input parameters. For instance, HRQoL was based on the PROPEL trial population, which primarily comprised individuals at an earlier disease stage, and therefore did not capture HRQoL effects in advanced stages of LOPD, such as reliance on invasive respiratory support. The HRQoL impact on informal caregivers was likewise not captured in the analysis, though this is aligned with the NICE Committee's methodological preferences in TA912. Similarly, sparse mortality data in LOPD may limit the accuracy of predicted life expectancy on BSC, or the survival benefits associated with ERT. Despite these limitations, there was no decision uncertainty even under the most extreme input parameter assumptions, and it is highly unlikely that alternative specification of the economic analysis would alter the conclusion that ERT is not cost-effective.

Given the robustness of the model to alternative assumptions and parameter values and the lack of decision uncertainty, further research aimed at resolving parameter uncertainty is not justified. The only other example we identified of a comparison between ERT and BSC is from Kanters and colleagues [14], who compared alglucosidase alfa with BSC in The Netherlands. This model produced similarly high ICERs to the present study and suggested that identifying patients most likely to benefit from ERT (thereby optimising the target population) and exploring initiation and discontinuation rules could potentially improve cost-effectiveness. While such research may help reduce costs and improve cost-effectiveness, discussions with stakeholders have highlighted significant concerns regarding the acceptability of more restrictive policies which may limit access to treatment.

A more valuable focus for research would be on improving evaluation methods for high-cost technologies in future, particularly when cost-ineffective comparators are involved. This would help ensure that patients continue to have access to innovative and effective therapies in the future, while balancing the ethical considerations of providing expensive treatments for rare diseases with the need to ensure equitable access and sustainable healthcare funding.

Conclusions

This study reports the findings of a patient level simulation-based cost-effectiveness analysis evaluating ERT compared with BSC as a treatment for LOPD in a UK NHS setting. Our findings indicate that while ERT offers quality of life and survival benefits, its high cost results in ICERs far in excess of those considered an appropriate use of NHS resources. Even under the most optimistic assumptions, ERT remains cost-ineffective and is associated with significantly higher costs than possible QALY gains can justify. This means that ERTs are likely to generate very substantial negative net health effects for the wider NHS population.

Whilst the withdrawal of these treatments from current NHS practice is not proposed here, these findings highlight the long-term consequences of commissioning ERTs without an explicit value assessment, with significant implications not only for the efficiency of current NHS spending, but also for future decision-making. NICE should consider mechanisms within its HTA processes to address the legacy of inconsistent or out-of-process decisions in future appraisals. This may include the use of the multiple technology appraisal processes to re-evaluate all technologies in a given indication against BSC, ensuring a more consistent and sustainable approach to healthcare resource allocation.

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Declarations

Competing interests The authors have no competing interests declare that are relevant to the content of this article.

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