be viewed as biases or an expression of true preferences is a matter for further discussion.

HC4
UNDERSTANDING THE PAYER DILEMMA WITH BIOSIMILAR MABS: STRIKING THE NEW VALUE BALANCE BETWEEN BUDGET NEEDS AND PATIENT OUTCOMES
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OBJECTIVES: The first infliximab biosimilars reached the EU in September 2013, representing the first biosimilar monoclonal antibodies (mAbs) to obtain EMA approval. Although commercialization in the major European markets will only start in February 2015, payers in Nordic and Eastern European countries have already faced the dilemma of striking the balance between potential savings accrued from use of less expensive infliximab biosimilars and demands for robust proof of clinical efficacy and safety. This work identifies payers’ evidence expectations, their reliance on randomized controlled trials and how potential solutions may improve the current recommendations to target patient populations. METHODS: Exploratory qualitative primary research with payers (N=12) from France, Italy, Spain, UK, Germany and Netherlands. Collection of data about the current and future attitudes towards biosimilar health technology assessments at the national and, if applicable, local levels will be conducted, as well as perceived price and access trade-offs. RESULTS: (1) Payers will mainly defer to the EMA the decision on acceptability of biosimilar indication extrapolation (indications where biosimilars do not have direct clinical trial data). (2) It is understood that mAb biosimilar clinical development is more onerous and costly than small molecule generics, thus payers do not expect the same magnitude of discounts offered vs. originator. (3) Although eager to obtain savings, payers are not willing to implement pharmacy-level substitution or enforce biosimilar use in originator-experienced patients; (4) Use in savings from broad patient populations, payers will not implement pharmacy-level substitution or enforce biosimilar use in originator-experienced patients; (6) Use in naive patients will be recommended in most markets. CONCLUSIONS: Across the EU, payers acknowledge physicians’ concerns over long term safety and efficacy of biosimilars. Nonetheless, they will rely on the regulators’ evaluations and expert panels to justify implementing recommendations, and in some markets, restrict formulary access based on cost. Moreover, they have conservative discount expectations at launch, with the long-term aim of postponing further competition from other biosimilar manufacturers.

RESEARCH ON METHODS – Modeling Studies

M01
QUASI-MONTE CARLO SIMULATION AND VARIANCE REDUCTION TECHNIQUES SUBSTANTIALLY REDUCE COMPUTATIONAL REQUIREMENTS OF PATIENT-LEVEL SIMULATION MODELS: AN APPLICATION TO A DISCRETE EVENT SIMULATION MODEL OF THE RADIANCE STUDY
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OBJECTIVES: Patient-level simulation models provide increased flexibility to overcome the limitations of cohort-based approaches in health-economic analysis. However, computational requirements of reaching convergence is a notorious barrier. The objective was to assess the impact of using quasi-monte Carlo simulation (QMC) and variance reduction techniques (VRTs) on computational requirements. METHODS: A recently published discrete event simulation model assessing the cost-effectiveness of an adjunctive antipsychotic treatment for depression was used. The following VRTs were implemented: antithetic variables, common random numbers (CRN) and the combination (Anti_CRN). In addition, QMC was conducted using the Sobol low discrepancy sequence. The minimal number of patients required to reach convergence as the reference situation of 1,000,000 simple monte Carlo simulations (MCS) was recorded. Precision was defined by the standard error (SE) of the incremental net monetary benefit (INMB) at a willingness to pay of £20,000 per quality adjusted life year gained. VRT simulations were replicated 100 times. INMB estimates were compared with the reference situation using mean squared error (MSE), mean absolute error (MAE) and percentage of under- and overestimations. RESULTS: Reference INMB (SE) was £1,413 (76). The average number of patients required to reach reference precision were 929,628, 35,692, 41,683 and 36,803 for antithetic variables, CRN, Anti_CRN and Sobol respectively. This implied a computation time reduction ranging between 7% and 96% compared to simple MCS. MSE was 246,036, 16,314, 155,950 and 7,474 respectively. MAE was 588, 105, 36,803 for antithetic variables, CRN, Anti_CRN and Sobol respectively. Antithetic variables and Anti_CRN structurally underestimated INMB (99% and 100%). CRN marginally overestimated INMB in 76 replicates. CONCLUSIONS: QMCS and VRT reduce computational requirements in terms of simulated patients and computational time up to 96%, enhancing the practical feasibility of patient-level simulation models. This particularly applies to Sobol and CRN. Antithetic variables should be used with caution and its structural bias warrants further research.

M02
TRANSITION PROBABILITY ESTIMATION USING REPEATED SAMPLING FROM A FITTED MIXED MODEL
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OBJECTIVES: Markov model is one of the most used decision analytic models in health care. Transitions between health states in a Markov model is driven by transition probability matrix. When the number of patients and observed transitions are limited, transition probability estimation becomes challenging. The objective of this exercise is to demonstrate how transition probabilities can be estimated by simulating data from a statistical model fitted to patient-level data. METHODS: An economic model for a hypothetical, in nMOV secondary to pathological myopia (submitted to NICE in June 2013) was adapted for forthcoming Asian reimbursement submissions: BCVA (Best Corrected Visual Acuity) scores were available for limited number of East Asian patients (N=35) from a phase III, 12 month, randomized, double-masked, multicenter, active-controlled study (RADIANCE). To populate a transition probability matrix with 8 health states based on BCVA scores, a statistical model was proposed to simulate a larger hypothetical patient cohort. A mixed-effects model was fitted on the observed BCVA scores with baseline BCVA score as covariate, patients as random effect and an autoregressive AR(1) error correlation structure amongst the repeated observations. This model was used to simulate a hypothetical cohort of 35,000. Transition probabilities were estimated using traditional division by row sum method. Several simulations were run to confirm consistency of results. RESULTS: From baseline to month 3, percentage of patients with BCVA 2 ≥ 20 letters gain was 22.45% in observed data vs 22.49% in simulated data, and percentage of patients with BCVA ≥ 20 letters loss was 0.08% in observed data vs 0.009% in simulated data. BCVA change from baseline to month 3 in simulated data (mean=13.3, SD=8.3) was verified with that of the observed data (mean=13.3, SD=7.3). CONCLUSIONS: Transition probability estimation by simulation from a fitted statistical model can overcome the challenges posed by small patient cohorts and multiple state transitions.

M03
EXTRAPOLATION OF TRIAL-BASED SURVIVAL CURVES USING EXTERNAL INFORMATION
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OBJECTIVES: In cost-effectiveness analysis (CEA), mean survival difference (QALY-difference) over a lifetime horizon is required. Parametric models are necessary to extrapolate survival outcomes beyond the Randomized Controlled Trial (RCT) period. However, mean survival is very sensitive to the assumed model and different mean survival models may result from models fitting similarly well to the RCT data. We investigate the idea that other sources of information, external to the trial data, could be used to inform model choice and estimation. METHODS: We explored survival curve models and model fitting. We investigated how external information can be used to put constraints on spline-based survival models. We illustrate with a Technology Appraisal (TA) of head and neck cancer where RCT evidence had 5 year follow up. A US cancer database (SEER), general population data and expert opinion were used to impose constraints on overall survival, conditional survival, and hazard ratio. RCT and external data were fitted simultaneously within a Bayesian framework. RESULTS: Standard survival time distributions were insufficiently flexible to simultaneously fit both the RCT data and an external data source. Spline-based survival models were sufficiently flexible, although there were difficulties choosing initial values. A good fit to all sources of internal and external evidence was achieved within one integrated model using splines on the log hazard. Gutxumia in addition to radiotherapy improved the expected survival by 4.7 months [95% CI: 0.4, 9.1] compared to radiotherapy alone. CONCLUSIONS: The method enabled us to estimate models consistent with all evidence. Clinical knowledge is essential to guide the interpretation of the external data sources. The method could be used to analyze other RCTs on other cancers and with other treatments. Other flexible models than splines could be investigated.

M04
ESTIMATING SURVIVAL DATA FROM PUBLISHED KAPLAN-MEIER CURVES: A COMPARISON OF METHODS
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OBJECTIVES: Health technology assessment of treatments often requires estimates of their survival curves. Individual patient data (IPD) is often available and the survival function is usually assumed to follow a specific parametric distribution (e.g. Weibull). In other cases, survival curves are based on pooled data from multiple clinical trials. Survival analysis is often conducted using the Kaplan-Meier (KM) method, without directly using the KM curves. The KM method is widely used and is considered the standard for reporting survival data from randomized clinical trials. However, when data are pooled from different studies, the KM method may not be appropriate, and alternative methods may be required. We compared four methods to generate survival estimates from published Kaplan-Meier curves: the KM method, the AIC method, the C-index method, and the goodness of fit (GOF) method. METHODS: We generated survival estimates for a hypothetical intervention with complete survival data from 11 randomized clinical trials. Four survival curves were obtained, each representing a different level of survival benefit (5-10%). These survival curves were generated using the KM method. We then used the KM method, AIC method, C-index method, and GOF method to generate survival estimates from each of the four KM survival curves. RESULTS: The AIC method produced the most accurate survival estimates, followed by the GOF method, then the KM method, and finally the C-index method. CONCLUSIONS: The AIC method is the most accurate of the four methods, followed by the GOF method. The KM method is not appropriate for pooled data, and alternative methods may be required. The AIC method is the most accurate of the four methods, followed by the GOF method. The KM method is not appropriate for pooled data, and alternative methods may be required.

M05
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