Modelling visual acuity distributions to inform a simplified cost effectiveness analysis

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Introduction

> Cost effectiveness models are an important step and requirement in seeking reimbursement recommendations from HTA bodies.
> Clinical trials in ophthalmology frequently focus on the mean change in visual acuity from baseline, however cost effectiveness models submitted to HTA bodies have frequently used a Markov structure with health states to group patients based on visual acuity scores to apply costs and utilities.
> Previous model structures are not without their limitations, with external assessment groups (EAG) commenting on the number of health states, the ability to replicate trial results in the models and assumptions required to incorporate evidence synthesis.[1]
> Additionally, accurately capturing the distribution rather than focusing on the mean change is an essential requirement when costs and utilities express a non-linear relationship with vision.
> Previous research in migraine has utilised parametric models to estimate the distribution around the mean migraine headache days to allow simplified modelling of the mean and reduce the number of health states, incorporating summary data and facilitate extrapolation.
> The aim of this research was to utilise learnings from other disease areas to facilitate a simplified cost effectiveness analysis structure that could lead to more accurate modelling. This aim was achieved by fitting parametric models to visual acuity data and seeing if the distribution of visual acuity could be modelled without the use of a Markov structure.

Methods

Dataset

> A review of freely available patient level data was conducted to identify the most appropriate dataset. Only a small number of trials were identified where patient level data was publicly available.[2]
> Most of the studies where patient level data were publicly available were conducted by The Diabetic Retinopathy clinical research network (DRCR), who have made trial data available for several trials that have been conducted.[3]
> Given the robust sample size and burden of disease, Protocol T which assessed treatment efficacy in patients with diabetic macular oedema (DMO), was selected.
> The DRCR Retina Network made available the patient level data collected from the Protocol T trials and have published the results of the analysis. [4]
> Protocol T was a randomised clinical trial that compared aflibercept, bevacizumab and ranibizumab for eyes with visual impairment from centre-involved DMO. During the Protocol T trial, a retreatment regimen was followed for 2 years, with patients asked to return after 5 years.

Distribution fitting

> The patient level data were used to fit negative binomial, beta binomial, and Poisson distributions to Early Treatment of Diabetic Retinopathy Study (EDTRS) scores. These distributions were deemed appropriate due to the discrete data that is bound between 0 and 100.
> The analysis fitted separate distributions at each study visit and for each eye, with a separate analysis to consider correlation between eyes.
> Analysis were conducted for the ITT population, this included patients whose vision was 'off chart' and therefore not captured on the EDTRS score.
> As the aim of the research was to fit a robust distribution to the data, treatment arm was not factored into the analysis however assessment of a multimodal distribution were considered.

Comparison to Markov health states

> To understand the differences between the distribution fitting and using Markov health states, utility values were applied to the patients EDTRS, the distribution fitted EDTRS and by Markov health state.[5]
> A comparison was then made between the true patient average utility compared to the two modelled approaches.

Outputs

> Distributions were considered through comparison across summary scores, goodness-of-fit statistics and visual inspection.
> For the comparison between average utility values, the outputs were considered through root mean square error.

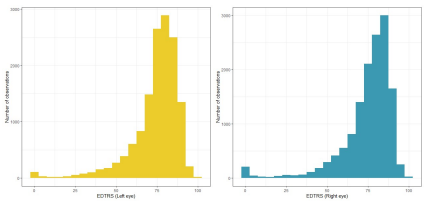
Sensitivity Analysis

> Scenario analysis considered alternative transformations of visual acuity, using logMAR scores and analysis of estimating Markov health state occupation based on mean score.
> Sensitivity analysis excluded patients which were 'off chart' , with a separate regression to estimate the proportion of patients who were 'off chart'.

Results

> The EDTRS scores for the left and right eyes showed a similar distribution, with a skewed distribution with a noticeable proportion of patients at 0 EDTRS, representing the off-chart patients.
> A histogram of the EDTRS is presented in **Figure 1**, grouping patients by 5 EDTRS which represents one line of vision.
> The summary scores of the EDTRS for the right eye and left eye were validated against the published analysis.

Figure 1. Histogram of EDTRS by eye



Results

> A heat map showed the EDTRS scores for the left and right eye, with most of the data concentrated in the top left, shown in **Figure 2**. However, patients with an EDTRS of 0 in either eye did not correlate with the other eye suggesting that being off chart in one eye is not a predictor of vision in the other eye.
> The distribution of EDTRS by study visit (**Figure 3**) showed some changes in the characteristics of the distribution, with the later follow up visits showing a less skewed distribution. This may be explained by inclusion criteria and the impact of treatment.

Figure 2. Heat map of EDTRS by eye

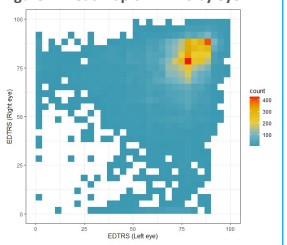
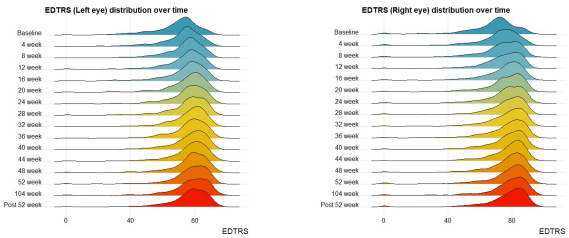


Figure 3. Distribution of EDTRS by eye by visit



> The distributions fitted to the data are presented in **Figure 4**, with the Poisson distribution been considered the best fitting curve
> Excluding 'off-chart' patients, presented in **Figure 5**, improved the analysis with the negative binomial and normal distribution being closer to the observed data, however the Poisson distribution being the best fitting.

Figure 4. Comparison across fitted distributions

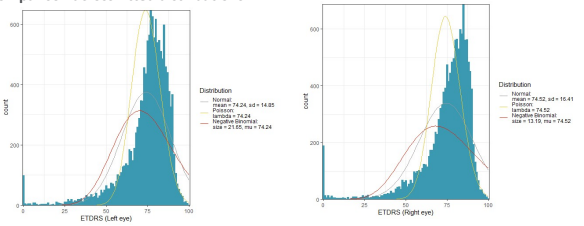
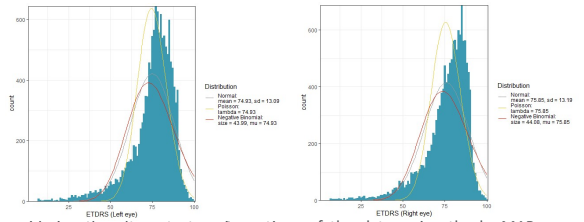


Figure 5. Comparison across fitted distributions, excluding patient with 0 EDTRS



> When considering the alternate transformations of the data, using the logMAR score didn't improve the fitting and the results remained consistent.
> The average utility based on the patient data were similar for the three approaches given simplifying assumptions to apply utility values dependent on vision in both eyes.

Conclusions

> Visual acuity data from DMO patients presents a challenge to fitting robust distributions due to the heavily skewed distribution. This study shows that this approach still offers a valuable modelling option when no patient-level data is available.
> This study offers an independent review, aiming to address feedback from EAG.
> A key limitation of this analysis is that the accuracy of the distribution could be assessed more robustly in a full cost-effectiveness model, where the differences in approach would be assessed based on impact to ICERs and potential to impact HTA decisions.
> For a distributional approach to be implemented further research into correlation would be beneficial as the legal definition of blindness is based on vision in both eyes.
> Additionally, further research would be required to explore the distribution of response to treatment and if those that response to treatment need to be tracked separately to those that don't to maintain the accuracy of the modelled distribution.
> This approach has many advantages, the primary advantage is the reduced data requirement for cost effectiveness models in ophthalmology and allowing direct input of mean visual acuity allowing for alignment between trials and evidence synthesis.
> This approach could be further explored in other ophthalmic diseases to see if one distribution is possible or if different equations are required for different diseases.
> The analysis was restricted by the limited data available for the patients who are off chart and the severity of disease.

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