DYNAMIC SURVIVAL MODELS FOR INCORPORATING EXTERNAL EVIDENCE WHEN EXTRAPOLATING OVERALL SURVIVAL: A CASE STUDY.

The University Of Sheffield.
School Of Health And Related Research

Kearns B[1], Stevenson M[1], Triantafyllopoulos K[1], Manca A[2],
[1]The University of Sheffield [2]The University of York

Background

Generating extrapolations of overall survival is often a key task in economic evaluations. As extrapolation goodness of fit cannot be assessed, considering clinical plausibility is important. We illustrate this using an existing evaluation, for which two extrapolation approaches had been used. Both approaches had limitations, with the plausibility of their extrapolations criticised. Cost-effectiveness estimates were sensitive to the extrapolation method used. This re-analysis introduces dynamic relative survival models (DRSMs) and demonstrates how they can provide plausible extrapolations by incorporating general population mortality.

Existing NICE technology appraisal [1]

Decision problem:
Compares nivolumab against current practice (docetaxel) for previously treated squamous non-small-cell lung cancer. Two-year follow-up showed reduced deaths with nivolumab [2]. The submission used a 3-state partitioned survival model, which was assessed and critiqued by an independent evidence review group (ERG). Extrapolations of overall survival were identified as key drivers of cost-effectiveness.

Original extrapolation approaches:
Company: Fit parametric models to the entire data. Choose log-logistic based on within-sample goodness of fit and clinical plausibility. Survival gain = 1.31 years. Incremental cost-effectiveness ratio (ICER) = £86,000.

Limitations: Extrapolates a decreasing hazard, which eventually falls below that of the general population. Does not reflect impact of ageing on hazard.

ERG: Use 40+ weeks data, fit exponential. Survival gain = 0.64 years, ICER = £132,000

Limitations: Ignores observed downward trend in hazard. Discards information. Arbitrary choice of 40+ weeks. Does not reflect impact of ageing on hazard.

Dynamic relative survival models:

A novel extension to dynamic survival models [3].

$$Y_t \sim \text{Poisson}\left(\left[\exp\left(\beta_{1,t}\right) + \lambda_t^P\right] * \tau_t\right)$$
$$\beta_{1,t} \sim \text{Normal}\left(\beta_{1,t-1} + \phi * \beta_{2,t-1}, Z_1\right)$$
$$\beta_{2,t} \sim \text{Normal}\left(\phi * \beta_{2,t-1}, Z_2\right)$$

Y_t is the number of deaths at time t, λ_t^P the general population hazard rate, τ_t the at-risk sample, ϕ a dampening parameter, $\beta_{1,t}$, $\beta_{2,t}$ are latent variables of time-varying level and trend for the ***excess*** (disease-specific) log-hazard.

Local level model: ϕ = 1, $\beta_{2,t} = 0$. Excess hazard extrapolations are constant.

Local trend model: ϕ = 1. Excess hazard extrapolations are linear.

Damped trend model: Excess hazard extrapolations are linear in the short-term, constant in the long-term.

Advantages: Uses all of the data, giving more weight to more recent outcomes when extrapolating. Can base model choice on clinical input into the likely long-term term behaviour of the excess hazard. Extrapolated hazards will never fall below general population hazards.

Health-economic re-analysis; methods and results:

We replicated the company's original submission [1]. Survival data were obtained by digitising results from the clinical trial [2]. All analyses were performed in R. Incremental life years, quality-adjusted life years (QALYs) and costs were 1.31, 0.76 and £65,355 in the original submission vs 1.27, 0.74 and £65,891 in the re-analysis.

Within-sample fit and extrapolations from the two original approaches and the three DRSMs are displayed in Figures 1 and 2, respectively for the docetaxel group. The DRSMs combine flexible within-sample fit with plausible extrapolations reflecting the impact of ageing and never fall below general population hazards. The DRSMs make different assumptions about the future excess hazard: for the local trend model it tends to zero, implying a cure. The remaining two models assume that there will always be an elevated risk of death due to the disease. ICERs (survival gains) were £86,000 (1.22) local trend; £106,000 (0.77) damped trend; and £120,000 (0.57) local level.

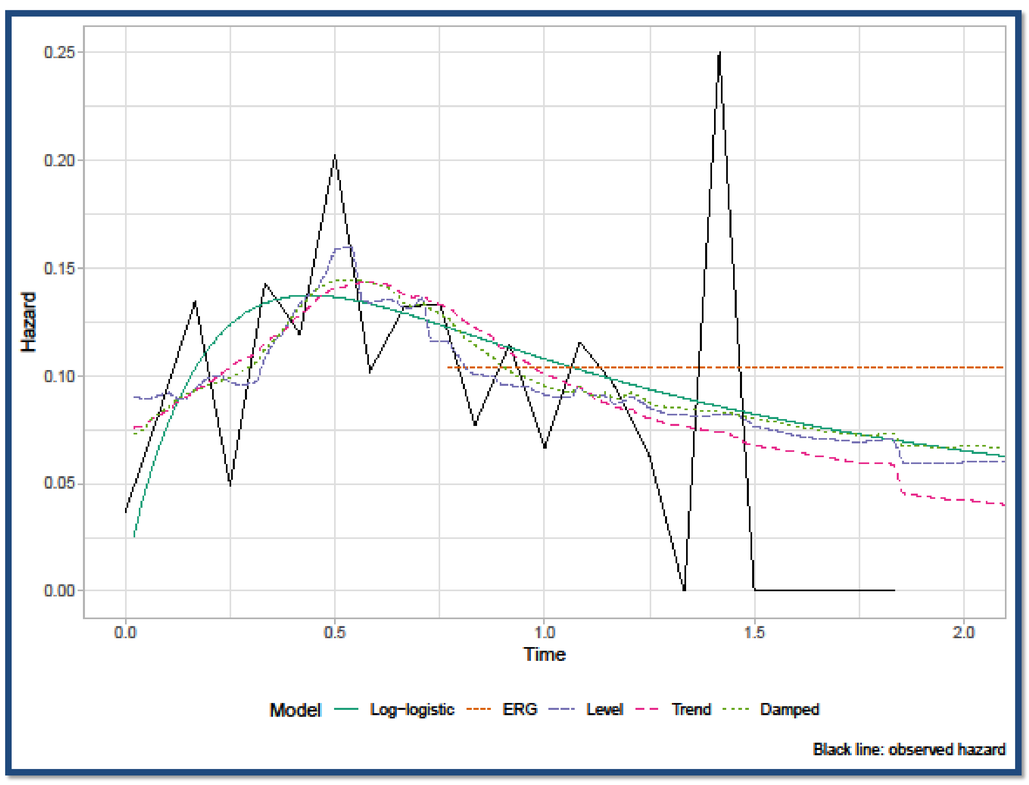
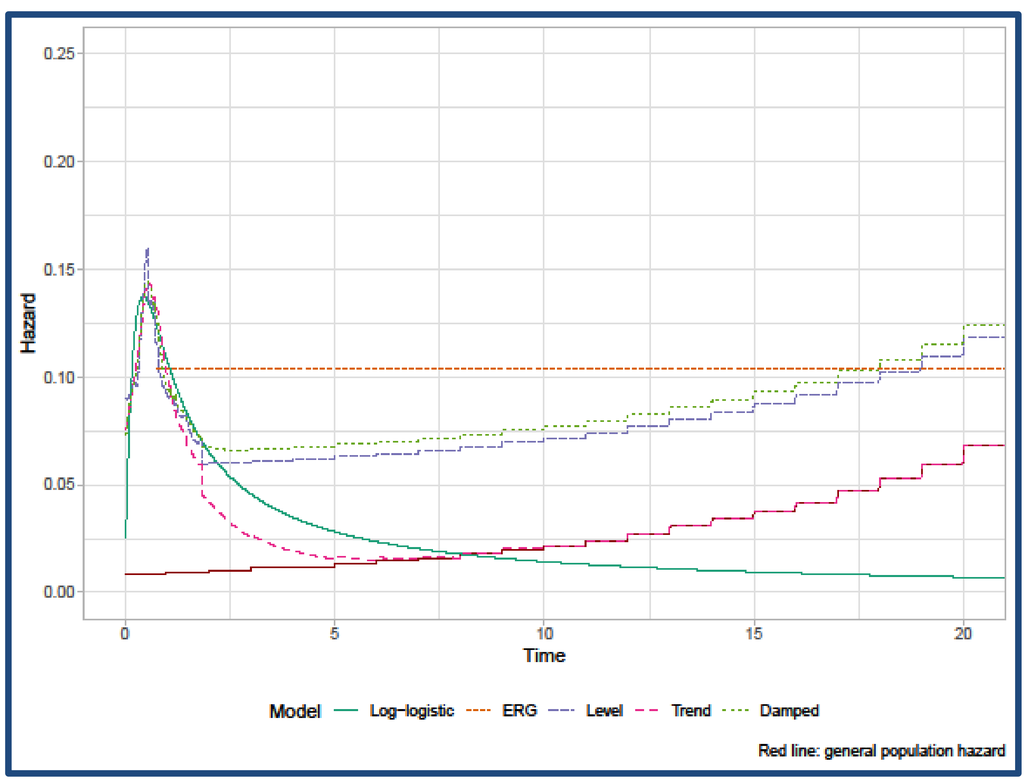


Figure 1 (left): Within-sample estimates and observed data.

Figure 2 (right): Extrapolations and general population hazards.

Data are for the docetaxel group; results were similar for the nivolumab group.



Conclusions

Dynamic models can incorporate all of the data without letting early outcomes unduly influence estimates at the end of follow-up. This is more efficient than discarding data before 40 weeks. DRSMs provide flexible within-sample fits, incorporating external evidence to give plausible extrapolations. Model choice may be based on clinical input into the natural history of the disease and treatment effects. Future work could assess model performance in simulation studies: see poster PNS327.

References: [1] NICE *Nivolumab for previously treated squamous NSC lung cancer* www.nice.org.uk/guidance/ta483 **[2] Brahmer J** *et al* (2015) *Nivolumab vs docetaxel in advanced squamous-cell NSC lung cancer* NEJM **[3] Kearns B** *et al* (2019) *Generalised linear models for flexible parametric modelling of the hazard function* MDM

Acknowledgements and funding: This research was funded by the NIHR Doctoral Research Fellowship (DRF-2016-09-119) 'Good practice guidance for the prediction of future outcomes in health technology assessment'. BK was supported in the preparation of this work by the HEOM Theme of the NIHR CLAHRC Yorkshire and Humber. www.clahrc-yh.nihr.ac.uk. The views expressed are those of the authors, and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Presented at ISPOR Europe 2019 (PCN444)

b.kearns@sheffield.ac.uk **www.scharrheds.blogspot.co.uk**
@benjaminkearns2
@scharrheds

FUNDED BY NIHR | National Institute for Health Research