evaluation of the found publications demonstrated that the best reflection of the conditions of routine practice (generalizability) in PRCTs can be obtained mostly through the development of broader inclusion criteria, minimizing the exclusion criteria or broadening the scope of patients evaluation. We found also suitable tools, which can be used both during the design and evaluation of reliability of PRCTs: PRECIS, PR-tool, Pragmascope tool or CONSORT. **CONCLUSIONS:** Properly assessed PRCTs data in conjunction with information about the efficacy from RCTs will serve as a whole to facilitate business decisions in medical practice, as well as health organizations and rationalization of cost-reimbursement of used or new medical technologies.

PRM156

HOW TO INCREASE PATIENT RETENTION RATE DURING THEIR PARTICIPATION IN LONGITUDINAL STUDIES

El Kebir S[1], Gauchoux R[2], Nichols SE[3]
[1]*Registrat-Mapi, Lexington, KY, USA,* [2]*Registrat-Mapi, Lyon, France,* [3]*Registrat-Mapi, Lexington, KY, USA*

OBJECTIVES: Collecting patient data in longitudinal studies is often a concern in terms of data accuracy and patient follow-up. Physician assessment alone might be not sufficient or feasible. Multiple strategies can maximize patient retention. The methods to achieve these goals are intensive and made even more complex in global studies where regulatory requirements vary across individual countries. The objective of this research is to summarize the means used to improve patient retention. **METHODS:** The selected methods for patient retention have been used for three ongoing longitudinal safety registries requested by the European Medicines Agency and/or the Food and Drug Administration **RESULTS:** Three studies were conducted to assess safety follow-up over 20, 10 and 6 years, one of them was Pediatric and all were evaluating drugs in Inflammatory Bowel Disease area. A total of 8, 000 children and 13,250 adults have to be enrolled by Gastroenterologists in 27 countries. Maintaining long-term interest from investigators is essential. This is aided by careful site selection and training and provision of targeted study materials like patient profiles and newsletters as we as fair compensation. To mitigate patient attrition, these studies implemented direct-to-patient contact. This strategy minimizes loss-to-follow-up and enables data collection directly from the patients, increasing data quality. Data can be supplemented through additional contacts with relatives/legal guardians and/or other Health Care Providers. This methodology needs to be detailed in the protocol and study material to provide, to patients and the regulatory bodies, a clear overview of the procedures and responsibilities in each country. **CONCLUSIONS:** A correlation between good comprehension of the stakes and study procedures by the sites and patient retention is commonly established. However, specific actions which target maintaining patient interest and commitment is also important to successful retention. The means must be adapted to the design and the patient population.

PRM157

METHODOLOGICAL CHALLENGES OF IQWIG'S EFFICIENCY FRONTIER CONCEPT ELICITED BY MULTIPLE PATIENT-RELEVANT ENDPOINTS – WHY PRIORITIZATION OF ENDPOINTS CANNOT BE AVOIDED

Neidhardt K, Wasmuth T
Novartis Pharma GmbH, Nürnberg, Germany

OBJECTIVES: The Institute for Quality and Efficiency in Health Care (IQWiG) in Germany evaluates benefits/harms and economic implications of medical interventions. For the purpose of cost-benefit analysis, IQWiG has developed the efficiency frontier concept to determine the maximum reimbursable price for pharmaceuticals. Within this concept benefits/harms are evaluated for each patient-relevant endpoint. If a compound shows additional/less benefit or less/more harm in several aspects of benefit, the creation of several efficiency frontiers would be required. The objective of this contribution was to assess whether the existence of multiple patient-relevant endpoints is a common feature within benefit assessments according to article 35a Social Code Book V which would entail multiple efficiency frontiers. **METHODS:** IQWiG's homepage was browsed for completed benefit assessments. Between January 2011 and May 2012, 21 benefit assessments were published by IQWiG. All assessments were screened in detail for information on patient-relevant endpoints and endpoint-specific benefit assessments. **RESULTS:** In 11 dossier assessments, benefit was endpoint-specifically assessed, whereas in 10 assessments, no endpoint-specific assessment was performed. Within the 11 dossier assessments, 19 subpopulations with endpoint-specific assessments were identified. For each subpopulation, between one and five endpoints were assessed by IQWiG. In total, 50 patient-relevant endpoints were detected. On average 2.63 patient-relevant endpoints per subpopulation were assessed. **CONCLUSIONS:** Since benefits/harms are evaluated for each patient-relevant endpoint the existence of multiple patient-relevant endpoints constitute a challenge for the compilation of the efficiency frontier and the subsequent determination of the maximum reimbursable price. Recommendations will likely be imprecise due to endpoint-specific benefits/harms. Prioritizing and weighting benefit and harm aspects can therefore not be avoided within IQWiG's proposed efficiency frontier concept if the decision maker requires precise recommendations for the maximum reimbursable price. Thus, an aggregation of benefit and harm parameters into one single efficiency frontier is needed.

PRM158

PLACEBO-CONTROLLED CLINICAL TRIALS: A DIFFICULT BALANCE "JUSTIFICATION VERSUS FEASIBILITY" FOR ACADEMIC SPONSORS

Duracinsky M, Taron C, Matei M, Chassany O
Assistance Publique-Hopitaux de Paris, Paris, France

OBJECTIVES: In investigator-based clinical trials, the use of placebo is often justified as it increases the probability from the peers' expertise of 1/ gaining a public grant; 2/ publishing results in higher-rank journals. **METHODS:** Among the 139 randomized clinical trials (RCT) evaluating drugs and currently managed by the Paris Hospitals, 68 are placebo-controlled. Aim is to analyze the hurdles in obtaining the placebo and its justification. **RESULTS:** Half of the studies had difficulties in obtaining the placebo. In rare cases, the study was unfeasible. When the placebo concerns a new drug, the company may accept to provide the drug and its placebo, at the eventual expense for the institutional sponsor to provide all the data without any further compensation. It may be considered as a disguised industrial sponsorship, the institutional sponsor while taking the responsibility of the study, being relegated to a role of a CRO. Obtaining a placebo of an old drug is trickier since the company may not sell anymore its product and generic companies are not able and/or interested to manufacture the placebo. The request of a manufacturer can be so expensive (up to 200.000€) that is exceeds by far the price of the verum, and of the grant. The rationale for using a placebo as comparator is to ensure a double-blind. However, when the drug administration is short (e.g. emergency setting), or when the endpoint is "hard" (i.e. mortality, imaging, biology), it is unlikely that any placebo effect from subjects and/or investigators may impact the endpoint assessment. In such situations, the comparator may be "no treatment" with whenever possible a blind assessment. **CONCLUSIONS:** Placebo-controlled RCT are challenging for institutional sponsors. Investigators and methodologists when writing a protocol and peers' expertise of a grant or a publication submission should consider the necessity and the feasibility of placebo.

RESEARCH ON METHODS - Conceptual Papers

PRM159

SENSITIVITY ANALYSIS VERSUS UNCERTAINTY ANALYSIS IN HEALTH ECONOMIC DECISION MAKING

O'Day K[1], Bramley T[2]
[1]*Xcenda, Palm Harbor, FL, USA,* [2]*Xcenda, LLC, Palm Harbor, FL, USA*

OBJECTIVE: To distinguish sensitivity analysis and uncertainty analysis, characterize their differential roles in health economic decision making, and to provide practical examples of their use and presentation in health economic analysis. **METHOD:** The role of one-way sensitivity analysis is to quantify the impact of varying a single parameter on the output of a model. However, this obscures an important distinction between parameter uncertainty and variability. Sensitivity analysis quantifies parameter variability in terms of the percentage change in a model output for a given percentage change in a model input. Sensitivity is therefore an objective property of the model. Uncertainty analysis, on the other hand, propagates a decision maker's subjective parameter uncertainty through a model to estimate the conditional uncertainty of the model output. Accordingly, the functional role of sensitivity analysis is to help a decision maker to understand and validate the internal model structure in order to gain trust in the model itself; whereas the functional role of uncertainty analysis is to assess the potential impact of a decision maker's subjective parameter uncertainty on confidence in a particular model-based decision. These distinctive roles are both critical in health economic analysis and decision making. We provide examples of sensitivity analysis versus uncertainty analysis, show how to report the results of sensitivity and uncertainty analyses, and discuss the implications of this distinction for conducting one-way and probabilistic analyses. **CONCLUSION:** Confidence in model-based decision making requires 1) confidence in the model itself, and 2) confidence in the model output given one's subjective parameter uncertainty. Sensitivity analysis and uncertainty analysis, respectively, serve these differential roles.

PRM160

A NEW VALUE-BASED PRICING FRAMEWORK FOR THE OPTIMAL PRICING OF PHARMACEUTICAL ASSETS

Hawryluk EA, Malhotra M, Chawla V, Doyle J
Quintiles Global Consulting, Hawthorne, NY, USA

Three common methods of estimating optimal prices for pharmaceutical assets are willingness-to-pay, health economic price appraisal, and reference price benchmarking. **PROBLEM:** Each method has significant drawbacks. Willingness-to-pay, assessed through primary research, can be limited by lack of knowledge of product list prices and the disconnect between respondent answers and real-life price acceptance. Health economic appraisals, utilizing cost-of-treatment models to estimate the price at which new products are cost-effective, are subject to error, interpretation, and are rarely accepted by stakeholders who drive price decisions. Reference price benchmarking, using market analogues to gauge price points for new products, does not take into account unique differences, perceived or real, of assets. None of these methods are able to quantify market intangibles such as unmet need and strength of competition. **SOLUTION:** To address these weaknesses, the authors have developed a mathematical framework using all three pricing methodologies to triangulate on a price range. The Value-Based Pricing Framework equation is a collection of activities that allows for the economic quantification of an asset's attributes, critical to determining an asset's overall value-based price. These activities include: 1) Willingness-to-pay Assessment: utilizes qualitative and quantitative feedback from decision makers to understand price expectations and thresholds vis-à-vis current competitors and comparators; 2) Reference Price Benchmarking: Assesses pricing structure of comparators to predict performance; and 3) Health Economic Analysis: Estimates product pricing as a function of health economic differentiation and determines cost-savings that can be offset in price. **CONCLUSION:** Value-Based Pricing is a structured way of estimating asset price based on its perceived value by various stakeholders. This flex-

ible and adaptable framework can be applied to any therapeutic area and used to evaluate any number of varying product profiles. It involves understanding how stakeholders value asset attributes and how their willingness-to-pay helps quantify each individual attributes' contribution to a price.

PRM161

A PARADIGM SHIFT IN HEALTH ECONOMIC EVALUATIONS FOR DEVELOPING COUNTRIES - OPTIMIZATION MODELLING FOR ASSESSING WHICH MIX OF MALARIA PREVENTION STRATEGIES ACHIEVES A DEFINED PUBLIC HEALTH TARGET AT THE LOWEST BUDGET

Van Vlaenderen I[1], Sauboin C[2], Van Bellinghen LA[1], Standaert B[2]
[1]*CHESS, Ternat, Belgium,* [2]*GlaxoSmithKline Vaccines, Wavre, Belgium*

Malaria remains one of the leading causes of ill health with the majority of cases and deaths occurring in young children in Sub-Saharan Africa. Key interventions currently recommended for preventing childhood malaria include Insecticide Treated Nets, Indoor Residual Spraying, Intermittent Preventive Treatment in infancy, and Seasonal Malaria Chemoprevention. One-to-one comparisons applied in cost-effectiveness and budget impact analyses fail to examine the health and economic impact of multiple interventions implemented simultaneously, and are therefore unable to evaluate the optimal integration of available malaria preventive interventions and partially efficacious vaccines currently in development. Moreover, an incremental cost-effectiveness ratio with recommended willingness-to-pay threshold provides limited guidance in developing countries. **OBJECTIVE:** Defining an approach to identify the optimal sequence of introducing different preventive interventions, achieving progressively increasing public health targets for malaria control in children <5years old at the lowest budget. **METHODS:** Our suggested optimization approach integrates two distinguished models to assess combinations of interventions. A vector model simulates the impact of varying coverages of vector control interventions on vector infectiousness capacity and associated reduction in Entomological Inoculation Rate (EIR) for children. A human host model applies this reduced EIR to simulate disease incidence at varying coverages of interventions directly acting within humans. These connected models provide all potential intervention combinations achieving a pre-defined public health target (e.g. reducing childhood mortality with ≥50%). Considering malaria policy evolutions at increasing public health targets, a lower bound is set on intervention coverages at each optimization step. The remaining options are ranked according to their budget impact considering cost of interventions and disease management in a health system perspective. **CONCLUSIONS:** Using the optimization process with progressively increasing public health targets provides an indication on the optimal sequence of introducing interventions at the lowest budget. Therefore, this approach can support decision-making in prioritization of malaria preventive interventions.

PRM162

APPROPRIATE COMPARATIVE TREATMENTS FOR EARLY BENEFIT ASSESSMENT (EBA) IN GERMANY. COMPARING THE SUGGESTIONS BY THE JOINT FEDERAL COMMITTEE (GBA) AND THE PHARMACEUTICAL COMPANIES

Ruof J[1], Scherer J[1], Schulenburg JM[2]
[1]*Roche Pharma, Grenzach-Wyhlen, Germany,* [2]*Leibniz University Hannover, Hannover, Germany*

OBJECTIVES: The selection of the appropriate comparator plays an important role within the EBAs for innovative medicines in Germany. According to the law the appropriate comparator typically has to be identified according to the standards of evidence-based medicine. If there are several alternatives, the economics have to be taken into consideration. Our aim was to explore differences in comparators as suggested by the GBA and the pharmaceutical companies. **METHODS:** The review includes EBAs that were started in 2011. The Joint Federal Committee's (GBA) webpage was used to obtain the respective company dossiers as well as the IQWiG (Institute for Quality and Efficiency in Health Care) benefit assessments. The appropriate comparators as stated by the companies and the GBA (according to the IQWiG assessment) were extracted and compared. **RESULTS:** Twenty-four EBAs were started in 2011. In 10 EBAs the pharmaceutical company applied the comparator that was suggested by the GBA within the benefit dossier (Tafamidis Meglumin, Telaprevir, Abirateronacetat, Boceprevir, Ipilimumab, Fampridin, Belatacept, Apixaban, Eribulin, Fingolimod), although in some of those cases data for the suggested comparators e.g. for subgroups where not developed within the phase 3 clinical trials (Abirateronacetat, Fampridin, Fingolimod). In 9 EBAs no agreement was reached (Linagliptin, Pirfenidon, Belimumab, Cannabis Sativa, Retigabin, Aliskiren/Amlodipin, Collagenase, Cabazitaxel, Ticacrelor). For five drugs no full dossier submissions and/or IQWiG assessments were conducted (Bromfenac, Dexmedetomidin, Pitavastatin, Regadenoson, Olmesartan/Amlodipin/Hydrochlorthiazid). In seven EBAs GBA suggested 'Best Supportive Care' (BSC) as appropriate comparator. In two cases optimized standard therapy was chosen and in one EBA physiotherapy. **CONCLUSIONS:** Ongoing EBAs indicate a high level of disagreement between comparators as suggested by GBA and respective companies. Definition of BSC is different across various diseases and evidence levels for BSC as appropriate comparator is scarce.

PRM163

THE USE OF EXPECTED VALUE OF PERFECT INFORMATION ANALYSIS WITHIN ECONOMIC EVALUATIONS AND HEALTH TECHNOLOGY ASSESSMENTS IN THE UK

Almond C[1], Brereton NJ[2]
[1]*BresMed Health Solutions, Sheffield, South Yorkshire, UK,* [2]*BresMed, Sheffield, UK*

OBJECTIVES: The expected value of perfect information (EVPI) assesses, at a given willingness-to-pay threshold, the expected gain in net benefit from further research to decrease uncertainty in a decision. If the EVPI exceeds the cost of obtaining new information then further research is considered valuable. The parameters for which further research is believed to be most valuable can be assessed by calculating the expected value of perfect parameter information. The objective of this analysis was to assess the use of EVPI in economic evaluations and health technology assessment (HTA) from the perspective of the NHS in the UK. **METHODS:** An unrestricted search was performed in MEDLINE for literature that contained references to EVPI and cost-effectiveness analysis or HTA. The literature obtained was assessed to establish the extent to which EVPI is used in economic evaluation and HTA. Guidelines from the National Institute for Health and Clinical Excellence (NICE) were also checked for references to EVPI. **RESULTS:** The literature search indicated that out of 73,795 results for HTA or cost-effectiveness analysis, only 70 (<0.01%) of these also reported EVPI. There were 21 examples of calculating the EVPI in an economic evaluation from a UK perspective; the earliest was published in 2004. The NICE guide to the methods of technology appraisal (2008 update) states that value-of-information methods can be used within a probabilistic sensitivity analysis (PSA) to assess the contribution of uncertainty from each parameter to the overall decision uncertainty. However, the specification for manufacturer/sponsor submission of evidence does not explicitly request the EVPI to be calculated as part of the PSA. **CONCLUSION:** The EVPI is a measure which can aid decision makers by quantifying the value of further research in an area, but it is not widely reported in published economic evaluations.

PRM164

ENSURING THE VALUE OF A MEDICAL DEVICE INNOVATION PRIOR TO MARKET LAUNCH

Hidefjall P
KTH Royal School of Technology, Huddinge, Sweden

In order to ensure that new products entering health care markets are cost-effective over existing products Health Technology Assessment programs are implemented in health care systems. Whereas HTA agencies can screen out underperforming products it is equally important that manufacturers implement procedures to ensure that no underperforming products are developed and brought to market in the first place. By analogy, there are standards that companies need to comply with to ensure that their products are safe; similar standards or methods to ensure that new products are cost-effective could be developed. Based on 20 years experience of medical device innovation in industry, academia and consulting a conceptual model to ensure cost-effective innovation is proposed. The method divides the value assurance process into 3 Stages: concept generation, concept validation and market entry strategy. During the concept generation phase solutions to a critical problem with an unmet clinical need and a related disease burden are generated and evaluated with the core group of clinicians and multiple stakeholders according to costs, risks and benefits. The most promising concepts are iteratively tested and validated according to freedom to operate, safety, efficacy, ease-of-use, invasiveness, procedure success rate and head-to-head comparative cost-effectiveness until a candidate product can be addressed to a target patient group and practitioners at a profitable price. Finally, markets with the best clinician community support, largest size, highest attainable prices and lowest barriers to entry are addressed. This may sound as commonsense, but there are some important evolutionary principles hidden: 1) downstream market selection criteria are translated into early upstream tests; 2) multiple concepts are generated to handle early uncertainty; and 3) iterative tests are performed until a satisfying concept is selected. This model should ensure a product will pass HTA cost-effectiveness evaluation if eventually exposed to it.

PRM165

VALIDATING HEALTH ECONOMIC MODELS: DEVELOPING A METHODOLOGICAL APPROACH

Hart WM[1], Chandler F[2]
[1]*EcoStat Consulting Ltd, Sidestrand, Norfolk, UK,* [2]*GlaxoSmithKline, Uxbridge, Middlesex, UK*

Models developed in Microsoft EXCEL of increasing complexity are being used as an integral part of the submission process for new pharmaceutical products and for technical assessments produced by national agencies. The credibility of the health economic models utilised depends on their validity. Firstly, in terms of reflecting the appropriate clinical process using the correct data and assumptions and secondly, in terms of ensuring a correct functioning of the model based on the relationships between variables and formulas embedded in the model. In this research, the authors concentrate on the latter aspect of validating health economic models. While recognising that models should be validated, there is a paucity of detailed techniques available in the literature that show researchers and users of health economic models how to validate them. Hence, we have attempted to develop a methodological framework that may be helpful to both those reviewing complex models and to model developers themselves who could incorporate validation processes while they develop their own models. The authors have reviewed the literature, looked at other disciplines (e.g. finance) where modelling plays a central role, investigated different software options in addition to the inbuilt validation tools in EXCEL. The evolving methodology has been applied to a number of existing real-life models in order to develop a consistent approach. By applying the developed methodology, errors have been identified at the design/review stage in a number of budget impact and cost-effectiveness models of varying degrees of complexity. A consistent approach to validation is a useful tool to test the often highly complex processes and relationships with thousands of formulas in health economic models. It may also encourage modellers to take a more disciplined and organised approach in the development process and give increased confidence to end-users that the models they are using can be relied upon.