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Accounting for study heterogeneity when modelling the multi-state natural history of rare diseases.

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Introduction

Natural history modelling

In order to determine whether a new treatment can be reimbursed or funded, it is compared to the current standard of care in a cost-effectiveness analysis (CEA). A multi-state natural history model (NHM) can be used as the basis for comparing different strategies, representing the progression of a disease through different health states.

Rare disease context

However, constructing a NHM for a rare disease is more problematic since large cohort studies (which are ideal for populating NHMs) are usually unavailable. Data sources to populate the model are thus sparser and more heterogeneous. When combining these together, the heterogeneity should be accounted for as a failure to do so leads to biased predictions of lengths of stay in disease states [1], which are crucial to a CEA.

This analysis assessed the impact of a failure to account for study heterogeneity in a NHM on the results of a CEA. A variety of disease progression data for Duchenne Muscular Dystrophy (DMD) were used (described elsewhere [2]), with costs/utilities from the literature [3]. To illustrate how a new treatment (for DMD) could be assessed using a NHM, and what costs or effectiveness associated with this treatment would be required, a cohort was simulated with slower disease progression. The ICER threshold was set to £100,000 per QALY, since a treatment for a rare disease such as DMD would qualify as a highly specialised technology under NICE appraisal.

Methods

Disease structure

A five-stage multi-state NHM was adopted, based on ambulatory status and shown in Figure 1.

Accounting for study heterogeneity

Three methods for predicting disease progression rates/probabilities that account for the study heterogeneity in the data were compared to a method that simply grouped the data together with no adjustment and an assumption based method used by Landfeldt et al [3]. These three methods were: a one-stage frailty model; a two-stage model assuming proportional baseline hazards; and a two-stage model assuming stratified baselines [1]. Statistical details of the five methods are provided in the middle column. Note that methods 2-5 were fitted to the DMD data sources.

Analysis

Annual transition probabilities were calculated from the five methods (conditional on zero frailty for the one-stage frailty model). Annual costs and utilities were obtained from the literature [3]. A treatment cohort was simulated assuming a 25% reduction in the annual transition probabilities between transient states, with an annual cost of £100,000. Costs and quality adjusted life years (QALYs) were discounted at 3.5%. These (limited) assumptions were consistent with Landfeldt et al [3].

Various sensitivity and threshold analyses were undertaken to determine to what the incremental cost-effectiveness ratio (ICER) was the most sensitive.

Figure 1

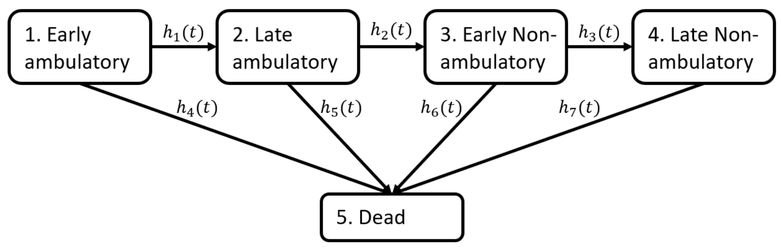

Figure 1: Structure of the DMD multi-state NHM.

Details of the 5 methods

Studies are denoted j, annual transition probabilities between states a and b as p_{ab}, and hazard functions on the k^{th} transition as h_k (with age as the timescale).

Method 1: assumption based approach

- $p_{12}(age) = p_{23}(age) = p_{34}(age) = 0.159$
- $p_{k5}(age) = \begin{cases} 0 & age < 18 \\ 0.094 & 18 \leq age < 35 \\ 0.094 * 1.15^{age-35} & age \geq 35 \end{cases}$

Method 2: no adjustment model

- $h_k(age) = \lambda_k \gamma_k age^{\gamma_k - 1}$

Method 3: one-stage frailty model

- $h_k(age) = \lambda_k \gamma_k age^{\gamma_k - 1} \exp(\alpha_{jk}), \quad \alpha_{jk} \sim N(0, \sigma_k^2)$

Method 4: one-stage frailty model

- $h_k(age) = \lambda_{jk} \gamma_k age^{\gamma_k - 1}$
- $\lambda_{jk} \sim N(\lambda_k, \sigma_k^2)$

Method 5: one-stage frailty model

- $h_k(age) = \lambda_{jk} \gamma_{jk} age^{\gamma_{jk} - 1}$
- $\begin{pmatrix} \lambda_{jk} \\ \gamma_{jk} \end{pmatrix} \sim \boldsymbol{N}\left(\begin{pmatrix} \lambda_k \\ \gamma_k \end{pmatrix}, \begin{pmatrix} \sigma_{\lambda k}^2 & Cov(\lambda_k, \gamma_k) \\ Cov(\lambda_k, \gamma_k) & \sigma_{\gamma k}^2 \end{pmatrix} \right)$

Table 1

Table 1: Lifetime differences in costs and QALYs and ICERs obtained from the five methods.

Method	Δ Costs (£)	Δ QALYs	ICER (£)
Assumption based	£1,517,000	0.772	£1,964,000
No adjustment	£1,520,000	0.325	£4,672,000
One-stage frailty	£1,427,000	0.307	£4,648,000
Two-stage proportional	£1,399,000	0.304	£4,605,000
Two-stage stratified	£1,229,000	0.324	£3,798,000

Figure 2

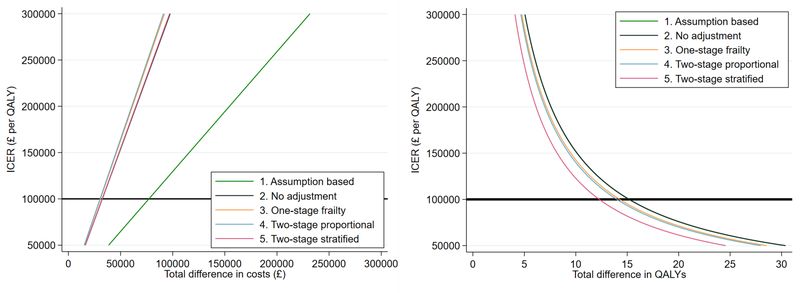

Figure 2: Threshold analysis on the total difference in costs and QALYs required to obtain an ICER of £100,000 per QALY.

Results

Base case

Table 1 shows the lifetime differences in costs and QALYs between the standard of care and (simulated) treatment cohort, and the ICER obtained from these, for each of the five methods.

The two-stage stratified method accounts for more between-study differences (since baseline hazards are not assumed to be proportional), and estimated the lowest difference in costs across the methods. The other data-based methods gave similar ICERs, with the no adjustment method giving an ICER £874,000 higher than the two-stage stratified method, while the assumption based approach estimated a much greater difference in QALYs and thus a significantly lower ICER. This was due in part to a greater difference observed in the time spent in the early ambulatory state for this method between the standard of care and treatment cohort, where quality of life is higher than later states.

Threshold and sensitivity analyses

Figure 2 shows the results of the threshold analysis to determine the required difference in costs and QALYs between the standard of care and treatment cohorts to obtain various ICERs.

Since the QALYs were very similar between the four data-driven methods, the required total difference in costs to obtain an ICER of £100,000 per QALY is also similar (£30,400 - £32,500). With the costs fixed, the two-stage stratified model required a total different of 12.3 QALYs to obtain an ICER of £100,000 per QALY.

The sensitivity analyses found the treatment cost to be the biggest driver of differences between methods, and of obtaining cost-effective ICERs.

Conclusion

Accounting for study heterogeneity is a key aspect of rare disease NHMs. Given the heterogeneity present in the data, it is likely that greater flexibility in modelling this variance (i.e. the two-stage stratified method) is preferable. The very large difference in ICERs between this and the no adjustment method shows the importance of appropriate modelling of study source regarding decision making.

While the results from this analysis are more intended as a proof of concept, it is worth noting that (even at the higher rare disease threshold) the ICERs obtained are far from being cost-effective. In order to be reimbursed, a new treatment would likely need to be more effective *and* cost less (such as a 50% reduction in transition probabilities at a cost of £5,000 - £6,000 per year).

References

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[3] E. Landfeldt, L. Alfredsson, V. Straub, et al. (2017) Economic Evaluation in Duchenne Muscular Dystrophy: Model Frameworks for Cost-Effectiveness Analysis, *Pharmacoeconomics* **35**(2): 249-258.

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