panel hearings. In two recent highly publicised Food and Drug Administration advisory panel recommendations for orkambi (cystic fibrosis; Vertex Pharmaceuticals) and flibanserin (hypoactive sexual desire disorder; Sprout Pharmaceuticals), testimonials from patients involved in the trials appeared to play an important role in influencing positive recommendations. Feedback from patients participating in clinical trials can provide important information on the potential benefits of a drug beyond the clinical endpoints measured in a trial. However, critics suggest that the purposively selected patient testimonials used within these regulatory interactions are not sufficiently robust sources of data. The authors argue that patient testimonials which influence regulatory decision making should be considered as qualitative data and therefore appraised in-line with other qualitative data submitted as part of a new drug application e.g., qualitative data supporting content validity of patient-reported outcome measures. Testimonials are unlikely to be considered either credible or rigorous in their current format, particularly as samples are often heavily biased towards patients who have experienced positive outcomes whilst on the product. Patient interviews planned a priori can provide valuable insights on the efficacy of a new medication and other important factors such as tolerability and adherence. The authors propose a structured framework to eliciting and analysing these data through qualitative interviews 'nested' within clinical trials. The authors present a procedural checklist for ensuring that credible and robust data are collected. This includes ensuring representative sampling (e.g., patients on both treatment arms and with varying socio-demographic and clinical profiles), utilising trained qualitative interviewers experienced in qualitative data collection and analysis, and timing of interviews (e.g., during and/or after the clinical study).

PRM252

A PRACTICAL GUIDE TO ADDING PATIENT HETEROGENEITY INTO PHASE III TRIALS: RESULTS FROM IMI GETREAL WP2

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OBJECTIVES: Phase III trials typically exclude patients with certain baseline characteristics, such as older age or co-morbidities, and thereby hamper learning of new drugs' effectiveness in real-life. A simulation study was conducted to support implementation of new inclusion criteria for Phase 3 trials in schizophrenia without increasing sample size nor compromising detection of the new drug effect. **METHODS:** A simulation study was performed examining the impact of re-introducing through stratifying by each of the following excluded patients population: age > 65 years, duration of illness < 3 years, patients with previous suicide attempts, patients with history of alcohol or substance abuse, and patients treated in private practices. Patients with these characteristics were multiplied in a synthetic trial population until their real-life proportion in schizophrenia was reached. The simulation used data subsets from the 10,281-patient observational SOHO cohort study. A "base case RCT" was created by applying typical Phase 3 exclusion criteria. A series of "synthetic RCTs" were defined by replacing patients with SOHO patients that were initially excluded. The real-life drug effect was predicted from each synthetic RCT through regression models and compared with the real-life effect in SOHO. **RESULTS:** Perhaps surprisingly, effects of all 3 investigated drugs were found to be larger in real-life than in the base case RCT. Synthetic RCTs were created by replacing patients of the base RCT with patients with a given baseline characteristic. Prediction of real-life effects improved with increasing replacement in terms of mean squared prediction errors and coverage of confidence interval. However, the impact of introducing these "real-life" populations was not equal among factors. For instance, introducing older patients minimally improved prediction of real-life effects, while allowing inclusion of just 5% of patients with past suicide attempts (who make up 25% of the real-life schizophrenia population) significantly improved effectiveness predictions.

PRM253

RAPID AND AUTOMATED TEST FOR CONNECTEDNESS OF EVIDENCE NETWORKS IN NETWORK META ANALYSIS

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OBJECTIVES: Develop a method to quickly test whether a network meta-analysis evidence network is connected. BACKGROUND Network meta-analysis, or mixed treatment comparisons, is a method to combine evidence on multiple treatments that have been compared in randomised controlled trials that form a connected network of treatment comparisons. Evidence networks consist of nodes, representing treatments, and edges, representing clinical trials comparing two treatments. If nodes corresponding to treatments are not connected, they cannot be compared. Connectedness is typically tested by visual inspection, however this is time consuming when there are many separate networks representing different outcomes, subgroups, and scenarios, and also prone to error, especially in large networks . Path finding algorithms can be used to automate testing for connectedness, but these are slow and inefficient. We present a fast and simple approach to test connectedness. **METHODS:** Our method constructs a symmetric square matrix, called the direct connection matrix, with the number of rows and columns equal to the number of treatments in the network. We fill this matrix with ones where treatments of the corresponding row and column have been compared in a trial, and zeros otherwise. The diagonal is filled with ones. Exponentiation of the matrix to the number of treatments, minus one, gives the indirect connection matrix. Non-zero entries of this final matrix represent treatment combinations that can be compared using available evidence, and vice versa. This test is easy to implement in software and can be conducted rapidly. We prove the validity of the method mathematically and illustrate with application to a network of anticoagulants for the prevention of stroke in atrial fibrillation. **CONCLUSIONS:** We have developed a simple and rapid test of connectedness of networks that is easy to automate and can be applied to any network meta-analysis.

PRM254

THE NEED TO REVISE DISCOUNT RATES IN BELGIUM, THE NETHERLANDS, POLAND AND THE UK

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OBJECTIVES: To demonstrate the need to revise discount rates in the cost-effectiveness analysis (CEA) methods guidelines in Belgium, the Netherlands, Poland and the UK. **METHODS:** We identify what discount rates are recommended in the CEA guidelines of the countries above and examine what rationale has been provided in each case. We assess the recommended guidelines in the context of the current theory and empirical evidence on discounting. **RESULTS:** The UK requires discounting of 3.5% for cost and effects in its basecase guidance, but also recommends 1.5% for public health interventions and for specific life-saving interventions. No adequate justification has been provided for this disparity. Applying different discount rates for the same goal of achieving health gain from the same pool of resources is illogical and yields inefficient outcomes. Belgium, the Netherlands and Poland all recommend differential discounting of costs and effects. The discounting guidance in these countries pre-dates recent work that further clarifies the basis for differential discounting. This is significant, as this recent work shows how, under certain assumptions, the differential between costs and effects can be linked to growth in threshold. In turn, this may imply that the differential employed in these countries may be too great. Finally, assuming that the discount rate applied to costs should approximate government borrowing costs, it is likely that the cost discount rate is too high in the base case of all of the countries considered here. **CONCLUSIONS:** The choice of discount rates is important as they are highly influential on the cost-effectiveness of many interventions. Applying different discount rates to different interventions is not justified. Similarly, the rates applied in countries recommending differential discounting lack firm justification. Resource allocation in all the countries considered would likely be improved by the application of a lower common discount rate.

PRM255

ESTABLSHING THE COST-EFFECTIVENESS OF GENOMIC-BASED DIAGNOSTIC TESTS: ARE CURRENT METHODS SUFFICIENT AND APPROPRIATE?

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OBJECTIVES: The clinical value of genomic tests is not always apparent, and very few have demonstrated cost-effectiveness. The objective of this conceptual paper is to understand whether the principles and methods of cost-effectiveness analysis (CEA) are appropriate for the evaluation of genomic-based diagnostic tests, such as whole genome sequencing. **METHODS:** Literature on CEA methods to evaluate genomic tests was systematically searched using 'pearl growing' methods. Data were extracted to identify challenges and solutions to conducting CEA in this context. The key characteristics of genomic tests from an economic perspective were summarized and used to distinguish further challenges. **RESULTS:** Our review highlights two main differences between CEA of genomic tests and that of other technologies: the complexities of evaluating tests for multiple disorders and the potential for genomic information to have consequences for future generations requiring infinite time horizons. Another common feature, not unique to genomic-based diagnostic tests but commonly identified in the literature, was the valuation of non-health benefits. Alternatives to evaluate the diagnosis of multiple disorders are discussed: an iterative approach assessing each diagnosis independently; an aggregate approach combining the cost and benefits from all disorders into a single evaluation; a pragmatic approach that identifies the most important disorders combined with a qualitative assessment of the direction of bias for disorders not included in the full analysis. Consideration of the potential for infinite time horizons suggests CEA should focus on systems that could store, and share, genomic information between generations. **CONCLUSIONS:** The challenges shared with other health technologies, particularly diagnostic tests, suggest that the general principles and methods of CEA are appropriate for genomic tests. Further methodological research would be valuable on approaches for assessing the value of sharing genomic information across generations, approaches to evaluate tests for multiple disorders and trading-off health and non-health benefits.

PRM256

THE CHALLENGES IN EVALUATING THE COST-EFFECTIVENESS OF COMPLEX INTERVENTIONS

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Standard cost-effectiveness methods and critical appraisal toolkits may not be adequate for complex interventions. We systematically reviewed and quality assessed cost-effectiveness studies of a complex intervention, propose a series of new questions to inform their critical appraisal and discuss how future research should be targeted to improve the methods. Reablement was used as an example of a complex intervention. Reablement is a multidisciplinary and multifactorial intervention to support people to relearn activities of daily living. The systematic review identified 12 cost-effectiveness studies on reablement, out of 3,311 unique records. The 12 included studies were data extracted and quality evaluated using a standard checklist. No study provided enough information to inform the decision on whether reablement is cost-effective and should be reimbursed by the payer. The issues included: (i) the use of a perspective not relevant for the decision-maker, (ii) lack of consideration for inter-sectoral effects, (iii) short time horizon, (iv) poor descriptive detail on the interventions, (v) limited comparators, (vi) poor quality evidence on effectiveness, (vii) limited evaluation of uncertainty and (viii) no consideration of the

opportunity cost. These issues informed the development of a new checklist, which was subsequently applied. Critical appraisals of cost-effectiveness studies should consider the aforementioned issues to conclude on their quality and potential to inform decision-making. More research is needed how to quantify the opportunity costs of complex interventions, particularly when multiple sectors are affected.

PRM257

THE VACCINE PORTFOLIO MANAGEMENT MODEL AS AN EFFICIENCY TOOL FOR JAPAN

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Health authorities may face a variety of options when deciding upon expanding their national pediatric immunization programs, ranging between an ad-hoc vaccine selection versus a targeted multi-year program to achieve efficiency goals. The vaccine portfolio management model allows the comparison of these two options over a fixed period of time. This optimization model is based on disease burden, vaccine impact and associated costs which are balanced against available vaccination budget and pre-defined public health priorities. Potential targets consist of reduction in disease events, or GP visits, or hospital occupancy rates, or deaths, or disease management cost. The model determines the optimal combination of vaccines selected per year, resulting in achieving the targeted public health outcome at the lowest annual budget. The financial results are then compared with those obtained after an ad-hoc selection of vaccines. The model was adapted for Japan in children up to 5 years old considering vaccines against pneumococcal disease, rotavirus, mumps and influenza disease based on published data. As an exemplary objective function we selected the reduction in hospital occupancy rates by 35% over a 5-year period. The portfolio model indicates that the optimal strategy consists of vaccination against rotavirus, influenza, and mumps at 90% coverage and 55% vaccine coverage against pneumococcal disease, requiring an annual budget of 331 million EUR. In case of a lower budget, the vaccine selection would prioritize first rotavirus, followed by influenza, then mumps and pneumococcal vaccine (depending on the available budget) to reduce hospital occupancy rates to a maximum extent. With an ad-hoc selection of vaccine introduction, the budget required to achieve the same objective function may increase by more than10% each year compared with the previous approach. A vaccine portfolio management model can therefore support decision makers in making efficient choices when expanding their national pediatric immunization programs.

PRM258

APPLYING SYMPTOM-BASED UTILITY FUNCTIONS IN HEALTH ECONOMIC MODELLING: A CASE STUDY OF UTERINE FIBROIDS

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BACKGROUND: A health economic model was developed to compare treatment strategies for uterine fibroids (UF). Bleeding and pain were identified as the principle disease-related symptoms affecting quality of life. Clinical trial data measured bleeding and pain through the pictorial bleeding assessment chart (PBAC) and visual analogue scale (VAS), respectively. However, the impact of PBAC and VAS on a single index measure of quality of life (QOL) is not widely studied. **OBJECTIVES:** Develop a symptom-driven utility function for patients with symptomatic UF, linking incremental changes in PBAC and VAS to a single index measure of QOL that enables the calculation of quality-adjusted life-years (QALYs). **METHODS:** PBAC, VAS, and EQ-5D levels based on clinical trial data were used in the analysis. Two ordinary least squares regressions (Reg1 and Reg2) were conducted with EQ-5D (UK value set) as the dependent variable. Reg1 (N=965) included PBAC and VAS as linear and quadratic terms to account for both linear and non-linear relationships. Reg2 (N=962) used a wider specification of independent variables including all regressors in Reg1 plus demographics and physical characteristics. **RESULTS:** The regression coefficients from Reg1 were -0.0001 ($p<0.01$) and -0.0044 ($p<0.01$) for a one-unit change in the linear components of PBAC and VAS respectively, an intercept of 0.9164, and adjusted R2 of 0.3135. The quadratic coefficient estimates were very small, positive, and not statistically significant. An increase in the linear components of PBAC (VAS) of 300 (30) results in a 0.0355 (0.1308) unit decrease in EQ-5D QALY-weight. Differences in the coefficients of PBAC and VAS on EQ-5D between Reg1 and Reg2 were small. **CONCLUSIONS:** The method described shows a pragmatic way to estimate QALY-weights in a health economic model that is responsive to incremental changes in patient symptoms for any intervention where PBAC and VAS data is available.

PRM259

QUALITATIVE DISCUSSION ON ISSUES OF PATIENT-REPORTED OUTCOME ASSESSMENT IN POST-MARKETING SURVEILLANCE FOR DISEASES IN THE ELDERLY

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Growing attention has been paid to patient-centric approach in clinical practice. The assessment of patient-reported outcomes (PROs) encourages communication between patients and physicians about goals of care. Post-marketing surveillance (PMS) is one of the available opportunities to collect large-scale, real-world data on patients' experiences and PROs. Since PROs must be answered by patients themselves by definition, elderly patients may face specific challenges and need extra support to conduct a PRO survey as part of PMS. Various difficulties in conducting a PRO survey in PMS are expected, such as: 1) Additional support required at the participating sites for elderly patients. For example, they may need someone to read out the questions or record the responses for them without influencing patients' responses 2) Lack of understanding of the value of PRO assessments for marketed products among internal and/or external stakeholders, despite increasing use of PRO tools in regulatory studies 3) Maintenance of motivation and understanding of the study procedures in relevant healthcare professionals throughout the study period Key elements for best practices would include: 1) Strategize recruitment of physicians depending on their environment and resources available: general practitioners vs. hospital physicians 2) Deepen the understanding of the value of PRO assessments and contents of PRO questionnaires among internal/external stakeholders 3) Reinforce cross-functional collaboration in order to accelerate site recruitment, patient enrollment and the return of patient surveys We will further discuss the above difficulties during the planning and implementation phases of PMS with a PRO survey, as well as best practices based on our experience so far in Japan. These considerations and experiences will highlight important implications in conducting a PRO survey in PMS as a valuable opportunity to obtain real-world patient-relevant data in elderly patients immediately after a new product is available in the market.

PRM260

A COST-EFFECTIVE ENHANCED RETROSPECTIVE OBSERVATIONAL STUDY METHODOLOGY TO CAPTURE ECONOMIC BURDEN EVIDENCE IN A RARE DISEASE USING NON-TUBERCULOUS MYCOBACTERIA INFECTION AS A MODEL

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OBJECTIVE: Gaining adequate market access and reimbursement can be particularly challenging for orphan drugs. Barriers include inadequate real world data on the disease's epidemiology and its burden of illness. We deployed a unique combination of methodologies used in a multi-layered observational data capture approach to collect de-identified, publication-worthy clinical and resource utilization data in a probability sample of patients with a rare disease (pulmonary nontuberculosis mycobacteria [PNTM]). We combine a new methodology ("blinded physician proportion survey") with a new use of an old methodology (Delphi expert survey). **METHODS:** First-round studies in France, Germany, Italy, Spain, and the United Kingdom consisted of a "blinded physician specialty proportion" survey to determine the probability of physician selection by specialty (2,585 participating physicians), a nationally representative chart review with participating physicians to determine target patients by region (619 physicians – 1,429 patients) and a Delphi study (an anonymous collaborative estimating methodology completed by six internationally recognized PNTM experts) to gain consensus on annual prevalence of PNTM for each target country. A second-round of survey and use of the collaborative estimating process is currently being completed consisting of a chart review with physicians of a nationally representative sample (n=30 per country) in a treatment refractory sub-group of PNTM patients to capture country specific treatment patterns and disease-related costs. "Refractory" is defined as at least one post-diagnostic positive culture despite 6 months of treatment. **RESULTS:** We developed a rigorous methodology to identify a sub-group population to address the gap of actual disease prevalence by country. Publication reviewers have consistently and congruently confirmed the first-round epidemiologic study methodology met their respective required scientific standards. **CONCLUSIONS:** Observational chart surveys in rare diseases that obtain a probability sample, a requirement for sample validity, can be used to provide essential disease-related metrics to populate market access and reimbursement evaluation procedures.

PRM261

A CONCEPTUAL SEARCH FILTER TO IDENTIFY REAL-WORLD EVIDENCE

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OBJECTIVES: Systematic reviewers utilise filters to focus searches of electronic databases to identify specific study designs. Established, tested search filters are available from groups which regularly conduct reviews such as the Cochrane Group, SIGN and CADATH. Although studies in the real-world are not new, novel phrases such as real-world evidence (RWE) are increasingly used to identify observational studies. Currently available search filters for observational and non-randomised studies do not adequately capture newer terms used. We have thus developed a method to identify frequently used MeSH terms in RWE studies and a search filter to include these terms. **METHODS:** A PubMed (MEDLINE®) search for RWE stated in the title/abstract was conducted. Articles with "real-world" and either "data", "evidence" or "research" in the title or abstract were selected; Case Reports, Comment, Editorial, Letter, News were removed. MeSH terms associated with articles were analysed and frequency counted; those relating to study design or outcome reporting were chosen for inclusion in the search filter. **RESULTS:** The MEDLINE® search identified 179 studies reporting RW and either data, evidence or research in the title. Of the 179, 151 were publication types of interest. The most frequently used MeSH terms related to RWE identified were 'Treatment Outcome' (n=30), 'Evidence-based Medicine' (n=17), 'Retrospective Studies' (n=15), 'Databases, Factual' (n=14), and 'Time Factors' (both n=14). A search strategy was developed combining MeSH and free-text terms to identify RWE. **CONCLUSIONS:** For every systematic review it is important to validate searches to ensure they are retrieving relevant studies; as new terminologies such as RWE are introduced to describe study design, reviewers need to adapt search filters. The method proposed allows searches to be adapted as terminologies are introduced and become more established.

PRM262

METHODOLOGICAL GUIDELINES FOR ECONOMIC DRUG EVALUATION STUDIES IN PORTUGAL: MAJOR GAPS AND NEW TOPICS IN THE STUDIES EVALUATED BETWEEN 2010 AND 2014

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