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PRM119

An exploration of techniques for addressing uncertainty in survival estimates used within partitioned-survival models

Ash Bullement[1], Simone Critchlow[1]

1. BresMed, Sheffield, UK

Objectives

Survival outcomes from partitioned-survival models are typically associated with uncertainty, particularly in oncology where projections of long-term survival estimates heavily influence the cost effectiveness of products. Long-term survival estimates are of particular relevance where data are limited due to the duration of trial follow-up used to inform modelled survival.

However, no guidance exists on how best to address the uncertainty of survival estimates used to inform economic modelling. Guidance from the National Institute for Health and Care Excellence (NICE) states that when there is uncertainty regarding the most appropriate assumption to use for extrapolation of outcomes beyond trial follow-up, the impact of the uncertainty on estimates of cost effectiveness should be explored by separate analyses of a representative range of plausible scenarios.

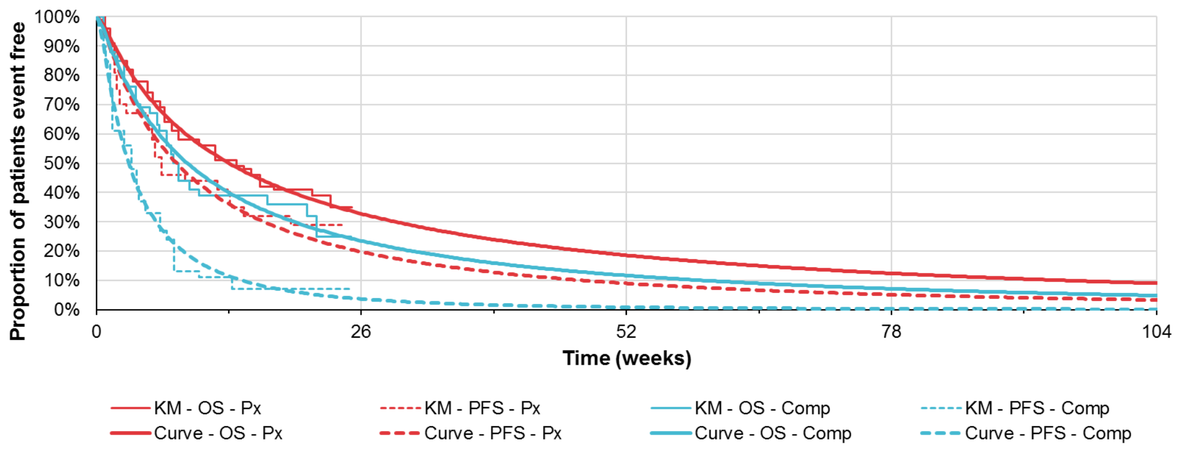
While NICE guidance suggests exploration of the potential uncertainty of curve fit type (i.e. choice of distribution), it does not consider the uncertainty of the parameters used to produce the curve itself.[1] This appears inherently counter-intuitive, given that individual curve fit parameters are typically sampled within a probabilistic sensitivity analysis (PSA). Our objective was to investigate alternative techniques for addressing survival uncertainty, along with recommendations for implementation in economic modelling in order to facilitate decision making.

Methods

A simplified replication of the three-state partitioned-survival model used to inform the technology appraisal of pixantrone for third-/fourth-line treatment of aggressive non-Hodgkin's lymphoma (NHL) (TA306) was used as a case study to explore possible techniques for addressing survival uncertainty.[2] This model was chosen due to the simplicity of the model structure and its generalisability to models constructed in similar disease areas.

The model comprises a simple three-state partitioned survival structure, where patients enter the model with pre-progressive disease, and then transition to post-progressive disease or death. The likelihood of moving between different health states was estimated using an area under the curve or partition approach informed by progression-free survival (PFS) and overall survival (OS) curves from the PIX301 trial.[3] Data were obtained via digitisation of published curves using specialist software, and a published algorithm was applied to recreate patient level data.[4] From these data, parametric curves were fitted. The base case parametric curve fits (log-normal for both PFS and OS) and the Kaplan-Meier plots are shown in **Figure 1**.

Figure 1: Base case curve fits and Kaplan-Meier plots



Key: Comp, comparator; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; Px, pixantrone.

A time horizon of 23 years is used in the model (reflective of the lifetime of patients with NHL), with a cycle length of 7 days and discounting applied at a rate of 3.5% per annum (in line with NICE guidance).[1] Further details regarding the model can be found within the company submission to NICE.[2]

A range of techniques used to report survival uncertainty were sourced from those applied in previous submissions to NICE, as well as original methods developed for this study. The methods we have considered are:

1. One-way sensitivity analysis (OWSA) of survival parameters – testing the impact that varying parameters to their lower and upper bounds (based on the 95% confidence interval [CI] for each parameter) has upon the model outcomes
2. PSA of all model parameters
3. Multi-way sensitivity analysis (MWSA) of survival parameters (95% CI) and probabilistic sampling of survival curves alone (95th percentiles)
4. PSA of survival parameters alone, as well as confidence ellipses for the PSA of all parameters, all non-survival parameters and survival parameters alone

Finally, we present a comparison of methods, providing a range of uncertainty in a summary tornado diagram.

OWSA and PSA are recommended for use within health technology appraisal submissions to NICE and other bodies as standard, and therefore, further details regarding these analyses may be found in the NICE Guide to the Methods of Technology Appraisal.[1] The results of these analyses are shown in **Figure 2** and **Figure 3**, respectively.

To extend these analyses, a MWSA was conducted to establish the uncertainty attributable to all survival curve parameters in combination. To do this, all parameters contributing to a given curve were varied using a multivariate normal distribution at 95% confidence limits. In addition, probabilistic sampling of survival curves was conducted by sampling the 95th percentiles of survival results and their associated cost-effectiveness results. The results are shown in **Figure 4**.

A PSA including survival parameters alone was carried out in order to ascertain the impact of varying survival parameters on the overall incremental cost-effectiveness ratio. Within this analysis, all survival parameters were sampled from their respective distributions while all other parameters were fixed at their mean values. The results of this analysis are also shown within **Figure 3**. To attach an example metric to the proportion of uncertainty directly attributable to survival, the area of each associated confidence ellipse was calculated from the probabilistic results and compared. This produced a comparable percentage area. Confidence ellipses and the associated proportion of uncertainty attributable to each set of parameters are shown in **Figure 5**.

Results and Discussion

Variation of individual curve fit parameters in isolation demonstrated relatively large uncertainty on model results, but failed to clearly establish the uncertainty regarding the survival of patients due to the intrinsic correlation that exists between related parameters. Individual curve fit parameter variation also presented somewhat misleading results, as alternate aspects of each curve provided dissimilar magnitudes of uncertainty in model results.

MWSA and probabilistic sampling avoided the issue of not exploring the uncertainty associated with the entire curve (as opposed to contributing factors to the curve), but these methods present additional issues. Both methods demonstrated very different measures of uncertainty, both in terms of the magnitude and primary direction of uncertainty, but were also associated with methodological challenges:

- The MWSA still considers the uncertainty of curve fit parameters, not necessarily the uncertainty associated with the curve itself. As these parameters are all sampled at their respective 95% CI limits, there is a risk of underestimating the joint uncertainty of all parameters in combination, and hence the survival curves themselves.
- When exploring MWSA, there is potential for underestimating uncertainty as testing the 95% CI limits of the curve parameters may not have the same directional affect, which may result in a reduced level of uncertainty compared to alternative methods. For example, the OWSA in **Figure 2** shows opposite directions of effect for the OS shape and scale parameters for the comparator and consequently causes reduced uncertainty in the MWSA in **Figure 4**.
- Probabilistic sampling with 95th percentiles demonstrates very large uncertainty, driven by a relatively large interval.

As expected, varying only survival parameters in the PSA resulted in a scatterplot of points that lie within the extended scatterplot where all parameters are varied. The two may be compared to establish the influence of survival parameters on overall model uncertainty. Confidence ellipses showed that 15.1% of the total probabilistic spread of uncertainty was directly attributable to survival parameters, with 69.0% directly attributable to the non-survival parameters. The remainder of the uncertainty was attributable to the two sets of parameters interacting when varied simultaneously.

Conclusions

We recommend the use of techniques that illustrate uncertainty in all survival estimates simultaneously to account for the correlation between relevant parameters, as this accurately reflects the uncertainty inherent in parameters. The methods that meet these criteria include the use of 'whole curve' techniques (considering the variation of curves for all treatments in combination), and PSA of survival parameters in isolation. These broader methods that explored "whole curve" uncertainty appeared to reduce overall uncertainty in model results (leaving them in line with clinical results), while also presenting easily communicable differences in likely survival.

Further work would aim to explore how these methods of exploring the uncertainty in survival impact on other modelling approaches (such as discrete event simulation, or Markov models with state-transition probabilities), as well as models constructed in different disease areas more complex statistical models for survival (such as spline curve fits). In addition, further work may consider the impact of varying sections of a curve that are associated with increased uncertainty (i.e. the extrapolated proportion of each curve).

References

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2. National Institute for Health and Care Excellence (NICE). TA306 Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 2014. Available at: https://www.nice.org.uk/guidance/ta306/history. Accessed: 01 October 2016.

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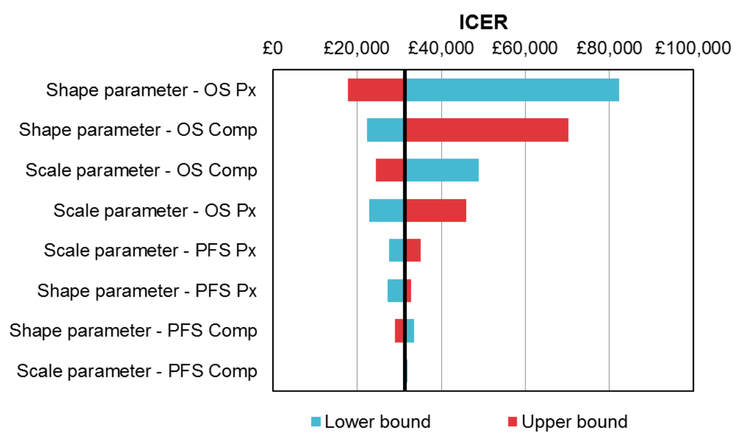
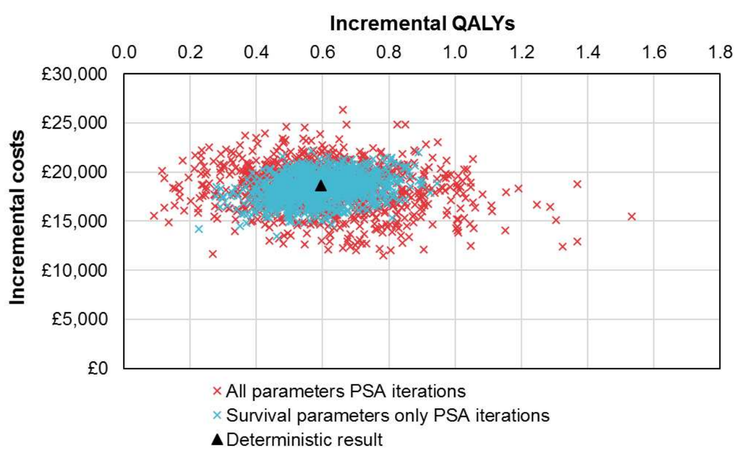
Figure 2: One-way sensitivity analysis of survival-only parameters



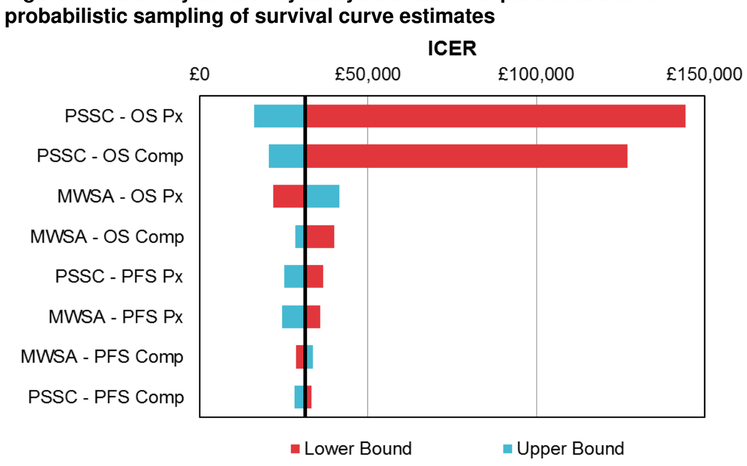
Key: Comp, comparator; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Px, pixantrone.

Figure 3: Probabilistic sensitivity analysis (all and survival-only parameters)



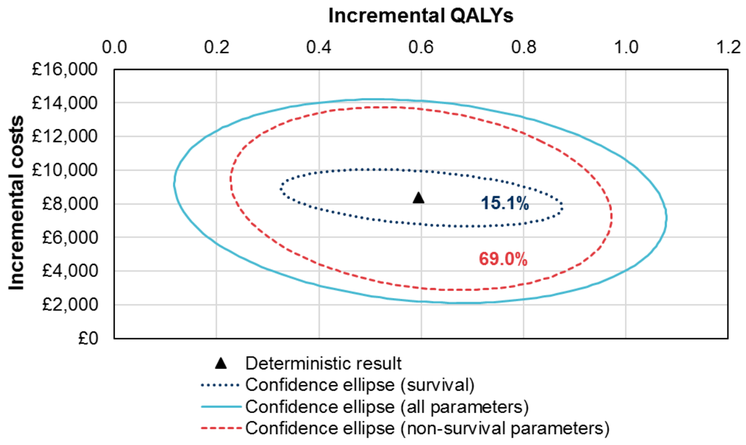
Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 4: Multi-way sensitivity analysis of survival parameters and probabilistic sampling of survival curve estimates



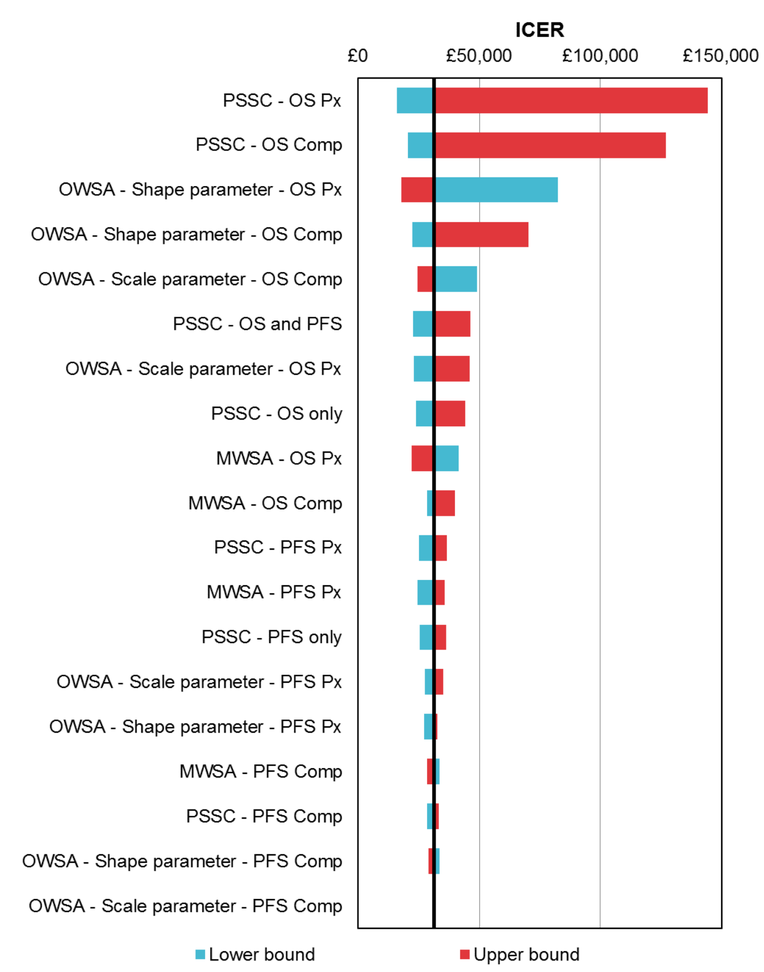
Key: Comp, comparator; ICER, incremental cost-effectiveness ratio; MWSA, multi-way sensitivity analysis; OS, overall survival; PFS, progression-free survival; PSSC, probabilistic sampling of survival curve; Px, pixantrone.

Figure 5: Uncertainty ellipses based on chosen varied parameters



Key: QALY, quality-adjusted life year.

Figure 6: Comparison of methods



Key: Comp, comparator; ICER, incremental cost-effectiveness ratio; MWSA, multi-way sensitivity analysis; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSSC, probabilistic sampling of survival curve; Px, pixantrone.

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