Of 630 articles identified, four studies passed the inclusion criteria, and three were included by searching reference lists. Subsequently, we add more than 150 conference papers to the screening three-step procedure. **CONCLUSIONS:** The use of modelling is promising in this context. It can be explained by the required features of any early cost-effectiveness evaluation seeking to inform decision making. We aimed at distinguishing from the previous works, addressing this methodology. It should be stressed the very small amount of the papers on the topic. In addition, we highlight the absence of ad-hoc checklist and coding to be used for the quality assessment of early model-based analyses and data extracted classification. This work also tries to advance in the definition of appropriate criteria to evaluate the reliability of the analysis in terms of impact on primary stakeholders.

PRM121
ASSESSMENT OF VALIDATION OF HEALTH-ECONOMICS DECISION MODELS IN INTERVENTION STUDIES OF SEASONAL INFLUENZA AND BREAST CANCER

de Boer PT[1], Frederix GW[2], Al MJ[3], Feenstra TF[4], Vemer P[1]
[1]University of Groningen, Groningen, The Netherlands, [2]Utrecht University, Utrecht, The Netherlands, [3]Erasmus University, Rotterdam, The Netherlands, [4]University Medical Center Groningen, Groningen, The Netherlands

OBJECTIVES: We aimed to review recently published health-economic (HE) decision models to assess the reporting of validation efforts. An infectious disease (seasonal influenza, SI) and a chronic disease (breast cancer, BC) were used as examples, giving a preliminary insight in the reporting of validation efforts in the overall HE literature. **METHODS:** A literature search was performed in Pubmed and Embase to retrieve full-text HE modeling studies, published between 2008 and 2014. Type of evaluation, model and intervention were extracted, as well as information on model outcomes, journal and funding. Reporting on model validation was evaluated by checking for the presence of the word validation and its conjugates, and by using AdViSHE, a tool which contains a structured list of relevant items for validation. **RESULTS:** The literature search resulted in 53 SI and 45 BC studies. In 41 studies (42%) the word validation or its conjugates was mentioned, but only in a small percentage in the context of model validation. The terminology used around validation was found to be ambiguous. Model validation efforts were reported in a minority of studies. However, some studies do show good reporting examples. Cross validation of study outcomes was reported most often, but the quantity and quality of this reporting varied. More validation efforts were reported in BC than in SI. **CONCLUSIONS:** Only a limited number of studies reported on model validation efforts, although it may be assumed that more efforts have been taken than were reported. In particular, the differences between SI and BC may not mean that less efforts were undertaken to validate SI models. Although validation is deemed important by many researchers, this is not reflected in the reporting habits of HE modeling studies. Better reporting of validation efforts would be desirable to further enhance decision-makers' confidence in HE models and their outcomes.

PRM122
SENSITIVITY ANALYSIS: HOW MUCH IMPACT DOES IT HAVE ON THE NICE DECISION MAKING PROCESS?

Hirst A, Guy H, Murphy D
WG Access Ltd, London, UK

OBJECTIVES: As part of economic evaluations submitted to NICE, probabilistic and deterministic sensitivity analysis are a requirement, with probabilistic sensitivity analysis being a stated preference in the NICE reference case. The aim of including sensitivity analysis is to identify the key areas of uncertainty, and determine the impact on results. The aim of this analysis was to assess what impact uncertainty in cost-effectiveness models has had on NICE reimbursement decisions and review what type of sensitivity analyses are conducted. **METHODS:** The five most recent NICE appraisals for breast cancer were selected, the sensitivity analysis results and methods were extracted. Once extracted the results of the sensitivity analysis were compared and contrasted. The sensitivity analysis results were considered in the context of the base case results. **RESULTS:** The methodology of sensitivity analysis conducted varied between submissions, whilst all appraisals conducted univariate sensitivity analysis only two reported tornado diagrams. The method of reporting results also varied between appraisals, of the four appraisals that had more than one comparator in the base case, only one appraisal conducted a multi-way cost-effectiveness acceptability analysis. **CONCLUSIONS:** There are many factors that impact a NICE committees decision, therefore it is not possible to draw a conclusion on how the uncertainty impacted the decision making process. Of the appraisals assessed, there was a wide range of differences between deterministic and probabilistic ICERs, however it appears that this did not impact the appraisal. The sensitivity analysis reported across NICE submissions lacks consistency in the observed sample, hindering the comparison between submissions.

PRM123
HOW TO MODEL SURVIVAL IN COST-EFFECTIVENESS ANALYSIS? DIFFERENCES BETWEEN MARKOV AND PARTITIONED SURVIVAL ANALYSIS MODELS

Minacori R[1], Bonastre J[2], Lueza B[2], Marguet S[2], Levy P[1]
[1]Université Paris-Dauphine, Paris, France, [2]Gustave Roussy, Villejuif, France

OBJECTIVES: The choice of a modeling approach is guided by key criteria including time, interaction between individuals, and the unit of analysis (cohort or individuals level models). Despite Markov cohort modeling (MCM) is widely used in the literature, the use of partitioned survival (PS) models tends to increase. Our objective is to explore the rationale for selecting either a Markov modeling approach or a PS approach to carry-out a cost-effectiveness analysis in oncology. Our study focuses on the differences between the two approaches. **METHODS:** A literature review focusing on survival modeling in economic evaluation was performed in order to establish a list of differences between the two modeling approaches. Besides, we reviewed NICE's technology appraisals (TA) in oncology medicines over the last two years (2013-2015) to analyze the practices and the arguments put forward to justify modeling choices. Data collected for each TA included: model type, rationale for

model selection, health states, hypotheses, survival analysis, clinical data sources and the treatment of uncertainty. **RESULTS:** Twelve economic evaluations in oncology were submitted to NICE by pharmaceuticals companies (PC) between 2013 and 2015. Seven PC submitted a MCM, two a PSM, two a semi-markov partitioned survival model, and one a semi-markov model (SMM). Differences between modeling techniques were classified into four items: clinical data sources (e.g. published aggregated data for MCM and limited IPD for PSM), structure (e.g calculation of transition probabilities for MCM), hypotheses (e.g. same transition probability of death between two health states for MCM), flexibility of the model (e.g. access to patient level data for comparators required in PSM). **CONCLUSIONS:** Being a more flexible modeling technique, Markov models remain more frequently used compared to PSM. Nevertheless, PSM represent a more straightforward option when patient level data are available but are inappropriate when such data are not accessible for comparators.

PRM124
PHYSICIANS' CHOICE AS A COMPARATOR IN CLINICAL TRIALS: CHALLENGES FOR PHARMACOECONOMIC MODELLING OF INNOVATIVE TREATMENTS TO SUPPORT HEALTH TECHNOLOGY ASSESSMENTS

Mbanya Z, Madrigal AM, Wright A
PHMR Ltd, London, UK

OBJECTIVES: To identify specific challenges for modelling to support health technology assessment (HTA) submissions using trial data where the comparator is the physician's choice (PC). **METHODS:** Most clinical trials are designed globally or internationally, with minimal consideration of individual market needs. It is increasingly common for investigational drugs to be compared against a mix of PC treatments because a standard of care (SOC) is not always clearly defined. We searched a clinical trials database for registered trials where PC was the comparator. Based on the standard requirements for pharmacoeconomic models to support HTAs, we evaluated trial information to identify specific modelling challenges. **RESULTS:** We found 49 registered trials using PC as the comparator and identified four specific challenges that require guidance from HTA bodies. (1) One or more drugs used in PC regimens may not be licensed for an individual market, rendering their use problematical. (2) Comparison made against individual PC drugs results in lower patient numbers for comparison, reducing analysis credibility. (3) Analysis against individual PC drugs requires breaking randomisation, which jeopardises trial design integrity. (4) Involvement of a PC mix results in the need for a full incremental analysis, which might lead to application rejections in circumstances where the new treatment may only have incremental benefits over some of the individual treatments. **CONCLUSIONS:** The use of PC as a comparator in clinical trials poses challenges that are likely to slow the process of access to effective, innovative treatments. HTA agency involvement early in the life cycle of a technology would facilitate a shared understanding of evidence requirements. HTA agencies should develop clear guidelines on how PC efficacy and cost should be used for pharmacoeconomic modelling.

PRM125
EVALUATION OF THE EFFECT OF CRUDE LEAVES EXTRACT OF INDIGOFERA SPICATA FORSSK.(FABACEAE) ON BLOOD GLUCOSE LEVEL OF NORMOGLYCEMIC, ORAL GLUCOSE LOADED AND ALLOXAN INDUCED DIABETIC RODENTS

Birru EM
University of Gondar, Gondar, Ethiopia

OBJECTIVES: to evaluate the effect of the hydro-alcoholic leaves crude extract of Indigofera spicata(ISP) on the blood glucose level(BGL) of normoglycemic, oral glucose loaded and alloxan induced diabetic rodents. **METHODS:** The animals were randomly divided into five groups (n=6) for all the aforementioned three models. In all models, group-I mice provided 2%tween-80, group-II were treated with 5mg/kg glibenclamide and the remaining three groups(III, IV &V) were treated with 100, 200, and 400mg/kg dose of the extract respectively. Statistical significance of differences in BGLs within and between groups was analyzed by SPSS version-21 using one way ANOVA followed by Tukey's post hoc multiple comparison. **RESULTS:** 200mg/kg and 400mg/kg extract treated groups of normoglycemic mice showed significant (p<0.05) BGL reduction compared to the pre-exposure level. In case of OGTT model BGL reduction was statistically significant (p<0.05) in only 400mg/kg exposed groups at the 120 minute of post-exposure compared to the initial level. However, the BGL reducing effect of doses of the extract at the 4th, 6th and 10thhours of post treatment on diabetic mice was found statistically significant compared to both the negative control(p<0.001) and their respective pretreatment levels(p<0.05). **CONCLUSIONS:** Generally the crude extract of ISP leaves have shown prominent anti-diabetic effect and can be therefore used as a good insight for novel anti-diabetic drug discovery and development with a call of further in vitro and in vivo studies.

PRM126
DISEASE PROGRESSION IN RHEUMATOID ARTHRITIS: KEY ELEMENT FOR COST-EFFECTIVENESS MODELLING

Hummel N[1], Gsteiger S[2]
[1]University of Bern, Bern, Switzerland, [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland

OBJECTIVES: To identify and assess disease progression models used in rheumatoid arthritis (RA) cost-effectiveness modelling. **METHODS:** We examined all studies identified in two recent systematic literature reviews on health economic decision models evaluating RA treatments. We identified the elements in these studies describing disease progression and classified them by outcome measure affected and by model type. **RESULTS:** Disease progression models concern in most cases the health assessment questionnaire (HAQ) score. The reported individual sampling models and discrete event simulation models make assumptions about improvement of the HAQ when treated, depending on the patient's type of response (e.g. remission, good, moderate or no response, measured by the American College of Rheumatology (ACR) response criteria or by the disease activity score 28 (DAS28)). Furthermore, they assume a long-term deterioration in the HAQ score and a rebound effect when the treatment stops, i.e. for example a complete loss of the initial

gain. Microsimulation and Markov cohort models use simpler models with average annual HAQ progression rates that can differ between treatments. A few of the Markov cohort models treat disease progression as separate states of the DAS28 and estimate transition probabilities between such states over time. Disease progression of a radiographic score was modelled in one study, assuming a decreased deterioration of the radiographic score while being on treatment. No study modeled the impact of disease progression models on ACR response criteria. Finally, the two reviews did not include any cost-effectiveness analysis using decision trees that contained a disease progression model. **CONCLUSIONS:** Health economic decision models in RA include disease progression predominantly through the HAQ score. The impact of disease progression on discrete outcomes such as ACR20/50/70 is rarely considered in health economic models in RA.

PRM127
THE FUTILITY OF COST-EFFICACY ANALYSIS
Elbasha EH, Cook J
Merck & Co., Inc., Kenilworth, NJ, USA
OBJECTIVES: Cost-efficacy analysis (CEA) (e.g., cost per cure or short-term response) is increasingly being used as an alternative or a supplement to cost-utility analyses (CUA) employing the incremental cost per quality-adjusted life-year (QALY) gained. The objective of this study was to investigate whether conclusions drawn from such CEAs were consistent with those of the gold standard CUA. **METHODS:** We developed a model comparing standard of care (SOC) with a new drug. At the end of therapy, patients incurred short-term costs and either achieved a response or not. Non-responders incurred additional long-term costs and lost additional QALYs compared with responders. We evaluated two scenarios. In Scenario A: the short-term cost was $40,000 and efficacy was 65% with SOC. Drug cost and efficacy were $50,000 and 90%, respectively. For responders, the long-term cost offsets were $10,000 and additional QALYs were 0.5. Scenario B differed from Scenario A in only two aspects: the drug was more costly ($60,000), and the additional QALYs were higher (2.0 QALYs). We computed average cost-efficacy ratio (ACER), incremental cost-efficacy ratio (ICER), and incremental cost-utility ratio (ICUR). The assumed threshold for cost-effectiveness was $50,000/QALY. **RESULTS:** We found that a lower ACER than SOC was neither necessary (Scenario A: $66,667 vs $61,539/responder and ICUR=$35,000/QALY) nor sufficient (Scenario B: $55,556 vs $61,539/responder and ICUR=$60,000/QALY) for a more efficacious drug to be considered cost effective. Although the drug had a higher ICER in Scenario A ($80,000 per additional responder) than Scenario B ($40,000/responder), the drug was cost-effective in Scenario A, and not so in Scenario B. We derived a formula that related ICER to ICUR. **CONCLUSIONS:** A lower average or incremental cost-efficacy ratio from a CEA was neither a necessary nor a sufficient condition for a new drug to be considered cost effective compared with SOC based on a CUA.

PRM128
THE LIMITATIONS OF ICERS IN SCREENING INTERVENTIONS AND THE RELATIVE NET BENEFIT ALTERNATIVE
O'Mahony JF
Trinity College Dublin, Dublin, Ireland
OBJECTIVES: To demonstrate the limitations of the incremental cost-effectiveness ratio (ICER) as a measure of improved cost-effectiveness in the context of periodic screening and to propose a new measure based on net benefit that quantifies the proportional gain in cost-effectiveness relative to the status quo. **METHODS:** We use published cost-effectiveness estimates of cervical cancer screening to show why the ICER is not an appropriate measure of improvement in cost-effectiveness when screening performance improves, either through enhanced test characteristics or better risk stratification. We then propose a new metric based on the net health benefit measure previously devised by Stinnett and Mullahy. **RESULTS:** It is shown how an improvement in screening may enhance cost-effectiveness, represented by an outward shift of the efficient frontier in the cost-effectiveness plane, but that this improvement is not necessarily reflected in the ICER. This is because the whole efficient frontier may shift when all strategies are affected by a common technological change, and so ICERs on the frontier can be insensitive to this improvement. It is also shown that the ratio of costs to effects of a given strategy before and after a technological improvement also does not provide a useful measure of improved cost-effectiveness. The alternative measure of the proportional increase in net health benefit following the adoption of a new technology is then demonstrated. This metric quantifies the increase in net health benefit resulting from the new technology over a range of threshold values. **CONCLUSIONS:** ICERs will remain important for the identification of optimal intervention strategies. However, they are not suited for all circumstances. The net benefit alternative proposed here is a simple quantification of improved cost-effectiveness. The results presented here most readily apply to screening interventions, but also have application in other cases in which a technological development enhances multiple strategies simultaneously.

PRM129
COST-EFFECTIVENESS ANALYSIS OF CEREBROLYSIN IN THE TREATMENT OF PATIENTS WITH ACUTE ISCHEMIC STROKE MODERATE AND SEVERE DEGREES OF SEVERITY IN THE RUSSIAN FEDERATION
Kulikov A, Abdrashitova G
I.M. Sechenov First Moscow State Medical University, Moscow, Russia
OBJECTIVES: To estimate the cost-effectiveness of neurotrophic and neuroprotective drug cerebrolysin as treatment for patients with ischemic stroke of moderate and severe degrees of severity for one year. **METHODS:** Information retrieval was conducted in the public domain. We used the pharmacoeconomic analysis method – cost-effectiveness analysis and analysis of the direct and indirect costs. For reference, we accepted the exchange rate was 1 EUR = 60,64 RUB. **RESULTS:** In this study the life-years gained (LYG) was used as a criterion of the efficiency. During the cost-effectiveness analysis we have found that the cost of one LYG less for the therapy

of ischemic stroke moderate and severe degrees of severity using a drug cerebrolysin compared with standard therapy, cost-effectiveness ratios (CER) were obtained 419656 RUB (6920 EUR) and 563183 RUB (9287 EUR), respectively. **CONCLUSIONS:** The standard therapy in combination with drug cerebrolysin has a lower CER compared with standard therapy, therefore, it is a dominant technology from the perspective of the cost-effectiveness analysis.

PRM130
USING MACHINE LEARNING TO DETECT PATIENTS WITH UNDIAGNOSED RARE DISEASES: AN APPLICATION OF SUPPORT VECTOR MACHINES TO A RARE ONCOLOGY DISEASE
Rigg J, Lodhi H, Nasuti P
IMS Health, London, UK
OBJECTIVES: Diagnostic algorithms to detect undiagnosed patients with rare diseases have the potential to improve patient health and reduce costs associated with misdiagnosis. Accurate algorithms are difficult to develop, typically having to overcome Challenges including the tendency for models to I) over-fit, arising from low degrees of freedom / high-dimensionality and II) under-predict the rare disease, arising from the low ratio of confirmed to unconfirmed cases (skewed outcome class distribution). Support Vector Machines (SVMs) are a highly successful class of machine learning algorithms with well-established methods for handling high-dimensionality and skewed outcome class distribution. SVMs therefore represent a promising method to detect patients with undiagnosed rare diseases. This study estimated risk scores for a rare oncology disease using SVMs. The performance of the models was compared to classical methods based on logistic regression. **METHODS:** Risk scores for confirmed diagnosis were estimated with logistic regressions (standard, weighted and Firth) and SVMs (regularization, weights and kernel parameters were optimized using internal cross-validation). Patients with high risk scores and without a confirmed diagnosis have a higher probability of being undiagnosed cases. Model development, validation and testing were carried out on separate random samples from linked primary and secondary care data in the UK (Clinical Practice Research Datalink and Hospital Episode Statistics). The key performance metric was maximizing Sensitivity at a Positive Predicted Value (PPV) of 10% based on test data. **RESULTS:** 334 confirmed cases were identified from approximately 1 million total cases. For a PPV of 10%, the Sensitivity for the best performing logistic regression (standard with no weights) and SVM (RBF kernel) was 44% and 58% respectively on test data. **CONCLUSIONS:** SVMs represent a promising method for detecting undiagnosed patients with rare diseases, out-performing more conventional approaches based on logistic regressions. Greater adoption of these methods for this purpose is encouraged.

PRM131
HEALTH ECONOMIC PROGRAMMING USING ROYSTON-PARMAR "HAZARD RATE" MODELS: PROVIDING FLEXIBILITY AND SPEED FOR EVENT MODELLING IN COHORT AND DES MODELS
Kay SW, Kay JF
Model Outcomes Ltd, Cheshire, UK
OBJECTIVES: Many diseases (e.g. oncology) display changing hazard rates over time that conventional parametric methods cannot replicate accurately. Various "flexible parametric" methods exist with increased number of parameters to alleviate this problem (Generalised Gamma and Generalised F distributions being examples). Royston-Parmar Hazard Rate Models (RPHRM) differ in one crucial regard – all key survival statistics (survival probability, cumulative hazard and hazard rate) can be calculated in closed form. This makes them ideal for HE models where speed of calculation is essential. It is relatively straight-forward to program such models in R to represent competing risks, non-proportional hazard ratios, adding RCT obtained hazard ratios to observational study standard of care baseline hazard estimates, and extrapolation under various scenarios. All of this is possible under both Semi-Markov Cohort and Patient Level Discrete Event Simulation, DES, modelling. We display theory and R example code that illustrates these features. **METHODS:** Publicly available example datasets were analysed using RPHRM within Stata (ado stpm2) under a maximum likelihood framework (Bayesian MCMC methods could be programmed). Parameters obtained were entered into various R functions. Key functions were those that derived the restricted cubic spline basis (and its derivative) associated with log time and its interaction with covariates deemed to have time varying effects. For DES modelling a Newton-Raphson algorithm was simple to program to generate event times. Competing risks were modelled by numeric integration (trapezium rule) to generate cumulative incidence functions from cause-specific hazards using established formula. **RESULTS:** Models were able to replicate the real features of the inputted data. Output was validated against published results. PSA was conducted successfully and quickly. Required R functions were relatively short. **CONCLUSIONS:** RPHRM is the most suitable of "flexible parametric" survival models for HE modelling. It can represent any baseline hazard and hazard ratio time path without requiring time-consuming calculations.

PRM132
CONDITIONAL COPULA MODELS WITH APPLICATIONS TO BIOMARKERS IN RHEUMATOID ARTHRITIS
Rakonczai P[1], Rojkovich B[2], Gáti T[2]
[1]Healthware Consulting Ltd., Budapest, Hungary, [2]Buda Hospital of Hospitaller Brothers of St. John, Budapest, Hungary
OBJECTIVES: Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes pain, stiffness and limited motion and function of joints. There are several biomarkers (HAQ,VAS,DAS28) known for measuring disease activity from different point of views. The main objective is to investigate the association among them based on advanced statistical methods. **METHODS:** Different biomarkers of 489 RA patients were collected in one of the largest Arthritis Center in Hungary from 5th Jun 1998 to 27th Feb 2015. Copula models are simple yet powerful tools for modeling joint distribution of multivariate variables. There are several parametric