PRM107

EXTRAPOLATING SURVIVAL IN A HETEROGENEOUS PATIENT POPULATION WITH METASTATIC MELANOMA; A CASE STUDY OF INTEGRATING STATISTICAL AND CLINICAL CONSIDERATION

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OBJECTIVES: While the follow-up time on Ipilimumab trials is in excess of 4 years, HTA models often require survival to be extrapolated to 10 years and beyond. However, patient level data on prognostic factors are rarely available; hence extrapolation methods assume a homogeneous study population and are based on statistical considerations only. Such approaches are criticized for disregarding clinical reality and may be biased. In this study a survival extrapolation model that accounted for heterogeneity was developed based on both statistically and clinically relevant considerations. The method was applied on survival data in patients with Metastatic Melanoma. **METHODS:** Survival data were taken from a randomized controlled clinical trial that compared dacarbazine plus placebo versus dacarbazine plus ipilimumab. Two parametric models were explored to extrapolate survival: a model assuming no heterogeneity in patients and another model that divided patients into three subgroups based on cancer stage observed at baseline and additionally included subpopulations of *a priori* unobserved long-term survivors. Survival of the subpopulations was extrapolated and summed to obtain survival in the overall population. Subgroup formation was guided by expert opinion of oncologists. The statistical and clinical validity of the models were assessed. **RESULTS:** Among commonly used distributions (exponential, Weibull, lognormal) the lognormal distribution fitted the survival data best in the no-heterogeneity model whereas Weibull distribution was used for the heterogeneity model. For statistical validity, both models fitted the data reasonably well. However, the no-heterogeneity model underestimated the long tail of the survival curves. The no-heterogeneity model implied decreasing mortality over time while the heterogeneity model implied increasing mortality, which is more clinically relevant. **CONCLUSIONS:** The no-heterogeneity model fitted the data reasonably well but was not relevant for extrapolation from a clinical perspective. The heterogeneity model captured the long tail of the survival curve best, and provided a statistically and clinically relevant model.

PRM108

BIVARIATE INDIRECT COMPARISON META-ANALYSIS MODEL IN ECONOMIC EVALUATION OF CANCER TREATMENTS

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OBJECTIVES: A three-state Markov model for cost-effectiveness analysis of cancer treatments requires information on both progression-free survival (PFS) and overall survival (OS). However, data is not always available on both of these outcomes. The objective of this study is to perform a Bayesian bivariate indirect comparison meta-analysis (BICMA) to obtain estimates of both PFS and OS for use in a cost-effectiveness analysis when data on these outcomes is incomplete. **METHODS:** In a UK Health Technology Assessment report on cost-effectiveness assessment of docetaxel with prednisone/prednisolone for the treatment of hormone-refractory metastatic prostate cancer, a two-state Markov model was specified using OS data from a single randomised controlled trial that did not report PFS. We propose the use of a Bayesian BICMA model that jointly estimates OS and PFS, and which in turn allows for the specification of a three-state Markov model incorporating a post-progression phase. Survival data for the trials included in the BICMA were reconstructed from survival curves, presented in the articles reporting the trials, using the method proposed by Guyot et. al. (*BMC Med Res Methodol* 2012;12:9) using the DigitizeIt and R software. **RESULTS:** The Bayesian BICMA model was designed to jointly model the correlated outcomes: OS and PFS using either non-informative or informative prior distribution on the correlation between the outcomes. An informative prior distribution on the correlation between PFS and OS was based on external evidence using prostate cancer trials presented in Halabi et. al. (*Clin Oncol* 2009;27(17):2766-71). Modelling the correlated outcomes jointly using this bivariate model allows prediction of PFS for the comparison of interest. **CONCLUSIONS:** In the absence of evidence on PFS, required for the specification of a three-state Markov model, the proposed method allows PFS to be constructed thus eliminating the need to reduce the cost-effectiveness analysis to a two-state Markov model.

PRM109

THE DETERMINANTS OF INNOVATION – A BRIEF STUDY OF ISSUES INFLUENCING INNOVATION IN THE PHARMACEUTICAL INDUSTRY

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OBJECTIVES: To examine factors determining the level of innovation in an organisation, examining two factors – market size and the strength of intellectual property rights for a particular drug class **METHODS:** The pharmaceutical industry is used as a case study as it not only relies heavily on R&D, but, with the division between brand name and generic drugs, can provide insight into how the removal of intellectual property rights might affect innovation. The estimation models were based on an economic model for innovation and market size developed by Acemoglu and Linn (2004). Drug approval data obtained from the US FDA was used for the innovation variable; a measure for market size was constructed using prescribed medicines expenditure data from the US Medical Expenditure Panel Survey. The analysis focussed on examining the relationships between the variables using various statistical estimation techniques, starting with a simple OLS log-log model, more general negative binomial and gamma models, as well as fully flexible non-linear smoothing regressions in the form of feed-forward neural networks. **RESULTS:** Brand name approvals increased by 2.64% and generic approvals by 4.2% for a 1% increase in income-based market size. The presence of generic drugs and, thus, weak intellectual property rights did not appear to have a negative effect on research and marketing activity by brand name drugs. Estimates were small, significant, and positive (feed-forward neural networks indicated an even stronger positive relationship between brand and generic approvals), suggesting that the presence of generic drugs might further innovation. **CONCLUSIONS:** It was shown that market size does affect the rates at which pharmaceuticals aim to bring their products to the market. While brand manufacturers react positively to increased market size, weak property rights do not appear to affect innovation output negatively.

PRM110

CROSSOVER ADJUSTMENT IN ONCOLOGY TRIALS USING A RANK PRESERVING STRUCTURAL FAILURE TIME MODEL (RPSFTM): WRAPPING BOOTSTRAPS AROUND ESTIMATES OF LIFE EXPECTANCY FOR CE MODELS

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OBJECTIVES: Oncology trials increasingly permit switching from standard care (SC) to the new treatment following disease progression. Methods to remove the effect of the active treatment in the SC arm are used by HTA agencies to estimate what the effect of the SC would've been had crossover not occurred. One method is using RPSFT models to derive counterfactual survival times without crossover. For CE modeling, these counterfactual survival times need to be parametrically extrapolated to estimate life expectancy. It is known that the RPSFT approach introduces additional uncertainty and e.g. the standard error of a hazard ratio calculated from counterfactual survival times needs to be inflated. Traditional methods of parametric survival analysis don't account for this increased uncertainty which could influence allocation decisions. **METHODS:** A dataset of 400 patients was simulated assuming a Weibull distribution for PFS and OS with 70% of the patients in the SC arm switching after progression. Life expectancy was calculated in two scenarios. In scenario 1 the RPSFTM adjusted OS had Weibull parameter estimates and covariance calculated directly from the counterfactual survival times. In scenario 2 the data was bootstrapped 1000 times. For each iteration a new RPSFT model, associated counterfactual survival times and Weibull functions were fitted. The mean and covariance of these 1000 parameter estimates was taken. **RESULTS:** Mean incremental life expectancy after adjusting for cross-over was the same with and without bootstrapping. When PSA was run, larger confidence intervals in the scenario with bootstrapping indicated, the traditional approach failed to account for the increased uncertainty and underestimated the probability of the new treatment being less efficacious (0.4% without compared to 13.4% with bootstrapping). **CONCLUSIONS:** Failing to appropriately reflect the uncertainty underlying parameter estimates of crossover adjusted survival times could impact HTA decisions when appraisals are based on the likelihood of a treatment being cost effective.

PRM111

THE USE OF DATA FROM PUBLISHED KAPLAN-MEIER SURVIVAL CURVES IN NICE HTAS

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OBJECTIVES: Reporting of survival outcomes from clinical trials is often limited to median survival times, hazard ratios, Kaplan-Meier curves and numbers at risk. The numerical results are not always sufficient for meta-analysis and cost-effectiveness analysis. Further information can be obtained by digitizing and analysing the Kaplan-Meier curves. The most basic analysis approach is to fit a non-linear model to the Kaplan-Meier curve and use this to estimate parameters such as the mean survival time. Methods have recently been developed for estimating individual patient data (IPD) from Kaplan-Meier curves. Once individual patient data is estimated, standard survival analysis approaches can be used to estimate parameters and also provide estimates of uncertainty in the curve fits. The objective of this study was to review the methods commonly used and assess the impact of the improved methods, where IPD is estimated, on the inferences drawn. **METHODS:** We conducted a systematic review of the methods that have been used in NICE HTAs to obtain data from published Kaplan-Meier curves. We examined the frequency of each method, how results were used and any feedback from Evidence Review Groups. Improved methods, estimating IPD, were applied to a selection of studies where this was not conducted in the original analysis. The impact of the improved methods on the conclusions of the studies was assessed. **RESULTS:** The review showed that most HTAs used non-linear models to approximate the Kaplan-Meier curves. It also showed that the improved methods, estimating IPD, can have a significant impact on conclusions drawn from survival results. **CONCLUSIONS:** The estimation of IPD from Kaplan-Meier curves is a valuable method that is currently underutilised. It has the potential to provide better estimates of survival parameters and to improve the characterisation of uncertainty in such estimates. This is especially important when survival curves are extrapolated.

PRM112

A BAYESIAN DYNAMIC MODEL OF ASTHMA IN THE REAL LIFE

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OBJECTIVES: Evolution of asthma disease severity over time can be highly dependent on the prescription patterns and drug compliance of patients. The purpose of the modeling is to analyze longitudinal observational data of cohort of asthma patients to describe and quantify the dynamics of adherence, prescriptions, and outcomes and their interaction over time. **METHODS:** We explored and analyzed 5 different observational studies following asthma patients in France over up to 2 years. Main patients' demographics along with prescriptions, ACT and 3-level GINA control scores could be defined every quarter and exacerbations at a given quarter were adjucated based on hospital admissions. Medication possession ratios could be defined quarterly and used as a proxy for adherence. A patient-