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

HC4
UNDERSTANDING THE PAVER DIlemma WITH BIOsimilAR MABS: STRIKING THE RIGHT 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 local data, preferences and how payers would like to see their recommendations to target patient populations. METHODS: Explorative 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 will not implement pharmacy-level substitution or enforce biosimilar use in originator-experienced patients. (4) Use in naïve 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 formularies based exclusively on cost. Moreover, they have conservative discount expectations at launch, with the long-term aim of increasing further competition from other biosimilar manufacturers.

RESEARCH ON METHODS – Modeling Studies
M01
QUASI-MONTE CARLO SIMULATION AND VARIATION REDUCTION TECHNIQUES SUBSTANTIALLY REDUCE COMPUTATIONAL REQUIREMENTS OF PATIENT-LEVEL SIMULATION MODELS: AN APPLICATION TO A DISCRETE EVENT SIMULATION MOVES IN MALIGNANT MELANOMA
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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. This objective was to assess the impact of using quasi-monte carlo simulation (Q MCS) and variation 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, Q MCS was conducted using the Sobol low discrepancy sequence. The minimal number of patients required to reach convergence was calculated as the reference situation of 1,000,000 single 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 year gained. VRTs 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 20,000 for Anti_CRN, CRN and Sobol respectively. This implied a computation time reduction ranging between 7% and 96% compared to simple MCS. MSE was 346,036, 16,314, 155,950 and 7,475 respectively. MAE was 588, 105, 163 and 5 respectively. Antithetic variables and Anti_CRN structurally underestimated INMB (99% and 100%). CRN marginally overestimated INMB in 76 replications. CONCLUSIONS: Q MCS 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 potential patients in mCNV 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 50,000. 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 ≥ 20 letters gain was 22.45% in observed data vs 22.49% in simulated data, and percentage of patients with 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=8.3). 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) between two treatment strategies when 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 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 various survival models and we show 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 and the general population data. Parametric spline 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. Cetuximab in addition to radiotherapy improves 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) are often unavailable and the survival data that are usually available are often fitted by non-parametric models (NLM) to directly to Kaplan Meier plots provided in the published literature. This method does not account for the uncertainty associated with the Kaplan Meier curve and can lead to biased estimates. Although the IPD are often missing, the Kaplan Meier curve itself can be digitised and used to approximate what the original IPD could have been. METHODS: We simulated trial IPD data from different survival distributions in order to assess the accuracy of the IPD reconstruction methods. The assessment of accuracy is made at multiple stages and ultimately the effects on the incremental cost effectiveness ratio (ICER) estimates are compared. To do so, a simple cost-effectiveness model was developed, assuming two health states (alive and dead), and assigning costs (£1,000 per month plus drug costs) and a utility score (0.70) to generate ICERs. Two additional methods to Traditional survival are compared with the NLM approach – those suggested by Guyot (G), and by Hoyle & Henley (HH). RESULTS: We find that the methods differ in accuracy at each of the following two stages; (a) model selection via the AIC and secondly (b) survival model parameter estimation. When an underlying Weibull function was assumed, the true ICER should be £28,924, compared against £31,182 £35,449 and £31,650 for the NLS, HH and G methods respectively. When an underlying loglogistic function was assumed, the NLS, HH and G methods produced ICERS of £26,507, £25,559 and £25,857, compared to a ‘true’ ICER of £25,779. CONCLUSIONS: These findings suggest that in datasets where the data is sufficiently complete to perhaps be considered as typical of ‘true’ shape of the underlying data.

QUALY-RELATED STUDIES
Q41
ECONOMIC ORPHANS? THE PREVALENCE OF CHILD-SPECIFIC UTILITIES IN NICE APPRAISALS FOR PAEDIATRIC INDICATIONS
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