**Poster Abstracts**

**Death by a thousand cuts? A case study how different data cuts impact survival extrapolation**

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Health technology assessments (HTAs) of new medicines typically include evidence collected from a registrational clinical trial (or trials). At the time of submission, it is typical that limited data are available in terms of the duration of follow-up, based on a pre-specified interim analysis. This is commonly seen in appraisals of new cancer drugs, where survival data are available only up until a given time point (usually described in terms of either the minimum or median follow-up of the cohort). Consequently, there are knock-on effects for the extrapolation of time-to-event outcomes (e.g., overall survival [OS]) used to inform decision making. In this presentation, we investigate some of the implications of using interim clinical trial data to support HTA decision making, focusing on extrapolation of OS from the JAVELIN Merkel 200 (JM200) trial [NCT02155647] as a motivating case study. Results from a previous analysis of JM200 will be described, wherein parametric survival models were fitted to four sequential data cuts. Relevant examples from the literature will also be described. In addition, implications for the selection and justification of the most suitable model(s) for use in HTA will also be considered. We will provide a short summary of recommendations for researchers that may need to handle multiple sequential data cuts for the same clinical trial for use in an HTA submission, as well as highlighting where further research is required (and where relevant, where this is ongoing).

**Does HTA Need Adjusting for Multiplicity?**

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One main objective of pivotal phase III trials is to demonstrate that the drug is effective, which, through the use of hypothesis testing, allows formal and confirmatory conclusions to be drawn regarding the efficacy of the experimental drug. In contrast, HTA employs the principles of evidence-based medicine primarily to estimate the magnitude and level of uncertainty regarding treatment effects. Hypothesis testing within this setting is not relevant since a dichotomous ‘go/no-go’ decision of whether the drug is effective or not is no longer of interest. Despite this, many benefit dossiers submitted to HTA authorities for value assessments contain countless statistical comparisons via statistical testing under the assertion that they provide evidence of the strength of effect. Consequently, there are calls for a need to consistently apply multiplicity adjustments similar to those employed within the regulatory setting. This poster provides an account of the different types of multiplicity in HTA submissions in contrast to regulatory decision making.

**Survival extrapolation incorporating general population mortality using relative survival and cure models**

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Different parametric survival models can lead to widely varying extrapolations and decision uncertainty in cost-effectiveness analyses. The use of relative survival (RS) methods, with or without a cure assumption, has the potential to reduce variability. We highlight key practical considerations and demonstrate software application of RS methods for estimating long-term survival.

Methods

686 patients from the German Breast Cancer Study Group, with a mean follow-up of 3.6 years, were divided into low (1/2) and high (3) grade cancers. Seven standard parametric survival models were fit to each group separately and all-cause survival extrapolated to a 30-year time horizon. The same seven distributions were then used in a RS framework, which incorporated general population mortality rates from a US lifetable, and fitted both with and without a cure parameter. Survival extrapolations, restricted mean survival time (RMST) at 30-years and long-term effects between high and low grades were compared along with goodness-of-fit and cure fraction estimates. The sensitivity of the RS models to alternative lifetable specifications was investigated.

Results

Variability in the 30-year survival extrapolations was extensive across the parametric models, with 30-year restricted mean survival ranging from 7.5 years to 14.3 years. RS methods without cure showed similar variability, whilst RS cure methods substantially reduced this variability. Long-term effects of cancer grade approached the null for most models, but at varying rates. Alternative lifetable specification had minimal effect on RMST differences.

Conclusions

RS methods can reduce extrapolation variability and make explicit assumptions regarding long-term cure. These methods should be routinely considered when conducting extrapolation of all-cause survival.