dation. RESULTS: Forty-two assessments were published. Of these, sofosbuvir was the only drug to receive all 12 positive recommendations. Clinical benefit was recognized as being an important criteria in 19 (58%) of the 33 reports. The main negative critique (reported in 11/33 cases) was lack of direct comparative evidence and the resulting uncertainty about cost-effectiveness. In three cases, positive recommendations were based on price negotiations with the companies. The 20 positive recommendations were restricted to subpopulations where the cost-effectiveness was highest (progressed patients, with fibrosis and facing transplantation). The annualization approach consistently overestimates the modelled risk over a 10-year horizon compared with the initial risk prediction for the same period. To illustrate, two modeling approaches are shown to be functionally equivalent. The selection of approach should be driven by what best represents the disease, treatment effect, and available clinical data.

RESEARCH ON METHODS STUDIES – I

RM1

ADJUSTING FOR TREATMENT SWITCHING IN RCTS – IDENTIFYING, ANALYSING AND JUSTIFYING APPROPRIATE METHODS: A CASE STUDY IN METASTATIC MELANOMA

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OBJECTIVES: Participants in oncology randomised controlled trials (RCT) are often permitted to switch from their randomised treatments onto alternative treatments. Practitioners may take this to mean that switching and consequently the overall survival (OS) benefit and cost-effectiveness of the novel treatment may be underestimated. Regardless, decision-makers frequently reject statistical analyses which adjust for treatment switching in health technology assessment due to poor justification of methodological assumptions. This study applies adjustment methods to an RCT comparing dabrafenib to dacarbazine in patients with BRAF V600E/K mutation-positive metastatic melanoma, and investigates which adjustment method best fits this specific case study.

METHODS: The adjustment methods applied included the Rank Preserving Structural Failure Time Model (RPSFTM), Inverse Probability of Censoring Weights (IPCW), and two-stage adjustment. The suitability of each method was assessed by incorporating their assumptions and common treatment-effect assumption required by the RPSFTM, our investigations did not find strong evidence against this.

CONCLUSIONS: Adjusting for switching showed an increased OS effect for dabrafenib. Methodological assumptions must be rigorously investigated to demonstrate whether and which adjustment methods are justified.

RM2

AVOIDING OVERESTIMATION IN ANNUALIZATION OF EVENT RISK FROM RISK FUNCTIONS FOR USE IN ECONOMIC MODELING

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OBJECTIVES: The standard approach to derive transition probabilities for use in state-transition cost-effectiveness models based on available risk functions with different time horizons is to use an exponential distribution (constant event rate assumption) to derive model cycle risk. However this does not remove any age effect on risk, resulting in potential overestimation of cycle-specific risks in the case age is included as a risk factor. We present an approach for annualization of event risk predictions that ensures the correct risk is predicted. METHODS: The proposed approach ensures that the starting age-specific event rate multiplied by the cumulative effect of increasing age during the time horizon of the risk function equals the original risk prediction. To illustrate and compare the standard and the proposed approach, 10-year risk is modelled and compared to the initial 10-year predicted risk using the latest Framingham risk function for primary cardiovascular disease (CVD) available in the literature. Results: The annualization approach consistently overestimates the modelled risk over a 10-year horizon compared to the initial risk prediction for the same period. To illustrate, for a 50-year old male with initial 10-year CVD risk of 20%, 30% or 40% the corresponding modelled risk is 25%, 37% and 49%, respectively. The proposed method for risk annualization provides the exact 10-year initial risk prediction. CONCLUSIONS: Careful application of methods is needed over lifetime. Risk functions for use in state-transition models is needed when age is included as a risk factor and the model cycle length differs from the time horizon of the risk function. The standard risk annualization approach will lead to an overestimation of modelled risk and a more favorable estimate of cost-effectiveness.

RM3

PARTITIONED SURVIVAL VERSUS STATE TRANSITION MODELING IN ONCOLOGY: A CASE STUDY WITH NIVOLUMAB IN ADVANCED MELANOMA

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OBJECTIVES: This analysis aimed to investigate potential differences in estimated outcomes between partitioned survival models and state transition (Markov) models in the common three-state model of pre-progression, post-progression, and death by using nivolumab trial data in advanced melanoma. METHODS: Each approach was applied separately to patient-level data from a phase 1b trial of nivolumab, which compared OP (pre-progression) vs. OP+P (pre-progression and post-progression) beyond maximum trial follow-up for melanoma patients. Alternative fits to the data were compared on the basis of Akaike Information Criterion (AIC) and the plausibility of the long-term extrapolation. RESULTS: The Weibull parameterization consistently overestimates the modelled risk and the cost-effectiveness was highest (progressed patients, with fibrosis and facing transplantation). The standard approach for time period adjustment of existing risk functions for use in state-transition models is needed when age is included as a risk factor and the model cycle length differs from the time horizon of the risk function. The annualization approach consistently overestimates the modelled risk over a 10-year horizon compared with the initial risk prediction for the same period. To illustrate, two modeling approaches are shown to be functionally equivalent. The selection of approach should be driven by what best represents the disease, treatment effect, and available clinical data.

RM4

PROPSITY SCORE MATCHING DOES NOT ALWAYS REMOVE CONFOUNING USING AN ECONOMIC EVALUATION BASED ON A NON-RANDOMIZED STUDY

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OBJECTIVES: To compare the economic results of a non-randomized study using propensity score (PS) methodology to adjust for confounding versus a restriction approach based on clinical opinion. METHODS: We used data from a published non-randomized study, which enrolled 259 patients with resectable perioperative (OP) and post-progression (OP+P) surgically resected non-small cell lung cancer (NSCLC), with a median age of 71 years. The population was stratified by age, gender, race, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, and surgeon. Patients were classified as either OP or OP+P (PS-matched patients). RESULTS: OP was composed of 77 HR EVAR patients (55.0%) and 77 OSR patients (39.5%), of which 48 (62.3%) were OSR-LR patients and 29 (37.7%) were OSR-HR patients. Unlike results obtained within the HR sub-population, the ICER of EVAR was estimated at $93,608 per life-year gained within the PS-matched sub-population. Differences in the results may be explained by confounding, although balance was improved within the PS-matched sub-population, underperformance remained on several patient characteristics. CONCLUSIONS: Results of this study highlight the fact that PS matching may not always fully adjust for confounding. Clinical opinion may be influenced by unmeasured confounders which may not be adjusted for by PS matching. Balance within patient subsets following PS matching must be evaluated when conducting economic evaluation based on non-randomized studies, especially in studies with small sample sizes.

VACCINE STUDIES

VA1

PUBLIC HEALTH IMPACT AND COST-EFFECTIVENESS OF MALARIA ROUTINE VACCINATION IN INFANTS

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OBJECTIVES: Final phase III trial results of the first malaria vaccine candidate RTS,S/AS01 (MSF) were published. Based on this vaccine, we aimed at estimating the public health impact and cost-effectiveness of RTS,S implementation in infants in 42 sub-Saharan countries. METHODS: We developed a stochastic individual-based Markov model of malaria outcomes. RTS,S efficacy was based on results of a phase 3b trial, published after all available data. RESULTS: The Weibull parameterization consistently overestimates the modelled risk and the cost-effectiveness was highest (progressed patients, with fibrosis and facing transplantation). The standard approach for time period adjustment of existing risk functions for use in state-transition models is needed when age is included as a risk factor and the model cycle length differs from the time horizon of the risk function. The annualization approach consistently overestimates the modelled risk over a 10-year horizon compared with the initial risk prediction for the same period. To illustrate, for a 50-year old male with initial 10-year CVD risk of 20%, 30% or 40% the corresponding modelled risk is 25%, 37% and 49%, respectively. The proposed method for risk annualization provides the exact 10-year initial risk prediction. CONCLUSIONS: Careful application of methods is needed over lifetime. Risk functions for use in state-transition models is needed when age is included as a risk factor and the model cycle length differs from the time horizon of the risk function. The standard risk annualization approach will lead to an overestimation of modelled risk and a more favorable estimate of cost-effectiveness.

VA2

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