the near future, and similar levels of efficacy and acquisition cost as key comparators In rare circumstances conducting an STA may not be cost-effective. It is possible that this can be predicted early in the STA process and we propose criteria to aid in this decision. When these criteria are met the possibility of "unreferring" the topic is likely to be the most cost-effective option.

PRM231

THE 2013 REVISION TO NICE'S DISCOUNTING GUIDELINES: DIFFERENTIAL DISCOUNTING HAS GONE BUT UNJUSTIFIED SELECTIVE APPLICATION REMAINS

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OBJECTIVES: To call attention to the problems resulting from the National Institute for Health and Care Excellence's (NICE) recent revision to their methods guidance on discounting, which recommends applying a lower discount rate than the reference case rate in selected cases. **METHODS:** NICE's reference case discount rate for costs and health effects is 3.5%. In 2011 NICE amended their economic appraisal guidelines recommending differential discounting of costs and health effects at 3.5% and 1.5% respectively in selected cases. A recently published article in Value in Health criticised this amendment on a number of grounds, including ambiguity over what are the eligible selected cases; the lack of rationale for selective application of differential discounting; the apparent inconsistencies that unjustified selective application give rise to; and, the size of the differential between the two discount rates. In April 2013 NICE published a comprehensive revision of their methods guidelines, in which equal discounting of costs and effects at 1.5% in selected cases is now recommended. **RESULTS:** While NICE's new 2013 guidance no longer includes an unjustified differential between the discount rate on costs and health effects, it still recommends the application of lower discount rates in selected cases. The revised guidance still offers no rationale for such selective application of lower discount rates. This means that many of problems described in the recently published critique of the 2011 amendment still apply to the new 2013 guidance, including a particularly worrying potential for age discrimination. **CONCLUSIONS:** NICE's selective application of lower discount rates in certain cases is not justified and leads to inconsistencies in the appraisal of different interventions. NICE is urged to again revise their discounting guidance, this time ensuring all interventions are treated equally and are subject to the same discount rates.

PRM232

A FLEXIBLE MULTI-STATE MODELLING FRAMEWORK FOR THE SIMULATION OF CANCER PROGRESSION AND CANCER CARE

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Most cost-effectiveness models for evaluation of cancer care compare interventions within a single treatment line. However, to investigate the full impact of a new treatment, also downstream effects must be taken into account. Furthermore, most models are based on observed clinical states, whilst these observations depend on the timing of examinations and the choice of diagnostic test. To evaluate the potential of new treatments and diagnostics, the underlying disease process needs to be modeled including the interaction with diagnostics and treatment.**OBJECTIVES:** To build a flexible framework for a disease model, that simulates cancer progression to obtain clinical, patient and economic outcomes, while taking diagnostics treatment pathways and surveillance schedules into account . **METHODS:** The modeling framework discerns two levels to describe disease progression, the level of the patient and the tumor. At the patient level, an individual is characterized by clinical states; "primary tumor only", "local recurrence", "regional recurrence", "distant metastasis, stable", "distant metastasis, progressing" and "death". The clinical state is derived from disease development at the tumor level. Seven tumor growth states are defined: "absent tumor", "dormant tumor", "micro tumor", "small macro tumor", "medium macro tumor", "large macro tumor", "symptomatic tumor". Melanoma progression was used as a case study. The model simulates, in parallel, 11 possible tumor sites, ranging from "local" to "regional" and "distant metastatic" locations. Sites were chosen because they are associated with different treatment and prognosis. The disease model is complemented with a treatment and surveillance module. In this module, treatment choices in each of the clinical states are specified. Treatment choice may depend on patient and tumor features, and subsequently influences rate of transitioning between tumor growth states. For surveillance, timing of surveillance visits, techniques used and their detection rate(s) are specified. **CONCLUSIONS:** The proposed framework provides a flexible and widely applicable cancer modeling design.

PRM233

HOLISTIC DATA GENERATION AND SYNTHESIS FOR HTA ASSESSMENT: BRINGING TOGETHER COMPARATIVE EFFECTIVENESS RESEARCH, PERSONALISED MEDICINE AND PATIENT-CENTRED OUTCOMES RESEARCH

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Defining value and generating innovation in health care relies increasingly on real world evidence. Consequently, there is an ongoing evolution in the data needs for health technology assessment (HTA). Three key elements of data generation are comparative effectiveness, personalised medicine and patient-centred outcomes. Integrating these three to support synthesis via systematic reviews, meta-analyses and modeling is necessary to maximise value and drive innovation. Effectiveness is not just about reduced morbidity and mortality. It now covers quality of life, patient satisfaction, intermediate endpoints, and screening/diagnosis/monitoring. Additionally, there is a shift away from effectiveness versus placebo to comparative effectiveness versus other technologies or standards of care in the real world, focusing on the effect on health outcomes in defined patient populations based on ethnicity, comorbidities or age. Personalised medicine signals another shift of focus away from broad, homogenous patient populations to small, more-or-less defined patient subgroups. For example, in oncology, markers such as KRAS, HER-2/neu and BRCA 1,2 are used for prognosis and to direct treatment. To reflect this evolution, comparative effectiveness research programme designs and analytical methods must be able to detect important treatment effects and outcomes for specific patient subgroups. The emergence of patient-centered care adds further complexity to HTA data requirements. The systematic collection of patient-reported outcomes (PROs) and their application to medicine is far from standard in clinical practice, although many clinical trial programmes now include the collection of PROs. For products in development, data generation plans must reflect ongoing changes and evolving complexities. We will review the growing range of methods employed in clinical effectiveness research, and show how personalised medicine and patient outcome programmes can strengthen HTA data packages.

PRM234

AN ANALYSIS OF HOW NOT TO USE COST-EFFECTIVENESS ANALYSIS FOR PRICE-SETTING

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OBJECTIVES: Cost-effectiveness Analysis (CEA) and the calculation of the Incremental Cost-Effectiveness Ratio (ICER) together with its comparison with a threshold such as Gross Domestic Product (GDP)/capita, have long been used to assess the value for money of a new intervention compared with a comparator that this new intervention precisely seeks to displace. In this paper we show the paradoxical increase in cost-effective price using data from middle, low and very low income settings. **METHODS:** Using the introduction of rotavirus vaccination compared with no-vaccination as the example. We create a theoretical framework for calculating the ICER by gradually decreasing the investment for treatment of rotavirus related disease (the 'no-vaccination comparator') representing different countries with different GDP levels and decreasing levels of existing health care investment. We compare these results with an analysis of cost-effectiveness using real data from 9 countries representing a range of different GDP levels. **RESULTS:** The theoretical framework works well in situations where the GDP/capita exceeds $10,000 – as expected the cost-effective price decreases with a decrease in the GDP/capita. Below this the scant investment in health care infrastructure, thereby reducing potential cost-offsets, coupled with the significant increase in the potential effect gain, results in a much wider margin between a cost-neutral and cost-effective price that could effectively be set using this approach. **CONCLUSIONS:** Although Cost-Effectiveness Analysis is widely used to assess the value for money of a new intervention for a particular price, we would argue that where investment in health care is low and disease burden is high, the use of CEA leads to paradoxes in price-setting.

PRM235

RE-ENGINEERING OF THE DISTRIBUTION OF DRUGS IN THE HOSPITAL. TOC APPLICATION AND TRZ

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OBJECTIVES: Presents a reengineering process of the distribution of drugs into the hospital, analyzing all the options available in the market, and looking for alternative solutions that may be more cost-effective. **METHOD:** The processes and subprocesses in the cycle from prescribing, distribution, and drug administration, are defined and discussed based on studies of medication errors (ME). The differential analysis is performed on the subprocesses. As technique for finding creative solutions (new cost-effective alternatives) apply the Theory of Constraints (TOC), and the TRIZ methodology. **RESULTS:** Since patient safety can distinguish four processes: prescription (about 40% of ME), transcription, distribution (about 10% each), and administration (about 40% of ME). In the administration, avoided ME before they reach the patient are minimal (only 2%). In the prescription/transcription there are 4 options: manual prescription, preprinted sheets, electronic prescription, and assisted prescription. In the distribution has 3 options: clasical SUD, filling carts using automated carousels, and automated dispensing systems (ADS). For administration there are other 3 options: manual record, electronic registration, and registration across the barcode. The most expensive option would be the introduction of ADS in all plants (1.4 million€ for a hospital of 280 beds). But these teams only reduces errors about 10% of all ME. Applying the TOC and TRIZ, investment in electronic prescribing, and administration with barcodes is the most cost-effective. Dose-day (sending medication for one day but not rated by patient) could be the most efficient system by simplifying processes. The error difference between Dose-day, and SDU can be annulled by the advantages of the assisted prescription, and administration with barcode **CONCLUSIONS:** It is surprising to invest large sums in improving distribution processes (ADS) - where the fewest mistakes occurs - instead of prescribing and administration. The dose-day with barcode administration would be the most cost-effective theoretical-model.

PRM236

HOW CAN HEALTH ECONOMIC ASSESSMENT METHODS HELP DECISION MAKING IN PORTFOLIO DEVELOPMENT

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OBJECTIVES: The R&D costs of a new drug approximate $1.3 billion and are increasing due partly to regulatory hurdles and development costs. There is a need for smarter investments, which consider the requirements of regulatory bodies, increasing the chances of securing market access and high return on investment. We describe how health economic methods could support capital investment decisions in funding, valuing and bringing new pharmaceuticals to market. **METHODS:** A literature review was performed on health economic and capital investment methods. The different analyses were mapped to the commercial roadmap and R&D pipeline

of a biopharmaceutical company. An approach based on real options valuation model was proposed to support investment and market decisions and to predict the potential net present value (NPV) of a drug. The conceptual structure of the model was face-validated by health economic and valuation experts. **RESULTS:** A decision-tree based valuation method, populated partially by information from health economic tools, was adopted to analyse and clearly communicate R&D investment opportunities, to capture management flexibility and to improve strategic thinking. A feedback loop can be built into the model to analyse resiliency to assumption changes. In early phases, headroom and multi-criteria decision analyses indicate the likelihood of an investment being cost-effective. Phase I and II trials provide early evidence on drug efficacy and tolerability and initial cost estimates. Based on value of information, cost-effectiveness and budget impact models, only drugs deemed to meet authority requirements would be selected. Market intelligence and uncertainties and clinical success probability further enable identification of the optimal portfolio containing drug candidates that maximize NPV for given risk levels. **CONCLUSIONS:** Health economic methods are commonly applied during late stage development, but if implemented alongside capital investment tools from earliest R&D stages they could increase the likelihood of selecting the right products to compose an effective investment portfolio.

PRM237

MULTIVARIATE NETWORK META-ANALYSIS OF PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL

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Cancer treatment effectiveness is often quantified by analyzing time from treatment initiation to the occurrence of a particular event. Very commonly studies report data on overall survival (OS), where the event is death from any cause, and on progression-free survival (PFS), where the event is death from any cause or disease progression, whichever occurred first. Both OS and PFS can inform decision making. Separate meta-analyses of OS and of PFS data ignore the correlation between the outcomes. We introduce a method for the joint meta-analysis of OS and PFS that is based on a tri-state transition model with time-varying hazard rates modeled with fractional polynomials. In English, we assume that, at any time, patients can be in one of three health states: "alive but not progressed", "alive and progressed", and "dead". PFS corresponds to time spent in the first state, and OS to time spent in the two alive states. The proposed approach allows the joint network meta-analysis of OS and PFS, relaxes the proportional hazards assumption, extends to a network of more than two treatments, and simplifies the parameterization of decision and cost-effectiveness analyses. The data needed to run these analyses can be extracted directly from published survival curves. We demonstrate use by applying the methodology to a network of trials for the treatment of non-small cell lung cancer.

PRM238

USING LOWER COST, LOWER EFFICACY INTERVENTIONS CAN IMPROVE POPULATION HEALTH OUTCOMES UNDER BUDGET CONSTRAINTS

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BACKGROUND: The global economic crisis imposes severe restrictions on budgets allocated to health care. Innovative technologies in medicine may improve patient outcomes but such improvements come at a substantial cost, thus limiting the number of patients that may benefit from them. According to current cost-effectiveness analyses (CEA), most innovative interventions are associated with a higher efficacy and higher costs compared with the standard of care. These analyses do not account for the budget impact associated with implementing the interventions on all eligible patients. Even when a new intervention is highly cost-effective, health care systems may not be able to adopt it due to substantial budgetary impacts. Implementing a substantially lower-cost intervention to a substantially wider population, accepting inferior per-patient outcomes, may improve overall health outcomes under a restricted budget. **OBJECTIVES:** Develop an innovative health technology assessment (HTA) model that combines CEA and budget-impact analyses, thus enabling to compare the impact of intervention alternatives on the entire intended use population, under a pre-specified budget constraint. **METHODS:** We identified the following steps to be included in the model formulation: 1) Define the intended use and the target population. 2) Define two or more interventions, one of them at higher cost and better per-patient outcome, and the second with lower cost and inferior per-patient outcome. 3) Forecast the diffusion of the alternatives into the entire intended use population, under a pre-defined budget, in order to estimate the treated and untreated populations. 4) Calculate the clinical impact of each alternative on the treated population. 5) Calculate the clinical impact of no therapy on the untreated population 6) Compare the aggregated clinical impact of each alternative on the entire intended use population – both treated and untreated. Using the proposed population-based model may result in improved health care outcomes, especially in times of economic downturn and austerity.

PRM239

EVIDENCE-BASED METHODS IN FOOD SCIENCES AND NUTRITION

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Evidence-based medicine has emerged as the bottom line of Health Technology Assessments for drug evaluations. Over the last decade, evidence-based assessment of food and nutritional products has accelerated. Specific quantitative tools to synthetize evidence have been increasingly developed, and used for decision support. This work aims at highlighting the critical role of systematic reviews and model-based evidence synthesis in the field of food sciences and nutrition, especially with the view of safety assessment. To first set the scene of food assessment in Europe, the latest Guidelines on Systematic Reviews published by the European Food Safety Authority (EFSA) (EFSA, 2010) are described with the approach on how to handle observational data on the general population. Specific examples of large systematic reviews conducted for estimating food safety accounting for population variability and interactions between food contaminants and drugs are also presented. Details on the model-based meta-analyses of such safety data are described and discussed for the purpose of regulator's decision making. Systematic reviews have been to the context of food and nutritional epidemiology requiring more stringent quality assessment and more advanced management of variability. This resulted in a Bayesian random effect model accounting for population variability. Metabolic interactions between food and drugs were evidenced and variability metrics could be explicated in terms of "uncertainty factors" to be used by the food regulators to assess safety limits for food ingredients, contaminants or drugs and their combined use. Food regulator in EU is aligning and even sometimes anticipating drug regulators in terms of evidence-based safety assessment in the real life. Common tools for model-based evidence synthesis can be applied to quantify safety signals and interaction in the general population.

PRM240

COMPARATIVE EFFICIENCY RESEARCH: META-ANALYSIS OF COST-EFFECTIVENESS STUDIES

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OBJECTIVES: Cost-effectiveness analyses (CEA) have become widely used in several pathologies. Currently, new CEA studies comparing active vs control treatment have been incorporated each year. For this reason, the combination of CEA studies could give a more consistent and accurate estimate of an intervention's efficiency than one study alone. The aim of study was to develop a new method to do comparative efficiency research (COMER) based in individual patient data. **METHODS:** After, adjusted the marginal distribution and copula distribution of a hypothetical cohort, we stated the parameters and distribution estimated like our unknown theoretical distribution. We conducted an iterative analysis of a random Frank Copula distribution with a different range of sample size. We performed a comparison between samples and theoretical distribution in terms of incremental cost-effectiveness ratio (ICER), incremental monetary benefit(IMB) fixed a threshold (k= 20.000 monetary units) and goodness of fit for Frank copula, assuming a tolerance. **RESULTS:** The Theoretical distribution fixed, showed a cost of 604.34 monetary units for active and 516.12 monetary units for control, and a utilities of 0.529 for active and 0.492 for control. ICER for theoretical cohort was 2,380 monetary units per quality-adjusted life year gained and IMB was 653. With a tolerance of 500 monetary units for ICER and 50 monetary units for IMB, only 15.52% of simulations were near the theoretical ICER and only 6.12% of IMB. The amount of individual patients simulated was more than 500 patients per treatment to fit Frank Copula. **CONCLUSIONS:** Preliminary results showed that COMER based in individual patients' data could allow decision maker to know real add-value of a new intervention.

PRM241

EVALUATING THE ECONOMIC IMPACT OF TECHNOLOGICAL ADVANCES IN DIAGNOSTICS: THE CASE OF HIGH THROUGHPUT SEQUENCING FOR HEREDITARY BREAST CANCER

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Benefits of diagnostics tests generally centre on test accuracy measures. However, additional benefits of diagnostics may include: reduced laboratory time, reduced time to results and increases in the capacity of a laboratory to deliver more tests. New technological developments, such as high throughput sequencing (HTS) are challenging the current methods used in establishing the case for the introduction into clinical practice terms of economic impact. This is evident in the case study developed here examining *BRCA1/2* genetic testing in providing information on the risk of development of breast cancer. Current *BRCA1/2* testing technologies are limited by long (up to one-year) turnaround times, which together with limited resources to increase the volume of tests and associated genetic counselling, has driven the use of a 'risk threshold' to target women eligible for testing. HTS offers the opportunity of decreased turnaround time and increased volume of *BRCA1/2* tests, which will impact on the benefits and costs associated with the diagnostic service. Systematic reviews have identified Markov-type models as the dominant modeling methodology for the assessment of genetic testing. We propose that discrete event simulation (DES) is the appropriate model type to quantify the economic impact of HTS *BRCA1/2* testing as it allows evaluation of the impact of capacity constraints and increased turnaround time on the costs and benefits of this new diagnostic technology. Importantly, DES also allows for the assessment of structural uncertainty by considering changes in patient pathways when using a new diagnostic technology. While DES may be the most appropriate modeling methodology in assessing the economic impact of novel genetic tests; typically the type of data and information required to popuate these models in lacking. We conclude by highlighting the type of data required to both population appropriate models and to adequately assess the economic impact of these novel genetic tests.

PRM242

THE IMPORTANCE OF SENSITIVITY ANALYSES IN HEALTH TECHNOLOGY ASSESSMENTS

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In this paper, we critically evaulated analytical design of health technology assessment methodologies, particularly related to sensitivity analyses and willingness-to-pay thresholds. To this end, we have used two studies: the first one analyzing cost-effectiveness of a human papillomavirus vaccination of boys at age 12 against oropharyngeal carcinoma and anogenital warts and the second one examining cost-effectiveness of a universal programme of vaccinating children against pneumococcal disease. We have shown – as expected – that the impact of variation of parameters can be substantial, however, outcomes of sensitivity analyses are often understated both by marketing authorization holders and authorities. Few would