Economic modelling in ophthalmology – reimagining cost effectiveness model structures

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Introduction

> Economic modelling in ophthalmology presents unique challenges that distinguish it from other disease areas.[1] The most notable are patients may be impacted bilaterally or unilaterally and patients' quality of life is a function of vision in both eyes.
> To address these unique challenges, previous attempts at economic modelling have taken complex methods and/or had significant data requirements. Alternatively, models have simplified the decision problem through assumptions.[1-4]
> Since the first NICE submissions in ophthalmology, there has been substantial improvement in the amount of data collected, duration of follow up and the endpoints collected. Additionally, there has been extensive research into what is important for patients' quality of life.
> Recent cost-effectiveness models in diabetic macular oedema (DMO) use a state-transition Markov model, with health states based on visual acuity scores, first eye affected with second eye included and treatment pathways.
> The aim of this research was firstly to analyse trial data to understand the importance of addressing the unique challenges in ophthalmology. Secondly the research aimed to understand if established cost-effectiveness model structures could be redesigned to address key challenges.

Methods

Trial data analysis

> Publicly available clinical trial data from the Diabetic Retinopathy Clinical Research (DRCR) network was used, focusing on patients with DMO from the Protocol T trial.
> Patients were treated unilaterally regardless of second eye involvement. Therefore, separate analyses were conducted for patients who had bilateral DMO vs. unilateral DMO.
> Treated and untreated eye visual acuity were also classified to determine if patients treated in the better seeing-eye (BSE) or worse seeing eye (WSE). This was assessed at each visit.
> Visual acuity was assessed using ETDRS, which is on a scale of 0-100. For the comparison with published model structures, ETDRS health states of 85+, 71-85, 70-56, 55-41, 40-26 and <26 were used.
> The trial collected data every 4 weeks for 52 weeks, and again at week 104. Unscheduled visits collected data as either pre or post 52 weeks. Unscheduled visits were excluded from the analysis due to low sample size.

Assessment of better seeing-eye status

> To assess the proportion of patients treated in their better seeing-eye, descriptive statistics were reported.
> To determine if the change in treated eye status was linked to treatment efficacy, assessment was conducted at each study visit for the total population and stratified by randomised treatment.

Assessment of correlation in vision of the second eye

> Initial assessment explored the change from baseline in the fellow eye, considering patients who were impacted bilaterally or unilaterally.
> To assess the importance of modelling the second eye, the correlation of the change from baseline was conducted between the first eye and fellow eye.
> Bilaterally impacted patients were expected to see a change in vision over time however patients who were unilaterally impacted experiencing change in visual acuity would impact the assessment of BSE status.
> Correlation was assessed from study visit week 28 onwards, to avoid potential bias from inclusion criteria.
> Correlation was assessed using Pearson, Kendall and Spearman tests.

Distribution fitting

> Using study observations from week 28 onwards, distributions were fitted to the observed data across ETDRS scores.
> Distributions were by initially using a Cullen and Frey graph in R, the recommended distributions were further investigated and assessed for goodness of fit.

Estimating the proportion of patients classified as blind

> The definition of blindness is based on vision in both eyes, requiring patients to have less than 35 letters or fewer in the better seeing-eye. This presents a unique challenge for Markov models where the BSE status may be unclear and the proportion of patients whose second eye is below the threshold not being explicitly modelled.
> To support simplifying assumptions for economic models, the probability of patients being classified as blind based on mean visual acuity and change from baseline was conducted through simple logit regression.

Comparison with multi-state modelling

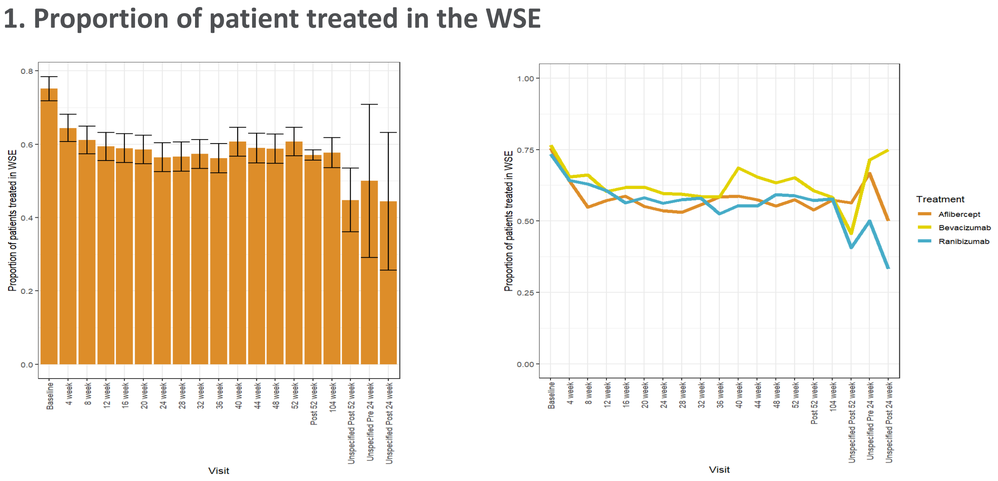
> To assess the suitability of modelling visual acuity through a distribution based on summary data, a comparison was conducted compared to multi-state-modelling (MSM) approaches which have been used to generate transition probabilities for cost-effectiveness models in DMO.
> The MSM used endpoints commonly reported across clinical trials to generate transition probabilities.
> When comparing the distribution approach to established MSM methods, goodness of fit was assessed using mi mean absolute error (MAE) and mean square error (MSE) metrics to assess predictive accuracy compared to observed data.

Results

Treated eye status

> The proportion of patients treated in the WSE was shown to vary over time, with a significant drop from baseline to week 4. From week 4, the proportion stabilises with no significant fluctuations.
> When considering the change by treatment arm, all treatment arms saw a decrease from week 4, however aflibercept saw a continued decrease to week 8. There are noticeable differences for bevacizumab at week 40, however, no differences were statistically significant.

Figure 1. Proportion of patient treated in the WSE



Correlation in visual acuity

> The correlation between eyes showed a positive correlation in most cases, the figure shows the correlation between the non treated and treated eye.
> The change in visual acuity were aligned across treatment arms, with no statistically significant difference.
> Assessment of correlation suggested positive statistically significant correlation at week 104 for the total population.
> The distribution across ETDRS by eye showed a more notable increase in over time in the treated eye, this is partially likely due to entry criteria.

Figure 2. Correlation between eyes

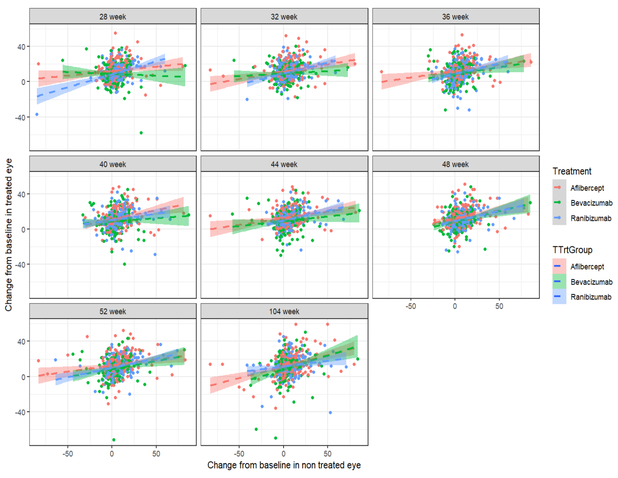
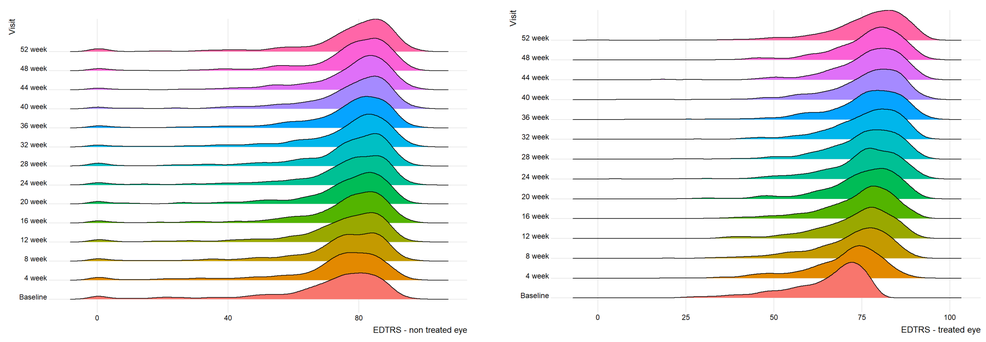


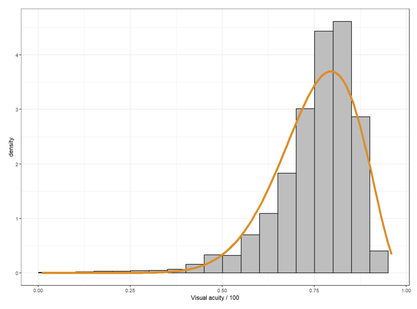
Figure 3. Distribution across ETDRS



Distribution fitting

> Assessment of the data suggested gamma, lognormal and negative binomial would be viable distributions. These distributions struggled to address the truncated nature of the data.
> A beta distribution is presented, showing potential for ETDRS data to be modelled through a distribution.

Figure 4. Fitted distribution



Blindness estimate

> Logit regression models including change from baseline as covariates produced good predictability, and improved outcomes compared to lagged absolute ETDRS, baseline ETDRS and other patient demographics.

Goodness of fit compared to MSM

> Comparison with MSM showed that the distribution approach could produce comparable results for later timepoints, however for timepoints less than week 28 the distribution approach was less accurate than MSM modelling.

Conclusions

> The analysis showed the importance of modelling both eyes and the interaction between eyes through assessment of correlation over time. As the second eye changes visual acuity, explicit modelling of BSE/WSE status would allow for accurate outcomes.
> Economic model structures using mean change in BCVA instead of time-dependent transition probabilities have the potential to simplify cost-effectiveness model structures and use endpoints reported from trials, enabling easier extrapolation.
> The impact of this research in cost effectiveness modelling would provide valuable context.
> Further research on modelling ETDRS distributions would be beneficial, as the approaches considered struggled to capture the nuances of the data, particularly its truncated nature.

References

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