unvaccinated with the seasonal influenza vaccine and persons vaccinated during seasons where vaccine was considered (by the CDC-reported vaccine effectiveness percentage (VE%=(1-relative risk)*100%)) a suboptimal match for seasonal flu strain. **RESULTS:** Published vaccine effectiveness for a suboptimal seasonal influenza vaccination ranged from 39%-63% from flu seasons 2006-2007 through 2013-2014. This was approximately the same protection observed in the large claims database for the same year ranges. When modeled together with cost it was shown that this mismatch of vaccination to circulating virus still equated to a substantial reduction in burden of disease when vaccinated. Validation of results still ongoing. **CONCLUSIONS:** The burden of disease of influenza significantly decreases even when the seasonal influenza vaccine is a suboptimal match to the prevalent circulating strain. It is recommended that all persons able to receive the influenza vaccination do so, whether or not the match is optimal. It has been demonstrated that a suboptimal match effectively decreases the burden of the disease.

PRM63

FEASIBILITY AND ACCEPTABILITY OF MINIMAL MODELING VALUE OF INFORMATION ANALYSES FOR REAL-TIME PRIORITIZATION DECISIONS WITHIN A LARGE CANCER CLINICAL TRIALS COOPERATIVE GROUP

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OBJECTIVES: Value of Information (VOI) analyses can help align research investments with areas that could have the greatest impact on patient outcomes, but many questions remain concerning its feasibility and acceptability to inform real-world prioritization decisions. Our objective was to develop a process for calculating VOI in "real time" to inform trial funding decisions within SWOG, a large cancer clinical trials group. **METHODS:** We adapted a novel and efficient modeling approach - minimal modeling VOI - using a sample of nine phase II/III trial proposals from the Breast, Gastrointestinal, and Genitourinary committees reviewed by SWOG's leadership between 2008-2013. We created decision models for each trial proposal and devised an efficient process to characterize prior uncertainty in treatment effect by linking evidence-based assumptions in a trial's sample size calculations with the historical success rates of SWOG trials. Expected clinical and economic VOI was calculated using Bayesian updating methods. We customized the process using iterative stakeholder input. **RESULTS:** The VOI modeling process was feasible and sufficiently captured key expected differences in comprehensive outcomes and attendant uncertainty for 8 of 9 trial proposals. Model construction and calculations took one researcher <1 week per proposal. We accommodated stakeholder input by: a) deconstructing VOI metrics into expected health benefits and incremental healthcare costs, b) assuming treatment decisions were based on health benefits alone, and c) providing both individual and population level results. Following this customization, SWOG generally accepted the VOI framework and results for the retrospective analyses and felt that VOI analyses would likely be useful in informing future trial proposal evaluations. **CONCLUSIONS:** We developed an efficient and customized process for calculating the expected VOI of cancer clinical trials that is feasible for use in real-time decision-making and is acceptable to stakeholders. Prospective use and assessment of this approach is currently underway within SWOG.

PRM64

ALTERNATIVE METHODS FOR GENERATING ARBITRARY MARGINAL DISTRIBUTIONS AND THE IMPLICATIONS FOR SIMULATION OUTCOMES

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OBJECTIVES: Generating multivariate random variables is essential in disease simulation applications. In this study we examine the implications of alternative approaches to generate marginal distributions and correlation matrix on simulation outcomes. **METHODS:** We adopt three alternative methods including Cholesky Decomposition (CD), CD with conditional matching, and the NORmal-To-Anything (NORTA) method to generate a hypothetical simulation sample with arbitrary marginal distributions and correlation matrix. As the comparator, we also create an independent and identically distributed (iid) simulation sample. The samples are individually populated in a previously developed type 2 diabetes microsimulation model to predict the major clinical endpoints over 15 years. The endpoints include all-cause mortality, diabetes-related mortality, and major cardiovascular events. We examine the goodness of fit by total deviance, i.e., the aggregated values of the relative difference between the individual predictions with the endpoints observed in the actual data, in the overall and stratified samples. **RESULTS:** The results show that, the model predications deviate from the observed data with an iid sample. Over 15 years, the model over-predicts all the numbers of endpoint events by 20%, with the total deviance of 0.73, and the over-prediction is particularly more pronounced in the younger patients. With a sample of a constructed multivariate normal distribution using the CD and CD plus conditional matching approach, the deviance is reduced to 0.41 and 0.58 respectively. A further improvement is observed when using the NORTA method, with the deviance of the endpoints between model prediction and actual data further reduced to 0.11. The reduction was mainly contributed by better approximations in the dispersion of the risk factors among patients. **CONCLUSIONS:** Random sequences generation has important ramification for simulation outcomes. Poorly-defined multivariate distributions may significantly distort the simulation performance. Given its flexibility for both continuous and discrete variables, NORTA method appears to be a preferable approach.

PRM65

AN EVALUATION OF COMPETING MODELS FOR PREDICTING CV EVENT RATES FROM LDL-C LEVELS IN SECONDARY PREVENTION

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OBJECTIVES: This study aims to evaluate four alternative models that each describe the relationship between LDL-C and CV event rates in secondary prevention. A secondary aim of this analysis is to promote an approach to develop more reliable disease simulation models in cardiovascular disease. **METHODS:** Data describing LDL-C and nfMI+CV Death outcomes were abstracted from several landmark secondary prevention statin trials in clinically stable patient populations (4S, CARE, LIPID, HPS, TNT, IDEAL, GREACE, AVERT, and LIPS). Linear (L), quadratic (Q), one-knot linear spline (S1L) and two-knot quadratic spline (S2Q) models were fit. RMSE, leave-one-out cross validated (LOOCV) and Monte Carlo cross validated (MCCV) RMSE (90% training, 1,000 replicates) were used to evaluate predictive performance. Predicted event rates based on LDL-C = 50mg/dL were estimated to illustrate the clinical implications of each model. To encourage full reproducibility and transparency, all raw data and code (R) will be made freely available for download online via authors Git repository. **RESULTS:** A total of eight models were fit and evaluated, including four distinct functional forms (L, Q, S1L, and S2Q) across two sets of data (all data (A) and data censured for high leverage studies(C)). Of all the models evaluated, S2Q-C exhibited the lowest RMSE (0.317) while L-C produced both the lowest LOOCVRMSE (0.463) and MCCVRMSE (0.389). Model selection had an impact on predicted percentage of events/yr at 50mg/dL (range= 0.769 to 2.09). **CONCLUSIONS:** This analysis suggests that a linear model may be among the most appropriate when describing the relationship between LDL and nfMI+CV Death in secondary prevention; however, other models (linear spline and quadratic) warrant further investigation. These findings along with additional research will help inform more reliable and accurate models of long-term outcomes and economic benefit of LDL-C lowering treatment modalities.

PRM66

THE WORLD HEALTH ORGANIZATION AND UNIVERSAL DIAGNOSTIC TESTING FOR SUSPECTED MALARIA IN CHILDREN: IS THE NEW POLICY COST-EFFECTIVE AND AFFORDABLE FOR SUB-SAHARAN AFRICA?

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OBJECTIVES: Malaria imposes a substantial global disease burden with 198 million cases reported worldwide in 2013. It disproportionately affects sub-Saharan Africa, particularly young children and accounts for 14% of the region's childhood deaths. In an effort to improve disease management, the World Health Organization (WHO) in 2010 recommended countries test children (age < 5) who present with suspected malaria fever and confirm diagnosis rather than treat them presumptively with antimalarial drugs, the standard of care to date. While all 47 African countries designated as malaria-endemic, have adopted the policy, significant barriers to implementation exist. These include costs, uncertainty about the overall health benefits, shortfalls in testing supplies and physician practice patterns. **METHODS:** We use a decision-analytic approach to assess the policy's cost effectiveness in three countries in sub-Saharan Africa: Angola, Tanzania and Uganda, each representing different prevalence/income combinations. Our model includes country-specific epidemiologic, cost and behavioral data, including that of physician and caregiver. Our primary data sources are national Malaria Indicator Surveys and information from each country's National Malaria Control Program. We use a Markov specification to account for multiple fever episodes and estimate the incremental cost-effectiveness of the testing policy through two-stage micro-simulation models. These models capture key dimensions of uncertainty associated with our projections. **RESULTS:** We find that diagnostic testing for malaria is cost-saving in Angola. In Tanzania the cost per life-year gained is $5.54 and $94.58 in Uganda. Both are cost-effective compared to the WHO standard of $150 per life-year gained. Our results are robust under varying cost, prevalence and behavioral assumptions. Probabilistic sensitivity analyses indicate that testing is cost-saving or cost-effective: 80% of the time in Angola, 89% in Tanzania, and 69% in Uganda. **CONCLUSIONS:** Our findings strongly suggest pursuit of policies that facilitate full implementation of testing, including promoting clinician adherence to test results.

PRM67

WHOLE-DISEASE MODEL APPROACH: METHODOLOGIES AND CHALLENGES IN COMMUNICATING THE ECONOMIC BURDEN OF RARE DISEASES

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OBJECTIVES: The concept of whole-disease model has rarely been applied in practice or considered in the published literature. No studies to date have addressed the applicability of this approach in rare diseases. This research aims to demonstrate the applicability, technique, and framework of the model designed to educate US Payers of the estimated patient-level costs and resource utilization, using a rare disease as a case study. **METHODS:** The lack of specific ICD-9-CM code, prevalence overestimation, poorly documented US epidemiology data, complex diagnostics, and off-label pharmacotherapy were evident in rare diseases. In order to estimate patient-level resource utilization, diagnosis costs, and 12-month treatment cost from the US Payer's perspective, a clinical guideline-based approach was developed. We reviewed diagnosis and treatment guideline recommendations to develop a resource utilization algorithm which was subsequently validated by clinicians to reflect the real-world clinical practice. Model cost inputs were derived from published resources including the most recent year Medicare Fee Schedules and H-CUP National Inpatient Sample database. Adverse event costs associated with the treatments were not accounted for in the model. **RESULTS:** An interactive, MS-Excel based economic model was constructed based on guideline recommendations. The model inputs were customizable, allowing flexibility in plan/Payer specific disease burden estimation. Cost of diagnosis, pharmacotherapy, and surgical therapies were calculated for a single patient over a 12-month period. **CONCLUSIONS:** The study demonstrates that the whole-disease model approach can be applied to rare diseases to provide the disease burden estimation, serving as an information tool for Payers, for diseases with small patient volume and unknown cost burden. The model also provides a platform for manufacturers to: 1) incorporate real-world data as they become available; 2) add/remove interventions as the market evolves and; 3) add various economic elements to further calculate budget impact or cost-effectiveness of an intervention over a product life-cycle.

PRM68

CALIBRATING AN INTEGRATED PHARMACOECONOMIC-PHARMACOMETRIC MODEL OF COPD TREATMENT: WHAT A DIFFERENCE THE VARIANCE MAKES

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OBJECTIVES: The objective was to calibrate a pharmacometric-pharmacoeconomic microsimulation model of COPD to ensure that variation resulting from model estimates was consistent with the underlying trial data, thereby providing more accurate estimates of the probability of the clinical and economic "success" of drug development options based on this model. **METHODS:** A Markov microsimulation model was developed to estimate monthly changes in key COPD severity metrics (FEV1 and exacerbations) in order to compare a hypothetical FEV1-increasing drug to placebo. The pharmacometric model, based on a model-based meta-analysis of COPD trials, was used to predict the exacerbation rate (ER) in a group of actual trial patients, given their known baseline FEV1.The hypothetical drug increased FEV1 and thereby decreased the ER in the treatment group. Costs and utilities were derived from the literature and applied to monthly model outcomes. The variance in exacerbations generated by this model was calibrated to the variance in the trials underlying the pharmacometric model. Model results were compared to those generated by a Markov model without such calibration. A common random numbers assumption for non-COPD mortality was tested for its effect on variation in health economic outcomes. **RESULTS:** In the reference case, relative to the uncalibrated model, the calibrated model resulted in similar outcome means but 15-17 times larger standard deviations (SDs) for exacerbations, 6-7 times larger SDs for 1-year costs, and three times larger SDs for QALYs. This led to more elliptical ICER scatterplots and flatter cost-effectiveness acceptability curves in the calibrated model. Use of common random numbers did not make a significant difference in these results. **CONCLUSIONS:** Integration of pharmacometric and pharmacoeconomic models provides a basis for outcomes variance calibration with actual data. Without calibration, variation induced within a typical Markov model may substantially misrepresent true clinical variation and lead to inaccurate probabilities of success versus clinical and economic thresholds.

PRM69

INFORMING UNCERTAIN MODEL PARAMETERS THROUGH MODEL CALIBRATION: HUMAN PAPILLOMAVIRUS (HPV) MODEL CASE STUDY

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OBJECTIVES: Numerous HPV models have been developed to evaluate the cost-effectiveness of HPV vaccination. However, uncertainty remains in some key model parameters such as the risk of transmission and partner formation and dissolution rates. We attempted to identify those parameters that influenced most calibration fits for an HPV type 6/11 agent-based model. **METHODS:** We developed an agent-based HPV model of HPV 6/11 infections and disease (warts) to explore the effect of partnership formation and natural history parameters on how well the model output fit observed data on HPV 6/11 infections and disease. Our heuristic model describes the population in terms of the three groups by individuals' sexual activity level. The activity level is positively correlated with the risk of infection transmission or acquisition. Persons belonging to the low and medium risk groups tend to have long lasting relationships with low probability of forming concurrent partnerships, whereas those in the highest risk (most active) group tend to engage in short and often concurrent partnerships. **RESULTS:** We found that the most sexually active group of people is responsible for forming a power-law tail in the partnership statistics reported in surveys and has the biggest impact on the infection spread, and that durations of short-term partnerships, along with risk group and age mixing patterns, have the biggest impact on the model fit. In combination, these factors also determine the characteristic shapes of the warts age-specific incidence curves with the peak occurring in the female population approximately five years earlier than in the male population. **CONCLUSIONS:** The transmission dynamics of HPV 6/11 infection and disease depend greatly on the short-living partnership networks. Accounting for the formation of such partnerships is critical to achieving acceptable model fits. Further research is necessary to explore how accounting for partnership formation affects cost-effectiveness analyses of HPV vaccination strategies.

PRM70

PRACTICAL ISSUES IN DEVELOPING ECONOMIC MODELS FOR TARGETED TREATMENTS

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OBJECTIVES: A reimbursement process for targeted therapies was introduced in 2011 requiring joint economic assessment of both the new treatment and associated diagnostic test. Thus the emphasis of the evaluation was no longer simply on the effectiveness of the new treatment in targeted patients but also in patients inappropriately treated due to false positive test results. A submission for subsidy of EGFR mutation testing to determine eligibility for first-line gefitinib treatment of patients with advanced NSCLC was undertaken. **METHODS:** An individual patient simulation was used to model current SOC for NSCLC, no test and first-line platinum-based doublet chemotherapy versus the proposed intervention, EGFR mutation test and gefitinib treatment for EGFR M+ patients and SOC for EGFR M- and EGFR unknown patients. The IPASS Study (NCT00322452) confirmed the benefit of TKIs in EGFR M+ patients, but also the potential harm to EGFR M- patients in the first-line setting. Data were thus available for EGFR M+ and EGFR M- patients treated with both gefitinib and SOC. This information was critical to development of a screening module and survival curves. **RESULTS:** EGFR testing regimens to target TKI treatment at various points in the patient's life from diagnosis through to palliative care were compared. The results were most sensitive to choice of comparator such as: inclusion of switch maintenance following doublet chemotherapy; proportion of patients receiving second-line therapies including targeted TKI; and use of subsequent untargeted TKI. EGFR testing+gefitinib was a dominant economic strategy when compared to commonly used treatment alternatives. Assuming the most conservative comparator strategies, EGFR+gefitinib remained cost-effective. Decreasing the specificity of EGFR testing (false positive rate) or including a mortality benefit to TKI worsened the ICER. **CONCLUSIONS:** Simultaneous reimbursement of the EGFR test and gefitinib for first-line treatment of EGFR M+ aNSCLC was a cost-effective alternative to no testing and chemotherapy.

PRM71

PROGRESSION OF VISION LOSS IN PATIENTS WITH GEOGRAPHIC ATROPHY- A DISEASE MODEL

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OBJECTIVES: Geographic Atrophy (GA) affects eight million people worldwide, limits visual acuity (VA) resulting in blindness. Our aim was to forecast the long term impact of GA on visual loss and blindness, and the expected benefits of early treatment. **METHODS:** The model was developed using Excel Visual Basic Application (VBA) with the following inputs: 1) population characteristics (gender, age at GA diagnosis, baseline VA, one eye versus two eyes involvement), 2) health states by VA (no visual impairment, visual impairment, blindness and death), 3) rate of VA decline. Data of natural progression of GA from Age-Related Eye Disease Study (AREDS) was used as the main input for this model. The key outputs of the model under no intervention/hypothetical intervention are: 1) time to loss of functional vision (VA>20/40), visual impairment (VA<20/80), and blindness (VA≤20/200), and 2) time to event curves for visual disability and blindness. **RESULTS:** In a simulated cohort of 500 patients diagnosed with GA (with a mean age of 70 years and VA= 20/60), the model estimated that 60% of them would develop blindness in the affected eye over their lifetime without intervention. On average, they experience four years with visual impairment and eight years with blindness. The model also showed that GA patients with younger age and worse VA at diagnosis, and faster rate of VA decline are at increased risk of attaining blindness. A hypothetical intervention with 25% and 50% efficacy avoided 1 and 3 years of blindness, respectively. Sensitivity analysis showed that treatment efficacy when compared to starting age, starting VA, and rate of VA loss, had the highest impact in reducing time spent in blindness. **CONCLUSIONS:** The simulation model based on natural history of GA progression showed that effective treatment started early at diagnosis can reduce the burden of vision loss among GA patients.

PRM72

REVIEW OF METHODOLOGICAL APPROACHES TO GENERATE PROPENSITY SCORES IN MULTILEVEL DATA

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OBJECTIVES: Propensity score matching (PSM) techniques are frequently used in analyses of retrospective or observational data. Several approaches have been developed to account for the hierarchical structure of data in PSM analyses. The aim of this study is to identify and review existing multi-level PSM methodologies. **METHODS:** Medline and PubMed databases were used to perform a targeted literature review to identify studies that use PSM methodologies in multi-level data. The following search terms were used: 'Propensity score', 'Multi-level data', 'Hierarchical model' and 'Propensity score matching'. Methodologies that specifically considered the challenges of performing PSM with hierarchical data were included in the final review. **RESULTS:** Six strategies were identified in the literature to perform PSM in multi-level data. These included 1) Complete pooling (CP); 2) Partial pooling (PP); 3) No pooling (NP); 4) Simple single-level modeling (SSLM); 5) "Two stage" modeling (TSM); and 6) "Dummy" modeling (DM). CP ignores potential clustering in the data and is the most commonly used approach. SSLM differs from CP in that it matches patients only within a given cluster. In contrast, the NP method generates separate propensity scores (PS) for each cluster and matches prior to pooling. The PP method uses random intercept models to generate PS and patients are matched across all clusters. The TSM approach first estimates random errors separately and applies them in a subsequent PS model that account for clustering, after which patients are matched as in the PP method. The DM method simply includes the cluster identifier as a fixed effect in the PS model. **CONCLUSIONS:** Performance of each approach is dependent on the number of clusters and the sample size in each cluster. A thorough investigation of data should be undertaken before selecting an approach to use PSM in studies with multi-level data.

PRM73

CONTRASTING THE RELATIVE RISK REDUCTION OF CARDIOVASCULAR EVENTS IN THE CORE DIABETES MODEL ASSOCIATED WITH SINGLE RISK FACTOR CHANGES ACROSS ALTERNATIVE RISK ENGINES: UKPDS68, UKPDS82 AND SWEDISH NATIONAL DIABETES REGISTRY EQUATIONS

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OBJECTIVES: The degree to which predefined risk factor (RF) changes alter life time benefits and costs in projections with the IMS-CORE-Diabetes-Model (CDM) has been previously reported. The objective of this study was to contrast the relative risk reduction of cardiovascular events by individual RF changes using alternative risk equations (RE), specifically: UKPDS-68 (UK68-RE), UKPDS-82 (UK82-RE) and the Swedish-National-Diabetes-Registry (SNDR-RE). **METHODS:** The CDM was applied to estimate annual probabilities for 1st myocardial infarction (MI), 1st stroke, ischemic heart disease (IHD) and heart failure (HF) for an intermediate risk type 2 diabetes individual (age 55 years, HbA1c 8%, SBP 140 mm-Hg, BMI 30 Kg/m2, TC 250 mg/dl, HDL 50 mg/dl and LDL 170 mg/dl). The relative risk (RR) in association with unit RF changes was determined for HbA1c (-1%), body-mass-index (BMI) (-1 Kg/m2), systolic-blood-pressure (SBP) (-10 mmHg), total-cholesterol (TC) (-10 mg/dl), (high-density-lipoprotein (HDL) (+5 mg/dl) and low-density-lipoprotein (LDL) (-10 mg/dl). **RESULTS:** The RR of CV endpoints associated with risk factor changes