addition, the Dutch National Health Care Institute commented on usefulness for decision makers, while a separate group of 50 HE experts could comment during a workshop at ISPOR Montreal 2014. **RESULTS:** 35 Validation techniques were identified and grouped into four categories: conceptual model validation, computerized model validation, data validation and operational validation. Around 30 HE experts commented in each of the first three Delphi rounds, resulting in a 15 item draft tool. The Dutch health care advisory institute suggested to add one more item. Participants from the ISPOR workshop delivered 19 filled-in questionnaires. A fourth round resulted in 17 responses. This led to a refined version containing 16 items, which is currently sent out for a final, fifth round. **CONCLUSIONS:** When filled out by the modellers, AdVISHE (Assessment of the ValIdation Status of Health-Economic decision models) supports model users in assessing the validation status of a model It will be useful as part of reimbursement dossiers, by providing systematic and transparent insight into the validation efforts performed and their results.

PRM80

MODELLING SURVIVAL IN THE PRESENCE OF DIFFERENT MECHANISMS OF ACTION: IPILIMUMAB AND VEMURAFENIB IN ADVANCED MELANOMA

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OBJECTIVES: Traditional indirect treatment comparison methods assume the underlying survival profiles of treatments are similar (i.e. proportional hazards). This assumption is unlikely to hold for the comparison of ipilimumab and vemurafenib: Whereas vemurafenib exhibits improved short-term survival compared with ipilimumab, pooled study data for ipilimumab consistently show that patients achieve durable long-term survival. We present a method to compare across trials with differing survival profiles by accounting for follow-on treatments and different patient baseline characteristics. **METHODS:** Comparative survival estimates for ipilimumab and vemurafenib were produced using patient-level data from trial CA184-024 for ipilimumab and published survival curve fits from BRIM-3 (along with registry data) for vemurafenib. The BRIM-3 vemurafenib overall survival curve was adjusted to account for (a) the effect of second-line ipilimumab (via a tunnel-state methodology) and (b) differences in patient baseline characteristics between BRIM-3 and CA184-024, by means of a model (Korn model), constructed to predict the outcomes for dacarbazine-treated patients. The resulting survival estimates were compared with naïve unadjusted survival curve fits, and estimates produced using a hazard ratio (from an indirect comparison) to the ipilimumab data. **RESULTS:** Estimated survival for ipilimumab was 3.3 years (mean). Predicted survival for vemurafenib, using a naïve comparison, was 3.0 years (mean). Adjusting for second-line ipilimumab and different baseline characteristics resulted in an estimate of 2.8 years for vemurafenib. When a hazard ratio was applied to the ipilimumab data, which underlies the here strong assumption that the vemurafenib overall survival profile is similar to that of ipilimumab, predicted survival for vemurafenib increased to 4.2 years.**CONCLUSIONS:** Depending on the methodology used, the mean predicted survival for vemurafenib varied from 2.8 to 4.2 years. Alternative methods that incorporate the long-term survival profile of ipilimumab (naïve comparison or more sophisticated adjustment methodology) demonstrate a higher number of life years with ipilimumab versus vemurafenib.

PRM81

HEALTH ECONOMIC MODELS IN ALZHEIMER'S DISEASE: A CRITICAL ASSESSMENT

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OBJECTIVES: Alzheimer's Disease destroys brain cells, causing problems with memory, thinking, and behavior severe enough to affect work, family and social relationships, and, eventually, the most basic activities of daily living. Different treatment options have been introduced and evaluated from a health economic perspective. However, given the specific characteristics of the disease an evaluation of existing models is needed. **METHODS:** The following databases were searched systematically: PubMed, Health Technology Assessment Database, NHS Economic Evaluation Database, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, DAHTA-database, PSYNDEX and PsycINFO. For the abstracts that met the pre-defined inclusion criteria, full text articles were obtained and evaluated for inclusion in the assessment. **RESULTS:** After eliminating duplicates the search indicated yielded 1'219 articles of which another 940 were excluded based on the title selection. Finally 59 articles have been reviewed in full text after abstract review. Out of those articles 39 were deemed to be relevant based on the research question. The majority of models (48%) have been Markov models, other methods being used were various statistical analysis applications, micro-simulation, and discrete-event simulations. Limitations of existing models include the following: Focus on cognitive function as disease progression only; lack of inclusion of correlation between disease progression and other factors (e.g. residential status); lack of complete structure of diagnosis and treatment of disease (e.g. including non-drug treatments). Based on the Drummond checklist for health economic models the quality of models proved generally to be high but the majority of those lack presenting a comprehensive pathway of the natural history of the disease. **CONCLUSIONS:** Current models do not allow decision makers optimally characterizing the disease, to better assess the costs and benefits of a wide range of potential interventions. Potential new models need to take the disease characteristics and specifics more appropriate into account.

PRM82

APPROACHES USED TO MODEL THE RELATIONSHIP BETWEEN PROGRESSION-FREE SURVIVAL (PFS) / TIME-TO-PROGRESSION (TTP) AND OVERALL SURVIVAL (OS) WITHIN HEALTH ECONOMIC MODELS OF CANCER THERAPIES

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OBJECTIVES: Within health economic models of metastatic cancer therapies assumptions on the relationship between progression-free survival (PFS) / time-to-progression (TTP) and overall survival (OS) are typically required; notably when OS data are immature or unavailable. A review was undertaken to identify the methods that have been used within health economic models regarding this relationship and to identify the rationale given for the approach taken, specifically in those situations where OS data were not available or immature. **METHODS:** All NICE technology appraisals in the advanced and/or metastatic cancer setting completed by December 2013 were reviewed. The review included all relevant appraisal documents publicly available on the NICE website containing information on the methods used and/or rationale for the approach taken to model the relationship between OS and PFS/TPP within the health economic model. This included the sponsor submission and updated analyses, the independent Assessment Report, and other reports/analyses in relation to the appraisal process. **RESULTS:** In those instances where OS data were immature or not available, PFS/TTP was typically assumed to be a valid surrogate of OS. Justification for this assumption was inconsistently reported. In some health economic models a quantification of the assumed relationship was informed by published evidence and/or expert judgement. In some cases attempts were made to explore the potential impact of this relationship in sensitivity analysis. **CONCLUSIONS:** The methods and/or rationale given for the approach used to model the relationship between OS and PFS/TTP in health economic models has been inconsistently reported and justified. Whilst some health economic models attempted to quantify this relationship, further transparency is required. A consensus needs to emerge on the most appropriate approaches to be used within health economic models to quantify this relationship, specifically when OS data are not available or immature and to identify the circumstances when particular approaches may be most relevant.

PRM83

COMPARISON OF METHODS TO ESTIMATE HEALTH STATE UTILITIES IN METASTATIC BREAST CANCER (MBC)

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OBJECTIVES: Patient-level utility values for different stages of MBC and toxicities commonly associated with chemotherapy regimens are useful for health economic assessments. Three methods to estimate utilities exist when direct utility data are not available: utility 'mapping' from existing disease-specific scales, vignette studies that describe the health states; or derivation of preference-based measures from an existing condition-specific scale. This study compares utility estimates in MBC utilizing the above methods. **METHODS:** Based on data from a phase 3 clinical trial in MBC (N=1102) utility mapping was conducted using a published regression algorithm to convert the EORTC QLQ-C30 questionnaire to the EQ-5D utility. Mean utility values were estimated for relevant health states: stable disease (SD), tumor response (TR), disease progression (DP) and common toxicities. Results were compared to previously published values obtained for a vignette study conducted in one hundred members of the general public. **RESULTS:** Observed MBC utilities were similar in mapping vs. vignette studies for SD: 0.697 vs. 0.715, and TR: 0.782 vs. 0.790. General public respondents in the vignette study assigned much lower utility to symptomatic DP (0.443) vs. imaging-based DP in mapping study (0.679); and disutility for toxicities: vomiting: 0.103 vs. 0.050; fatigue 0.115 vs. 0.029; febrile neutropenia 0.150 vs. 0.012 (vignette vs. mapping respectively). Hand-foot syndrome, stomatitis and hair loss were not associated with disutility in the mapping study (potentially due to small sample size) while disutility of 0.116; 0.151; and 0.114 were reported by the vignette study. **CONCLUSIONS:** Utilization of different methods to estimate utilities in MBC may lead to a wide range of estimated values with potentially significant implications for health economic evaluation. Caution must be exercised when comparing utility values derived using different methods. It is preferable to collect such data from patients directly and use vignettes as a last resort.

PRM84

COST-EFFECTIVENESS MODELS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): CROSS-MODEL COMPARISON OF HYPOTHETICAL TREATMENT SCENARIOS

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OBJECTIVES: To compare different COPD cost-effectiveness models with respect to structure and input parameters and to cross validate the models by running the same hypothetical treatment scenarios. **METHODS:** COPD modeling groups simulated four hypothetical interventions with their model and compared the results with a reference scenario of no intervention. The four interventions modeled assumed: 1) 20% reduction in decline in lung function, 2) 25% reduction in exacerbation frequency, 3) 10% reduction in all-cause mortality and 4) all these effects combined. The interventions were simulated for a five-year and lifetime horizon with standardization, if possible, for sex, age, COPD severity, smoking status, exacerbation frequencies, mortality due to other causes, utilities, costs and discount rates. Furthermore, uncertainty around the outcomes of intervention four was compared. **RESULTS:** Seven out of nine contacted COPD modeling groups agreed to participate. Differences in 5-year QALY gains ranged from 0.00020 to 0.039 for intervention one, 0.0089 to 0.075 for intervention two and 0.017 to 0.048 for intervention three. The difference in costs ranged from €561 to €912 for intervention one, €739 to €1350 for intervention two and €1140 to €1618 for intervention three. The 5-year cost-effectiveness ratios (ICERs) for the most comprehensive intervention, intervention four, was €17,000/QALY for two models, €25,000-€28,000/QALY for three models

and €47,000/QALY for the remaining two models. Differences in the outcomes could mainly be explained by differences in input values for disease progression, exacerbation-related mortality and all-cause mortality with high input values resulting in low ICERs and vice versa. Lifetime results were mainly influenced by the input values for mortality. The probability of intervention four to be cost-effective at a willingness-to-pay of €50,000/QALY was 90-100% for five models and about 70% and 50% for the other two models. **CONCLUSIONS:** Mortality was the most important factor determining the differences in cost-effectiveness outcomes between models.

PRM85

A DE-NOVO MODEL TO PREDICT OUTCOMES OF A NEW HYPOTHETICAL INTERVENTION TO REDUCE CV RISK IN POST MI PATIENTS

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OBJECTIVES: The risk of cardiovascular (CV) events in post myocardial infarction (MI) patients poses a significant burden on the UK health care system despite the current standard of care (SoC). The objective of this analysis was to develop a model to quantify the relationship between efficacy and outcomes of a new hypothetical drug given in addition to current SoC to reduce the risk of CV events in post-MI patients when compared to SoC. **METHODS:** A 6-state lifetime Markov model with a 1-year cycle length was developed from a UK health care perspective. Recurrent MI, stroke and CV death were modeled. The hypothetical drug was assigned efficacy values for its ability to reduce the incidence of CV events. The outcomes were measured in terms of QALYs and LYs. A linear regression model was fitted to estimate the expected outcome/patient based on relative risk reduction (RRR) in the incidence of CV events. All outcomes were discounted at 3.5% annually. **RESULTS:** The model structure addressed some of the limitations of previous economic models, namely increased risk due to stroke in MI patients and increased risk of subsequent events in the first year. For identical cohorts, the outcomes from the model compared well with other published studies. For a cohort of patients aged 40-years, the model predicted on an average, LYs of 17.6 and QALYs of 13.64. A hypothetical drug achieving a 5% RRR in CV events resulted in an incremental LYs of 0.28 and QALYs of 0.23. The increase in incremental QALYs and LYs per percentage point reduction in relative risk as compared to SoC was estimated to be 0.043 and 0.054 respectively. **CONCLUSIONS:** A de-novo economic model quantifies the relationship between the efficacy and outcomes of a hypothetical drug when compared to the SoC to reduce the risk of CV events in post-MI patients.

PRM86

ESTIMATING THE LIFETIME HEALTH OUTCOMES OF TYPE 2 DIABETES MELLITUS (T2DM) PATIENTS INADEQUATELY CONTROLLED ON METFORMIN PLUS SULPHONYLUREA RECEIVING EITHER CANAGLIFLOZIN OR SITAGLIPTIN USING THE UKPDS OUTCOMES MODEL V1.3

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OBJECTIVES: The goals of type 2 diabetes management are to control glycaemia and other micro- and macrovascular risk factors such as weight, blood pressure and lipids in order to prevent death and other complications due to the disease. The natural history of the disease makes it challenging to estimate the effects of treatments on these long term complications and mortality from standard clinical trials. Modelling is therefore a key bridging tool for predicting long term health outcomes from intermediate endpoints. The objective of this analysis was to estimate the relative effects of canagliflozin 300mg and sitagliptin 100mg on mortality, micro- and macrovascular complications in T2DM patients in triple line as add on to metformin plus sulphonylurea using the UKPDS Outcomes Model v1.3. **METHODS:** A probabilistic patient generator was developed which generated 10,000 patients with applied treatment effects based on data from head to head randomised clinical trials. Upon loss of glycaemic control ($HbA_{1c} \geq 7\%$), patients were assumed to switch to insulin. 1% point reduction in HbA_{1c} was applied on rescue. For model stability, patients were looped 1,000 times (creating 10 million patients in each arm) with 100 bootstrap simulations. Outcomes were discounted 3.5% annually. **RESULTS:** At the end of the 40 years simulation, patients initiating canagliflozin 300mg had 49 more survivors and 16,918 fewer diabetes-related deaths. Micro- and macrovascular complications were estimated in fewer patients on canagliflozin 300mg than on sitagliptin 100mg (between 5,948 fewer renal failures and 41,157 fewer myocardial infarctions). There were discernible relative risk reductions in all complications and diabetes-related death ranging from 1.40% (heart failure) to 2.96% (amputation). **CONCLUSIONS:** Results of the analysis using the UKPDS Outcomes Model v1.3 suggest that canagliflozin 300mg compared with sitagliptin 100mg as add on to metformin plus sulphonylurea reduces long-term diabetes-related mortality and complications.

PRM87

ALL-CAUSE MORTALITY VALIDATION OF THE CORE DIABETES MODEL AGAINST PREDICTIONS OF THE CHARLSON COMORBIDITY INDEX

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OBJECTIVES: All cause mortality (ACM) validations with the IMS CORE Diabetes Model (CDM) have demonstrated below average fit when compared to overall validation scores from 96 validation end points (EP) with a R^2-statistic of 0.651 (vs. 0.93 All-EP). Lack of fit was associated with a model overestimation of ACM when compared to contemporary outcome studies (ACCORD, ADVANCE, VADT). The objective of this investigation was to put these findings into perspective by comparing the model to mortality risk predictions from the Charlson-Comorbidity-Index (CCI). **METHODS:** The CCI was applied to predict the 10 year mortality risk for diabetes patients with age of 50,60,70 and 80 years and four different co-morbidity levels: no complications (NC), myocardial infarction (MI), MI and stroke (MI+S), MI+S and heart failure (MI+S+HF) and MI+S+HF and renal failure (MI+S+HF+RF). CCI mortality scores were compared to corresponding 10 year ACM predictions from the CDM. Base case (BC) analyses applied UKPDS-68 risk equations (UK68-RE) for CV risk and mortality. Two sets of sensitivity analyses were conducted using UK68-RE for CV risk but mortality tracked individually per complication event (non combined mortality approach) (SA1) and UKPDS-82 risk equations (UK82-RE) applied for CV risk and mortality (SA2). **RESULTS:** Across all age and co-morbidity states, CDM simulations demonstrated the closest match to CCI-scores in SA1 with an R^2-statistic of 0.877. This compared to R^2-statistics of 0.757, and 0.851 for BC and SA2, respectively. BC and SA2 analyses noteworthy underestimated ACM risk in analyses with increased co-morbitity level by 68% (BC) and 49% (SA2) vs. 17% (SA1) in (MI+S+HF) and 44% (BC) and 36% (SA2) vs. 3% (SA1) in (MI+S+HF+RF). **CONCLUSIONS:** The CDM demonstrated a closer match to CCI mortality scores (vs. outcome studies) with a trend to underestimate ACM. This trend increased with baseline age and (only BC and SA2) co-morbidity level.

PRM88

DETERMINISTIC VERSUS STOCHASTIC PREDICTION OF RISK FOR CARDIOVASCULAR EVENTS

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OBJECTIVES: Multivariate functions can be used to predict individual risk for cardiovascular (CVD) events and also to estimate baseline risk in economic models. We present a comparison of deterministic versus stochastic risk predictions using Framingham's [D'Agostino 2008] and REACH's [Wilson 2012] functions. Stochastic risk prediction accounts for patient-level heterogeneity, but involves a number of issues including increased complexity, data requirements, need for assumptions and computational burden. To our knowledge, this topic has not been studied in the CVD setting. **METHODS:** D'Agostino 2008 and Wilson 2012 modeled primary (PE) and recurrent event (RE) risks, respectively. Both studies considered fatal and non-fatal aggregate CVD events and estimated a Cox Proportional Hazards (CPH) multivariate risk function. In the deterministic prediction, the means of the risk factors were used to predict the population's risk directly from the functions. In the stochastic prediction, individual patient profiles (n=10,000) were generated using Monte Carlo simulation. Individual risks were then estimated from the functions and averaged to compute the population's risk. Multinomomial distributions were assumed for discrete variables (e.g. diabetes, number of vascular beds) and normal or log-normal distributions were assumed for continuous variables depending on skewness (e.g. age, total cholesterol). Probability distributions were parameterized based on the risk factors descriptives reported in the original references. Simulations were performed with and without considering dependence of risk factors. **RESULTS:** Due to the non-linearity of the CPH function, the stochastic prediction yielded 23% (PE) and 17% (RE) higher risks than the deterministic approach (14% and 10%, respectively, if age was kept constant). Differences between prediction approaches are even higher if the estimated correlation structure of risk factors is accounted for. **CONCLUSIONS:** When compared to the stochastic prediction, the deterministic approach leads to lower estimates of CVD risks. Therefore, economic models using this approach might underestimate treatment effect.

PRM89

ARE CYCLES NEEDED IN MARKOV MODELS? – THE CONTINUOUS MODEL AS A SIMPLER APPROACH

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OBJECTIVES: To present an alternative implementation for the conventional Markov models with area under the curve (AUC) approach: the continuous model (CM). To present how the CM avoids the need of determining cycles in theory and to compare the traditional and the CM approach in terms of results and complexity in an oncology model example. **METHODS:** The AUC model assumes that the survival function is known at any timepoint not only at the beginning and end of model cycle. The CM calculates the model outcomes for the whole timehorizon by using the values of the survival function in every timepoint, instead of the discrete timepoints defined by cycle length. The CM approach overcomes the issue of the artificial characterization of time using cycles, that is often criticized in Markov models. Using CM can also lead to more precise estimates. A simple oncology AUC model with three health states (progression free survival, progression and death) and four-weekly cycles was built and converted to a CM model in Excel®, using user defined Visual Basic functions. Results, generalizability and user friendliness were compared. **RESULTS:** The results of the two models were similar: for health outcomes differences were around 1%, for costs and incremental cost-effectiveness ratios around 0.5%. Calculations were done in a single cell/outcome instead of a column of 100-200 cells depending on cycle length and time horizon, giving less scope for bugs and facilitating easier debugging. As a result the implementation of the CM model was faster and technical validation easier. **CONCLUSIONS:** The CM approach requires more technical background from the developer; custom functions have to be built even for point estimates. However, results of a CM, requires smaller spreadsheet space, and provides more transparency and easier debugging, while providing similar or potentially more precise estimates compared to the AUC model results.

PRM90

A COMPARISON OF MODELLING TECHNIQUES: PATIENT SIMULATION VERSUS MARKOV MODELLING IN OPHTHALMOLOGY

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OBJECTIVES: Markov models are a currently popular means of estimating the cost-effectiveness of interventions; however they are associated with certain limitations which may make them ill-suited to inform some health care decisions. Patient simulation models offer an alternative methodology which may overcome some of these