Assessing the best fitting distributions

The time horizon for cost-effectiveness analyses that use survival data needs to be long enough to capture differences in outcomes between interventions[1]. NICC recommend a lifetime horizon[2]. However, clinical trials are often limited in their follow-up time, meaning survival data is rarely complete. Thus, extrapolation methods are required.

In an idealistic environment, survival curves would be applied to achieve the greatest accuracy of results possible. However, clinical trials often do not publish IPD. Such trials will however report a Kaplan-Meier (KM) curve, created using the IPD. Statistics taken from KM curves are often not enough for performing meta-analyses and cost-effectiveness analysis. This means that acquisition of an estimate of the IPD from KM curves is important and possible.

Methods

Methods of survival extrapolation used in HTA submissions were analysed. One regularly used method fits a survival curve directly to a published KM curve, but does not incorporate numbers at risk. Two methods used to extract the IPD from KM curves reviewed in this paper are proposed by Guyot et al[3] and Hoyle and Henley[5] which are compared against the standard least squares method. Consider the one reported at time point 0 (1) when numbers at risk are available and (2) when numbers at risk are not available at the start. RESULTS. The three methods resulted in the least error by providing the best fit, with all containing the true mean and median within their confidence intervals (CI). However, the Hoyle and Henley method estimates a mean marginally closer to the true mean than the other methods in both scenarios. When many numbers at risk are provided, the Hoyle and Henley method gives narrower CIs. Both extraction methods slightly outperform the least squares method. The three methods give median estimates closely matching the true median up to 0.194 above the true mean, although the CI for the Guyot method is far narrower in this instance. However, because of the skewed nature of survival data, the median is considered a better estimator of the central location of the data than the mean[4]. Therefore, the accuracy of the estimated median is regarded as more important than the mean.

The median in all scenarios, besides the Guyot method without numbers at risk, is identical, suggesting the Hoyle and Henley method and the least squares method perform better. However, the Guyot method is more often used with numbers at risk given narrower CIs. Also, the least squares method performed equally well in estimating the median and saves time in calculation. Consequently, extracting the IPD is not necessary in this case.

Overall, the Hoyle and Henley method performs slightly better than the Guyot method, although there are benefits and drawbacks to both methods. It is worth recognising that all the methods discussed gave CIs which included the values from the true IPD, however the least squares method gave larger CIs than the two extraction methods, meaning there is a larger degree of uncertainty in the results.

Discussion

To improve the accuracy of survival estimates and give more informative cost-effectiveness results, it is recommended that sponsors of trials use the IPD to estimate the underlying survival distribution.

The results discussed in this poster apply solely to this example and should not be seen as the answer to whether extraction of IPD is necessary in all survival examples.

Conclusions

The results show that there is little statistical difference between the currently used method (Least squares) and the methods for extracting IPD, for this particular example. However, advantages such as the ability to better define the true uncertainty and easier comparison of two or more interventions are benefits and drawbacks to both methods. It is worth recognising that all the methods discussed gave CIs which included the values from the true IPD, however the least squares method gave larger CIs than the two extraction methods, meaning there is a larger degree of uncertainty in the results.

References