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OBJECTIVES: Use of economic evaluation of health care technologies is intensively discussed in the government in Japan. In order to make evaluation results comparable, standardized method of evaluation is required. We proposed an economic evaluation guideline in Japan. **METHODS:** We organized a research team for developing guideline. After reviewing guidelines in HTA agencies in the world and current debate on issues, we investigated HTA reports and methodology of economic evaluation studies in several drugs, devices and procedures. Based on the review of these information, the research group discussed and proposed economic evaluation guideline suitable for Japan. **RESULTS:** Proposed guideline consist of 13 items: 1) Objective; 2) Perspective of analysis; 3) Comparators; 4) Method of analysis; 5) Time horizon; 6)Choice of outcomes; 7) Source of clinical data; 8) Costs; 9) Productivity loss; 10) Discounting; 11) Modeling; 12) Uncertainty; and 13) Budget impact analysis. Guideline sentences are classified into 3 levels, principal, recommended, and optional. **CONCLUSION:** This guideline is a proposal by a research team. However, it will be needed in the near future for using economic evaluation of health care technologies. Proposed guideline should be tested by adopting individual studies.

PRM219

DEALING WITH ZERO CELLS IN SPARSE NETWORKS IN BAYESIAN NETWORK META-ANALYSIS

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OBJECTIVES: Bayesian Network Meta-Analysis (NMA) models for binary data are well established and special precautions do not usually need to be taken in the case of zero cell counts. Furthermore, trials with zero cells in both arms are usually excluded from the analysis. However, in sparse networks with only one trial per comparison and zero cells in unique link studies, their inclusion may be mandatory. Zero frequencies may result in numerical instability and/or large variances. The objective of this study was to investigate the effect of different methods dealing with zero cells in sparse networks in Bayesian NMA. **METHODS:** A review was conducted to identify methods dealing with zero cells for binary outcomes in sparse networks in a Bayesian setting. The identified methods were applied to a sparse network with six treatments and one study per comparison. The outcome was grade 3+ Adverse Events and measured by Odds Ratio. A fixed effects model was fitted with binomial likelihood. The performance of the methods was assessed by the residual deviance and the Credible Intervals' (CrI) width was compared. **RESULTS:** We identified three methods: apply a continuity correction (a constant factor of 0.5 or the reciprocal of the opposite treatment size), use of informative priors on treatment effects and placing a distribution on the baseline model. We applied all methods and combinations of them. The model fit was adequate for all methods (residual deviance [10;12.3] for 12 datapoints). The use of different informative priors improved the variability estimates. CrI widths were reduced up to 15 times with respect to the original model with vague priors. **CONCLUSIONS:** Although the debate on the inclusion of studies with zero events in NMA is still open, our research shows that methods are available to address this issue. However, no clear recommendations can be provided.

PRM220

QUALITY ASSESSMENT OF OBSERVATIONAL STUDIES FOR SYSTEMATIC REVIEWS

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Observational studies are frequently included in systematic reviews, especially in those disease areas where RCTs are limited. While there are very specific tools for and guidance on assessing the quality of RCTs, the assessment of observational studies is less standardized. OBJECTIVE: To understand and assess the different tools used to review the quality of observational studies and to make recommendations based on our evaluation. **METHODS:** First, a systematic review of literature from 2005-present was conducted in Embase and Medline to determine the frequency of use of quality assessment for observational studies and the type of tools used to conduct the assessment. Second, we reviewed documentation from NHS guidance on quality assessment of non-randomized studies. Finally, we reviewed two years of approved HTA submissions to see what methods of assessment have been used for submissions. **RESULTS:** A total of 1429 articles were screened. Compared to a similar study on older literature, our review found an increase in the use of quality assessment for observational studies. However, we found that many studies continue to devise their own tool or adapt existing tools rather than use a tool in its entirety. Downs and Black, MOOSE, and STROBE were the most referenced tools, although STROBE was not originally intended for such use. Guidelines centered on "non-randomized" studies were mixed and were not always found to be applicable to observational studies, but instead mostly to single-armed clinical trials. **CONCLUSIONS:** There is still a need for guidance and standardization for observational studies assessment for use in systematic literature reviews. Although quality assessment of observational studies is still not standardized, there are a few methods becoming more frequent in the literature but are difficult to compare across systematic literature reviews because they have often been adapted by each author.

PRM221

AN APPROACH FOR QUANTIFICATION OF PATIENT ADVOCACY GROUP INPUT IN THE HTA PROCESS

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Patient input in HTA pathways by the appropriate disease Patient Advocacy Group (PAG) uses principally humanistic and social studies as an evidence base followed by critical evaluation against traditional CEA (Cost Effective Analysis) via a scientific process. Patient and Public Involvement (PPI) in HTA is associated with a low evidence base potentially limiting its value. Research presented at ISPOR 2012 by the same authors concluded a need to improve and standardize PAG input integration in HTA decision making. To investigate the way different forms of knowledge / experience are used by PAGs in NICE HTA for guideline development and new technology review. We will look at: 1) Influence of PAG structure, resource capability, internal process and the impact of PAG advisory board physician representatives on scientific validation of patient input in HTA participation, and 2) Part I results will inform further research into selection and ranking criteria of social derived data compared with CEA. An iterative PPI best practice approach will be followed. Selection criteria: Five UK PAG groups (Neurological, Autoimmune, Rare disease, Cardiovascular and Oncology) will be invited to participate. The NICE PPI Unit will nominate groups when needed. Inclusion criteria: 1) willingness to participate, 2) prior involvement in guideline / new technology assessments; and 3) presence of medical advisory board. Research elements: Application of GRIPP criteria (Guidance Reporting Involvement Patient Public) to ensure a strong evidence base will guide development of an on-line survey and subsequent focus groups and interviews. The survey, designed for SAP review, will study: size of PAG, internal process for HTA involvement, previous HTA involvement, data submitted, PAG knowledge gaps and involvement of medical advisory board. Follow up by focus groups and interviews with PAG and advisory board members to identify insights/themes.

PRM222

JUGGLING JURISDICTIONS: METHODS FOR CONDUCTING MODULAR SYSTEMATIC REVIEWS?

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A crucial component of a systematic review is a clear description of the disposition of studies throughout the various steps of the review process (de-duplication, abstract review, full paper review and final inclusion). This is commonly achieved using a PRISMA diagram that shows the number of inclusions and exclusions at each stage of the review. This may be supplemented with details of the reasons for exclusion. To create the PRISMA diagram it is necessary to keep an on-going count of exclusions and inclusions throughout the review process. However, this can pose a challenge where the scope of a systematic review changes from the original specification. This may happen where the set of licensed treatments or HTA requirements vary between jurisdictions or over time. In these cases, it may be time consuming to recreate the on-going counts of exclusions that correspond to the modified scope. We present a methodology for conducting a modular systematic review in which PRISMA diagrams and other descriptions of study disposition can be generated corresponding to any subsequent changes of scope. This is achieved by splitting the review into a set of 'component-reviews' defined by mutually exclusive treatment search terms that comprise the full set of possible intersections between the individual treatments. Throughout the systematic review process separate counts of abstracts, papers and studies are maintained for each of these component-reviews. The results from the component-reviews can then be combined to reflect any final review scope (based on individual treatments). We will illustrate the methodology with an example review of the comparative efficacy of licenced thiazolidinedione's (TZDs) versus placebo in patients with type 2 diabetes mellitus (T2DM) where there are two TZDs licensed in the USA (pioglitazone and rosiglitazone) but only one in Europe (pioglitazone).

PRM223

SOCIAL NETWORK ANALYSIS OF AUTHORSHIP NETWORKS AND THE IDENTIFICATION OF EXPERT ADVISORS

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OBJECTIVES: Systematic reviews are often supplemented with the use of external experts to provide guidance on the nuances of the area. This can help add context if a review is used to support trial design or health economic model development. The ideal expert would have a deep understanding of the area and be well connected to those individuals conducting trials. The aim of the current research was to assess whether social network analysis of coauthor networks could be used to rapidly and objectively identify individuals with the qualities desired in an external expert. **METHODS:** Publication lists from a recent systematic review of rheumatoid arthritis were used to produce a list of links between authors and publications. This was then imported into the Gephi program for social network analysis. Within Gephi, matrix multiplication was used to transform this network into a coauthorship network. Eigenvector centrality was then used to infer the amount of access individual authors have to the research community as a whole. The use of eigenvector centrality as a measure of influence within the author network was then validated by correlating the centrality scores of a random sample of authors against independent ratings of desirability of those individuals' expertise. **RESULTS:** The coauthor network for rheumatoid arthritis, while not completely connected, showed a high degree of connectivity (mean degree: 26, network diameter: 5). Eigenvector centrality allowed the identification of key experts, with the highest scoring experts each providing direct access to approximately half of the whole network. Eigenvector centrality measures were a reliable predictor of mean desirability scores from ten raters ($F(1,9)=20.35$, $p=0.0015$, R-squared=0.69). **CONCLUSIONS:** Social network analysis of coauthor networks provides an efficient and robust method for the identification of expertise, and can be used as part of the systematic review process.

PRM224

SYSTEMATIC REVIEW APPROACHES FOR HTA: HORSES FOR COURSES?

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Systematic reviews aim to identify, select, synthesize and appraise all high quality research evidence relevant to a particular research question, and are widely accepted as the gold standard for providing the best evidence for use in decision making. They are essential, routine components of submission data packages for health technology assessments (HTAs) of products undergoing evaluation for reimbursement and market access. Additionally, systematic reviews are often the source for clinical evidence used in health economic modelling to evaluate cost-effectiveness. Thus, they represent a substantial investment of resources, and incorrect or incomplete reviews could invalidate the proposed clinical and economic value of a product set out in a health technology submission and result in unfavourable reimbursement decisions and/or delayed market access. There are a number of best practice criteria set down for systematic reviews; the most widely recognised being from the Cochrane group. However, when carrying out a systematic review for HTA purposes researchers should be aware of the additional requirements set out by each agency. The Cochrane, UK National Institute for Clinical Excellence (NICE) and Germany's Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis (IQWIG) methodological guidelines for conducting and reporting systematic reviews were analysed and an 'inclusive' checklist of requirements was developed to ensure the systematic review and meta-analysis met the broad set of HTA requirements and minimise the risk of having to repeat the procedure or create the need for a HTA review group to carry out its own review, which could potentially lead to an unfavourable reimbursement decision or a restriction on use. An awareness of specific HTA systematic review requirements can help optimise the preparation of a data package for HTA submission and hence maximise the chances of success.

PRM225

CAN A MULTI-CRITERIA DECISION (MCD) OPTIMISATION MODEL HELP DECISION MAKERS IN THE OPTIMAL SELECTION OF VACCINES WHEN EXPANDING THEIR UNIVERSAL MASS VACCINATION PROGRAMME? THE CASE OF POLAND

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OBJECTIVES: The model aims to determine the optimal allocation of financial resources amongst various paediatric vaccines accounting for changes in budget and availability of new vaccines over time. This approach aims to inform decision makers who are seeking to extend their national immunisation programmes about the optimal mix of vaccines and sequence of their introduction, meanwhile accounting for their preferences in clinical and cost outcomes. **METHODS:** An MCD optimisation model was developed in Microsoft *Excel* that considered availability of new vaccines and budget changes over time, optimal mix of vaccines in previous years, budget investment time horizon, cumulative outcomes time horizon, maximal achievable vaccination coverage, specific target populations. The optimal mix of vaccines within an available portfolio was determined by manually programmed linear optimisation based on a defined objective function and budget constraints. The objective function includes maximisation of prevention of disease cases, GP visits, hospitalisations, deaths, and cost savings in disease management. A multi-criteria approach allows for redistributing weights across clinical and cost outcomes in the objective function. Vaccination against rotavirus, varicella, influenza and pneumococcal disease was evaluated, based on disease incidences and direct medical costs from Poland. Relative risk reductions induced by vaccination were based on randomised controlled trials and post-marketing surveillance data. **RESULTS:** Dependent on the definition of objective function, the allocation of budget across a portfolio of vaccines resulted in different recommendations. If deaths-avoided was weighted at maximum, pneumococcal vaccine was ranked first, followed by rotavirus and influenza vaccination. If cost savings received the maximum preference, vaccination against influenza was ranked first, rotavirus second, pneumococcal third, and varicella fourth. The use of a weighted objective function resulted in different vaccines introduction sequences. **CONCLUSIONS:** The use of an MCD optimisation model provides a tool to inform decision makers about the optimal allocation of financial resources over time.

PRM226

DON'T MAKE ME WAIT: THE VARIANCE REDUCTION TECHNIQUE FOR FASTER MONTE CARLO SIMULATIONS IN COST EFFECTIVENESS MODELS ON WEB

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With the rapid pervasion of internet technologies, demand for making health economic evidence, such as mathematical models, accessible through the web increases. Long running computations such as Monte Carlo simulation can impair user experience because of longer waiting time. Our aim is to employ mathematical techniques to reduce the computation time of probabilistic cost effectiveness Monte Carlo models, thus increasing their acceptance when used on the web. We employ the variance reduction technique to reduce computation time while obtaining outcomes with the same Monte Carlo error. The control variate approach is applied. It utilizes information about errors in estimates of known mean Net Monetary Benefit (NMB) quantities to reduce errors in estimation of the cost-effectiveness acceptability curve. The NMB mean value is calculated based on the deterministic counterpart of the model. The said technique has been applied to the published probabilistic decision tree-based Excel model for evaluating cost-effectiveness of breast cancer screening. In this model, different types of probability distributions can be chosen to model uncertainty of disease incidence, mortality rate and intervention effectiveness. By applying the control variate approach we were able to achieve outcome with the same error while performing 50% less simulations as compared to the plain Monte Carlo method. Such performance improvement is yet another step towards increasing user acceptance of web based health economic models with Monte Carlo simulations.

PRM228

SIMULATED TREATMENT COMPARISONS – AN ALTERNATIVE APPROACH TO INDIRECT COMPARISON WHEN STANDARD METHODS ARE NOT FEASIBLE OR APPROPRIATE

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Health technology assessments (HTAs) rely on comparative evidence about new treatments and competing therapies, which are typically derived using indirect or mixed treatment comparisons (ITC/MTCs). These are not always feasible or appropriate, particularly in rapidly evolving therapeutic areas, like oncology. For instance, some comparisons may not be possible due to incomplete evidence networks; or, heterogeneity between studies due to differences in design or population may make an MTC inappropriate. There is, therefore, a need for alternative techniques, such as Simulated Treatment Comparisons (STCs). This technique is designed to derive comparisons between treatments after adjustment for differences between the populations of the two studies. This targeted comparison requires individual patient-level data (IPD) for at least one of the treatments (the index), and are appropriate when the trials used for the comparison are sufficiently comparable in design and methods, but differ in the profiles of their population in measured risk factors. The differences can be adjusted analytically using IPD via regression equations. This produces endpoint estimates for the index treatment that reflect the profile of the comparator population. These can then be contrasted with published results for the comparator to obtain a measure of difference between treatments. Since only measured risk factors can be included in the adjustment, the potential for residual confounding remains. Another potential bias is a possible "study effect" whereby other differences between studies distort the comparisons. This can be assessed using the reference groups of the trials, if these received the same treatment. STCs have been used in HTA submissions, and it is likely that its use and that of other alternative techniques will increase particularly in areas with rapid drug development. In the presence of heterogeneity or incomplete evidence networks, STCs can provide comparative evidence where these may be otherwise deemed unavailable due to limitations of ITCs/MTCs.

PRM229

THE USE OF EUROPEAN ELECTRONIC HEALTH RECORDS TO INVESTIGATE CANCER TREATMENT PATHWAYS

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RCTs remain the gold standard for evaluation of drug efficacy and safety. However, the only way of identifying treatment pathways and improving understanding of costs and outcomes at different stages of care is via longitudinal observational studies. Observational data from electronic health records (EHRs) are increasingly being used to support pharmaco-epidemiological research. Coverage, data quality and validity of UK EHR databases such as the Clinical Practice Research Datalink (CPRD) have improved in recent years, and many papers confirm the validity of data in diagnoses such as cancer. Published data show that recording of cancer diagnosis and mortality in primary care electronic records is generally consistent with Cancer Registry (CR) data in England. The use of "read codes" in CPRD to identify an event (cancer diagnosis or referral to secondary care) and the possibility of anonymous linkage to secondary care databases (e.g. Hospital Episode Statistics [HES] for information about hospital management as an in- or out-patient, to other CR data, and accurate mortality tracking by the Office for National Statistics [ONS]) allows the data and diagnosis to be validated against multiple sources, as well as identifying treatment pathways in both secondary and primary care. There are some limitations, e.g. not all patients identified in GP practices via the CPRD are linked to other databases. Management data such as secondary care prescribing are difficult to access (not available in HES) but may be available from reviewing anonymized patient notes or by connecting to other datasets. For example, IMS Health links CPRD data with hospital pharmacy audit data and HES data. However these data have only become available recently, are expensive to access and currently patient population coverage is low. We will provide a detailed description of the possibilities for integrated database use to map treatment pathways for cancer patients.

PRM230

SHOULD THERE BE AN OPTION TO "UNREFER" NICE SINGLE TECHNOLOGY APPRAISALS: CASE STUDY OF ARIPIPRAZOLE FOR BIPOLAR I DISORDER IN ADOLESCENTS

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Single technology appraisals (STAs) are a key component of the development of NICE technology appraisals guidance, but are a time and resource intensive process. Societal costs are incurred during STAs by holding the NICE Appraisal Committee, via payment to the evidence review group (ERG) and in the opportunity costs of other technologies which are not appraised. In addition, the drug manufacturer also incurs substantial costs in preparation of their submission and throughout the STA process. Recently aripiprazole, an atypical antipsychotic drug for the treatment of manic episodes in adolescent bipolar I disorder, was subjected to an STA and received positive guidance. It was apparent to the ERG from the outset of the appraisal that the conclusion would be positive as: the drug had a small acquisition cost; was already in widespread use; would shortly be going generic; and had a profile similar to its comparators. As the budget impact over a 5-year period estimated by the manufacturer was less than the payment received by the ERG, it was unlikely that the STA represented efficient use of resources. Given a fundamental role of NICE is in assessing cost-effectiveness, the option of un-referring STAs in rare circumstances has appeal. It is proposed that if certain criteria are met then it would be more cost-effective to not proceed with an STA. These include: small patient population, commonly used in current clinical practice, patent expiring in