ural history model to project clinical and/or economic outcomes. **METHODS:** The subset of stage I-III colon cancer patients who will experience recurrence face a constant rate rd of transition from undetectable to theoretically detectable recurrence during a given interval. These same patients face a constant rate ru of transition from resectable (i.e. potentially curable) to unresectable metastatic disease with a minimum interval xdu between the point of detectability and the point of unresectability. A third constant rate parameter rs will determine when, on average, individuals develop recurrence-related symptoms prompting them to seek medical advice before the next scheduled evaluation. The mean point of symptom development will follow the point at which a recurrence becomes detectable by a span of at least xds. However, a normally distributed error term Eds will mean that, for a given simulated patient, symptoms may initiate before or after the patient reaches unresectability. **RESULTS:** A best-fitting set of these natural history parameters can be selected by calibrating to targets of time-to-detection of recurrence, time-to-death, and proportion of patients who present with recurrence-related symptoms prior to scheduled assessments. **CONCLUSIONS:** The data sources for these targets can be existing experimental, observational, or registry data where follow-up schedule and compliance levels are known.

PRM56

DIFFERENTIAL DISCOUNTING: QUESTIONING THE ASSUMPTION OF HEALTHCARE RESOURCE FUNGIBILITY OVER TIME

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OBJECTIVES: Recent work on differential discounting of cost and health effects has reached a degree of consensus in a previously strongly divided debate. Put simply, it holds that the discount rate applied to health effects should equal the discount rate for costs, less the growth rate of either the cost-effectiveness threshold or the consumption value of health, depending on the objectives of the health system. Assuming positive growth in the threshold or the value of health, this implies the cost-effectiveness of preventative interventions improves relative to the situation under equal discounting. **METHODS:** We show how recent analyses of differential discounting implicitly assume healthcare funds to be completely fungible over time. This assumption is difficult to justify in the context of publically funded healthcare systems that exhaust budgets annually. Assuming funds are not fungible results in alternative differential discount rates: in this case, the discount rate on costs should be adjusted upwards by either the growth rate of the threshold or the consumption value of health. **RESULTS:** Under these discount rates, interventions that impose costs in future periods become more cost-effective relative to the situation under equal discounting, rather than those which yield health gains in the future. Indeed, the cost-effectiveness of preventative interventions that reduce future healthcare costs will deteriorate under such alternative differential discounting. Consequently, interventions' cost-effectiveness may differ greatly between the two differential discounting schemes. CONCLUSION: Cost-effectiveness estimates can be highly sensitive to discounting; therefore the theory underpinning discount rates needs to be robust. This analysis shows that the current understanding of differential discounting needs to be re-examined. CEA authorities in countries currently employing differential discounting such as Belgium and The Netherlands and those contemplating it such as England and Wales should consider these issues carefully.

PRM57

REVISITING HPV VACCINATION: WHY EXISTING CEAS UNDERESTIMATE THE VACCINE'S COST-EFFECTIVENESS AND INCORRECTLY ESTIMATE ITS THRESHOLD PRICE

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OBJECTIVES: Existing cost-effectiveness analyses (CEAs) of Human Papillomavirus (HPV) vaccination assume cervical screening remains unchanged. However, current screening intensities are unlikely to be cost-effective due to the likely reduction in disease incidence in vaccinated women. Therefore, reductions in screening intensity are probable. The cost-effectiveness attributable to vaccination varies with screening intensity. The assumption of unaltered screening leads to an underestimation of vaccine cost-effectiveness relative to when screening intensity is reduced. Furthermore, failure to consider other screening intensities yields an incomplete efficient frontier in the cost-effectiveness plane. This can lead to an incorrect estimate of the price at which vaccination becomes marginally cost-effective for a given cost-effectiveness threshold. **METHODS:** We review cost-effectiveness estimates for a wide range of screening only and vaccination plus screening strategies from a model used to estimate vaccine cost-effectiveness in the The Netherlands. We indicate what comparison was used to estimate vaccine cost-effectiveness in previous studies, show what comparisons would be more appropriate and explain how these differ. **RESULTS:** We then show why the cost-effectiveness of adding vaccination to a given screening strategy is not the appropriate basis to determine if the vaccine is cost-effective or the threshold price. Rather, both should be determined by the ICER between the most costly efficient screening only strategy and the least costly vaccination plus screening strategy, even where this least costly vaccination plus screening strategy is not the optimal strategy for a given threshold. **CONCLUSIONS:** CEAs of HPV vaccination may no longer be policy or research priorities following widespread reimbursement and precipitous price reductions. However, the methodological issues raised here are pertinent to both any future CEA of an enhanced vaccine with protection against more HPV types and more generally to cases in which the cost-effectiveness of complementary interventions are not independent.

PRM58

METHODOLOGICAL REVIEWS OF ECONOMIC EVALUATIONS IN HEALTH CARE: ARE THEY USEFUL?

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INTRODUCTION AND OBJECTIVES: The increasing amount of economic evaluations in health technologies published during the last decades have generated the concern about their methodological features. The aim of this study is, firstly, to explore methodological reviews and to detect their main research topics and, secondly, to appraise their usefulness for economic evaluation practice. **METHODS:** We performed systematic searches in electronic databases (Scopus, Medline and Pubmed) of methodological reviews published in English, period 1990- 2010. We selected those articles whose main purpose was to review and assess the applied methodology. Then we classified data according to study objectives, period of the review, number of reviewed studies, methodological items assessed and their main conclusions. Additionally, we checked how generalizability issues were considered in the reviews. **RESULTS:** A total of 58 methodological reviews were identified, 42 were published during the period 1990 - 2001 and 16 during 2002-10. Items most frequently assessed (by 70% of the reviews) were: perspective, uncertainty and discounting. The type of intervention and disease, funding sources, country in which the evaluation took place, type of journal and author's characteristics were also described in the literature. Generalizability issues were only checked in 14 studies, mainly by those published after 2000. **CONCLUSIONS:** there is an increasing activity of reviewing economic evaluation studies aiming to analyse the application of methodological principles and to offer summaries of papers classified by either diseases or health technologies. These reviews are useful to detect literature trends, targets of the studies and possible deficiencies in the implementation of the methods to specific health interventions.

PRM59

ESTIMATING THE CONFIDENCE INTERVAL FOR THE COST-EFFECTIVENESS RATIO FROM A FAMILY OF REGRESSIONS ON NET MONETARY BENEFIT

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OBJECTIVES: To demonstrate a novel way of deriving the incremental cost-effectiveness ratio (ICER) and associated 95% confidence interval (CI) from the cost-effectiveness acceptability curve (CEAC) generated from a family of regressions on net monetary benefit (NMB). **METHODS:** Definitions and mathematical properties of the ICER, NMB, and CEAC are explored to construct a technique for deriving 95% CIs around the ICER estimated from the CEAC. **RESULTS:** CEA uses the ICER, a measure with statistical issues that preclude easy derivation of confidence intervals. NMB is defined for any willingness-to-pay (WTP) value as: NMB = (effectiveness X WTP) – cost. Because NMB is statistically well-behaved, regression analysis can estimate incremental net monetary benefit (INMB) as the parameter estimate associated with treatment. INMB = (delta effectiveness X WTP) – delta cost. The CEAC is generated from a family of these regressions where the unique members of the family are identified by unique levels of WTP used to calculate NMB. The ICER is the point on the CEAC where the probability of being cost-effective is 50%, because at that point INMB is zero and WTP equals delta cost/delta effectiveness; i.e., the ICER. That point on the CEAC can be identified numerically by simultaneously solving the two equations for INMB from the two regressions that flank estimated INMB of zero. Knowing estimated INMB and the WTP we have two equations and two unknowns, and we solve for delta effectiveness and delta cost. We use a similar procedure on the 95% confidence intervals for two estimated INMBs to find the 95% CI for the ICER. **CONCLUSIONS:** In the case where we estimate the ICER from a family of regressions on NMB to construct the CEAC we can also find the 95% CI of the ICER.

PRM60

ASSESSING RELATIVE CLINICAL VALUE ACROSS TUMOR TYPES IN METASTATIC DISEASE

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OBJECTIVES: In the absence of increasing budgets, new therapies and resource constraints have necessitated value trade-offs across tumor types and products. Traditional metrics such as median overall survival (OS) may not fully demonstrate the value of individual products in these comparisons. To highlight this, we assessed the value of different innovative cancer drugs relative to their clinical trial comparator using a variety of OS metrics. **METHODS:** We selected novel oncology products used in the treatment of metastatic disease with documented overall survival benefit over comparator at the time of launch. The selected products were: bevacizumab (colorectal cancer, non squamous non-small cell lung cancer), sunitinib (renal cell carcinoma), sorafenib (hepatocellular carcinoma), lenalidomide (multiple myeloma), ipilimumab (melanoma), trastuzumab (breast cancer). Key survival metrics including median OS, mean OS, and landmark survival rates from each analogue's pivotal trials were used to assess the relative value of each analogue. **RESULTS:** The relative value for each analogue differs depending on the survival metric used, suggesting that median OS does not fully capture the value of oncology agents. For example, lenalidomide's relative value is the highest in terms of median OS improvement; however its relative value is diminished when looking at mean OS. Ipilimumab, conversely, shows the highest value in terms of mean OS (attributing benefit to a proportion of patients achieving prolonged survival benefit). Furthermore, sorafenib (HCC) and ipilimumab (melanoma) demonstrate the highest relative value when evaluating 1 year survival improvement.

CONCLUSIONS: This exploratory analysis suggests that use of a broader range of metrics to assess and benchmark value across tumor types may be needed to appropriately inform decision-makers looking to maximize clinical benefit to patients while managing constrained resources.

PRM61

SAMPLE SIZE ESTIMATION FOR PROSPECTIVE OBSERVATIONAL STUDIES

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OBJECTIVES: Unlike randomized clinical trials (RCTs), prospective observational studies typically address objectives rather than test specific hypotheses. Nevertheless, a minimum sample size is required to allow for adequate exploration of the objectives, and estimation of sample size is an important part of the planning process for these studies. Sample size estimation for observational studies is more complex than sample size calculation for RCTs; subgroup analyses and modeling are to be expected in observational studies, and these analysis methods may require more assumptions and larger sample sizes. At the same time, sample sizes must not be so large as to raise concern that the study includes an unnecessarily high number of sites and patients. This is particularly true for product registries where a specific product is being observed. **METHODS:** This poster will provide examples/case studies of sample size estimations performed for a variety of prospective observational studies and objectives. These case studies will focus on the following **METHODS:** 1) Incorporation of planned propensity score matching to support comparisons of cohorts or subgroups; 2) Investigation of factors that influence outcomes within subgroups; 3) Estimation expressed as number of person-years rather than persons; and 4) Re-estimation of sample size based on interim results. RESULTS AND **CONCLUSIONS:** These methods illustrate the difference between sample size estimation in prospective observational studies and sample size calculation in randomized clinical trials.

PRM62

THE IMPACT OF CENTRE SELECTION ON THE GENERALISABILITY OF ECONOMIC EVALUATION RESULTS FROM MULTI-CENTRE RANDOMISED CONTROLLED TRIALS

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OBJECTIVES: Economic evaluation (EE) estimates for individual centres in multi-centre randomized controlled trials (RCTs) can differ significantly from the trial-wide result. The existing methods addressing the generalisability of EE results from RCTs (e.g. bivariate hierarchical modelling) assume that the recruiting centres are representative for their jurisdictions, but this assumption has not been generally verified. No explicit method of selecting centres and their recommended sample sizes has been described, despite having been suggested in the literature. **METHODS:** The working hypothesis is that transparent centre selection is a crucial step in assessing the generalisability of EE results from RCTs. Two questions arise: 1) What criteria underpin the current practice of selecting centres for RCT-based EEs? and 2) Can a valid quantitative algorithm be formulated to assist the centre selection process at the trial design stage? **RESULTS:** First, the use of modelling-based methods addressing generalisability has to be supported by evidence that centres are representative for the jurisdiction under scrutiny. There is, thus, a need to assess the current practice of selecting centres for RCT-based EEs. Second, a quantitative methodology for purposively selecting centres for RCTs coupled with EEs has to be devised in order to underpin an objective centre selection process. The proposed operational measure is a generalisability index (GIx) which aggregates relevant generic and intervention-specific covariates and can be formulated at both jurisdiction and centre-level. The GIx can be validated against centre-level cost-effectiveness estimates. **CONCLUSIONS:** A successfully validated GIx will provide evidence towards the legitimate use of existing generalisability techniques. The GIx will allow an objective generalisability assessment for centres that did not participate in the RCT. Describing the rationale for centre selection must become a standalone item in reporting checklists for RCTs and EEs. Furthermore, such a methodology will bridge policy and research by correlating jurisdictional interests with RCT design.

PRM63

MULTIPLE CHOICES - HOW TO MAKE RATIONAL DECISIONS ACROSS SEVERAL INTERVENTIONS WHEN FACED WITH DIFFERENT OUTCOMES AND PERSPECTIVES?

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OBJECTIVES: In any assessment to facilitate decision making to allocate limited funding across multiple innovations, the relative value of clinical outcomes or cost containment depends upon preferences. In the case of allocating funds across a portfolio of interventions, one could maximise cases-, hospitalizations-, or deaths-avoided; and/or minimize costs from a health care payer or societal perspective. The optimal mix of innovations to reach the preferred target can be investigated by applying operational research modelling. However, a composite outcome is required in order to maximise multiple endpoints consecutively depending upon preferences for different endpoints. **METHODS:** An optimization model was developed in Microsoft Excel® using the solver function to evaluate the optimal mix of vaccines to implement within a portfolio, in order to avoid specific clinical outcomes (GP-visits, hospitalisations, deaths) or maximise QALYs gained within specific constraints including budget. A composite endpoint was developed to take into account different endpoints, clinical and cost, weighted according to preferences defined by the assessor. The composite endpoint was used as the objective function. **RESULTS:** Depending upon the preference weights defined when determining the composite endpoint, the allocation of resources across a portfolio of several vaccines resulted in different recommendations. If deaths-avoided was weighted highest then the model would optimize on elderly influenza vaccination, adolescent HPV and infant pneumococcal vaccines. If cases-avoided was the highest preference then varicella, rotavirus and pertussis vaccines were recommended. If cost-offsets from a payer perspective were maximised then the recommendation would be to first implement adolescent HPV, elderly influenza and rotavirus vaccination. The combination of preferences to avoid mortality and/or morbidity and/or maximize cost offsets resulted in the recommendation to implement different vaccines from the portfolio. **CONCLUSIONS:** The use of a composite measure and operational research modelling provides a tool to facilitate resource allocation across a portfolio of interventions depending upon decision-maker preferences.

PRM64

THE ROLE OF THE INSTRUMENT DEVELOPER IN THE TRANSLATION OF PATIENT REPORTED OUTCOME MEASURES

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OBJECTIVES: Developers of patient reported outcome (PRO) measures are often involved in the translation of their measures into other languages, and they provide valuable guidance by reviewing concept elaboration and back translation review documents and participating in harmonisation meetings. **METHODS:** However, many of the translation problems that they help resolve are due to difficulties in translating concepts in the measure that are either culturally bound or idiomatic to the source language, and these are features that might be addressed more effectively at an earlier stage. **RESULTS:** The developer can have a positive impact on future translations right from the onset by considering the 'translatability' of concepts when they are developing their conceptual model and generating their item pool, thereby aiming to create a measure which can be translated more accurately. **CONCLUSIONS:** We will examine common linguistic and cultural features which may make measures difficult to translate, and how developers can avoid these to help create global PRO measures that can be applied to all cultures and be administered in global clinical trials and health research.

PRM65

SHOULD WE AGGREGATE COST-EFFECTIVENESS OVER AN INTERVENTION'S ENTIRE IMPLEMENTATION LIFETIME?

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OBJECTIVES: Recent work has suggested that interventions' cost-effectiveness should be assessed over their entire lifetime of implementation, not just over the period of use for a single cohort as typically modelled (Hoyle and Anderson, Medical Decision Making, 2010; Hoyle, PharmacoEconomics, 2011). Such lifetime modelling can capture changes in costs and effects over time. These changes in costs and effects can result from price changes, disease dynamics or the application of differential discounting of costs and health effects. **METHODS:** Suggesting cost-effectiveness be assessed over an intervention's complete lifetime carries assumptions regarding the nature of the decision problem in healthcare resource allocation. In particular, it suggests resources be allocated on the basis of the total cost-effectiveness over all periods in which it is implemented. This lifetime perspective can conflict with the alternative perspective that resources be allocated on the basis of relative cost-effectiveness within each given period. We discuss a number of simple theoretical examples in which the rank ordering of cost-effectiveness of two interventions is different under the two perspectives. The examples include when the prices of interventions trend and have different expected lifetimes, when differential discounting is applied in certain circumstances, or simply when the price of only one intervention falls following patent expiry. **RESULTS:** These examples prompt us to consider which perspective is more appropriate. We argue that as health care resource allocation is an ongoing, repeated resource allocation problem, not one over a finite horizon, that the lifetime perspective is not appropriate. CONCLUSION: Advances in decision analytic modelling need to carefully reflect the actual nature of policy choices. The per-period perspective appears more appropriate to healthcare resource allocation problems than the total implementation lifetime perspective. However, the actual resource allocation process is likely to more complex than either perspective alone might suggest.

PRM66

COMPARISON OF RECONCILIATION AND REVIEW METHODOLOGIES FOR THE TRANSLATION OF PATIENT REPORTED OUTCOME (PRO) MEASURES

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METHODS: The first is the reconciliation of two independent translations by an in-country investigator (a lead translator). The second is the back translation review - the reconciled translation is translated back into English and the project manager reviews the English translation(s) against the source text, then the translation is refined through discussion between the project manager and the investigator. Both stages are conducted via email, and the back translation review report is usually reviewed by the instrument developer once all issues have been addressed. We will present an alternative methodology whereby the reconciliation and back translation review are conducted through live conversations (in teleconferences or otherwise) involving forward translators and the instrument developer. **RESULTS:** We will compare these two processes in terms of the types of discussion