length in Markov models. The benefits of half-cycle correction has been widely published in the international literature. We measured the importance of half-cycle correction in the models submitted to the Hungarian HTA Office. We examined when it is adequate to use half-cycle correction and how big role should it have in the process of modelling. **RESULTS:** Our experience shows that only 11% of the submitted models incorporated half-cycle correction. In more than half of these cases the value of the incremental cost-effectiveness ratio (ICER) changed by less than 1% when half-cycle correction was used compared to the base-case scenario. We also found the possibility that in some cases the added benefit of half-cycle correction is not considerable. **CONCLUSIONS:** The necessity of using half-cycle correction is essential in models, when the cycle length is half year or longer and if the number of the cycles of the models is less than 200. In most cases the half-cycle correction results in only a little change in the cost-effectiveness ratio of the submitted models, therefore half-cycle correction should be executed carefully.

PRM102

A REVIEW OF CLINICAL TRIAL SIMULATION METHODS

Schuetz CA[1], Ong SH[2]

[1]*Archimedes, Inc., San Francisco, CA, USA,* [2]*Novartis Pharma AG, Basel, Switzerland*

OBJECTIVES: Randomized controlled clinical trials are the gold standard for determining causal inference. However, trials are expensive, and the results can be difficult to interpret. Our objective was to evaluate methods for clinical trial simulation to understand how the simulation approach can be used for improved trial planning and interpretation of trial results. Our primary focus was trials of type 2 diabetes and cardiovascular disease. **METHODS:** We systematically searched the MEDLINE database for clinical trial simulation studies. We used the MeSH terms: Markov model, Markov chains, simulation, simulation model, microsimulation, computer model, and required type 2 diabetes mellitus and cardiovascular diseases. We restricted the search to studies of humans published in English and found 92 publications. We also considered innovative clinical trial simulation methods from other areas to gain context. **RESULTS:** A number of established techniques — notably, the Archimedes Model, Markov models, and observational analyses— are used for clinical trial simulation. Markov model-based simulations are widely employed, but have structural limitations with regard to the physiological detail they can capture (e.g. multiple comorbidities). Retrospective, observational methods for clinical trial simulation are gaining utility as more databases become available. However, observational methods remain vulnerable to unknown biases. Finally, large-scale simulation models (such as the Archimedes model), with physiological underpinnings, provide accurate and clinically detailed trial simulations. These models are used to simulate trials of therapies not yet marketed, or to forecast late stage trials. Model-based simulations require validations to ensure accuracy. **CONCLUSIONS:** Clinical trial simulation is an increasingly powerful tool, complementing real-world clinical trials. Large scale simulation modeling has been shown to be valuable for estimating and interpreting clinical findings. Recent studies suggest that future developments will leverage both large-scale simulation models and increasingly rich real-world evidence.

PRM103

PROTOTYPE MODEL IN METASTATIC CASTRATE-RESISTANT PROSTATE CANCER (MCRPC): A TOOL TO POSITION NEW TREATMENTS IN THE PATIENT PATHWAY?

Karcher H[1], Dinet J[2], Amzal B[1], Marteau F[3], Obrzut G[4], Pieniazek I[4], Brulais S[5], Gabriel S[2]

[1]*LASER Analytica, London, UK,* [2]*IPSEN Pharma, Boulogne-Billancourt, France,* [3]*Ipsen Pharma SAS, Boulogne-Billancourt, France,* [4]*LASER Analytica, Krakow, Poland,* [5]*Ipsen pharma, Boulogne-Billancourt, France*

OBJECTIVES: New treatments registered in mCRPC are expected to alter the way patients are currently treated. It is hence essential for developers of any new treatment not only to position it within the current therapeutic landscape, but also to anticipate what this landscape will resemble at time of launch. To address this issue, we developed a modeling tool that recast a new treatment's value into the evolving therapeutic landscape. **METHODS:** We conducted a literature review of existing health economic models in mCRPC, including recent HTA reports and conference abstracts. Technical and contextual elements were leveraged to build a flexible prototype economic model for new treatments. The model encompasses disease management from asymptomatic mCRPC to patient's death. It aims at describing the future management of mCRPC in including the current way patients are treated and the following innovative features: flexibility to alter the target population definition and size and to add new therapies. New therapies' effectiveness and their expected positioning within the treatment pathway of mCRPC patients are assessed through the model. **RESULTS:** We have created a dynamic prototype model to position new options in the current and future therapeutic landscape for treatment of mCRPC in Europe. Economic models identified in literature were addressing specific reimbursement questions and were not flexible enough to be re-used for our purpose of assessing therapeutic landscape evolution. However, some technical elements on costs and effectiveness could be leveraged for our model. The tool itself enabled to identify information gaps: epidemiology and real-life data were missing for some new treatments. These could be simulated and introduced in our easily-actualizable tool. **CONCLUSIONS:** An actualizable modeling and simulation tool was developed in mCRPC. This tool enables dynamic identification of the best public health and economic outcomes out of a new potential therapeutic alternative.

PRM104

A REVIEW OF METHODS USED IN HEALTH ECONOMIC MODELS OF CHRONIC MYELOID LEUKEMIA INTERVENTIONS

Marsh K[1], Xu P[2], Orfanos P[1], Benedict A[3], Desai K[1], Griebsch I[4]

[1]*Evidera, London, UK,* [2]*Evidera, Lexington, MA, USA,* [3]*Evidera, Budapest, Hungary,* [4]*Boehringer Ingelheim Pharma GmbH, Ingelheim am Rhein, Germany*

OBJECTIVES: To describe the methods adopted by economic models of CML interventions, assess their strengths and limitations, and develop best practice recommendations. **METHODS:** Examples of different economic modeling approaches used to assess the cost effectiveness of CML interventions were identified in MEDLINE and EMBASE. The studies were reviewed to map the method employed, how and why these approaches were selected, and lessons learned by the authors. **RESULTS:** A total of unique CML models were reviewed. The large majority of these models were published in the last 10 years, with almost half being published in 2011. All but 1 of the models adopted a Markov structure, based around the following health states: chronic phase; accelerated phase; blast phase; and death. In line with best practice recommendations, over 75% of studies modeled progression and survival based on response to treatment. Extrapolation of trial data used a wide range of statistical models. Contrary to best practice recommendations, the fit of these models to the trial data and the validity of the extrapolation were not always tested. A variety of approaches were employed to estimate the health related quality of life associate with health states, including the direct valuation of health states, the use of standard health instruments (such as EQ5D), and mapping methods. **CONCLUSIONS:** Several approaches to the economic modeling of CML interventions were identified in the literature. A number of examples of good practice were identified, including the use of disease response outcomes when modeling progression and survival, and the systematic testing of the fit of survival distributions to trial data. Key challenges facing CML modeling are the validity of extrapolations of trial data given the long time periods over which these extrapolations are required, and the lack of data against which to validate them.

PRM105

MODELLING THE NATURAL HISTORY OF SCHIZOPHRENIA: COMPARISON OF NAÏVE VERSUS ADVANCED STATISTICAL METHODS

Millier A[1], Lenert L[2], Sadikhov S[3], Moreno S[3], Toumi M[4]

[1]*Creativ-Ceutical, Paris, France,* [2]*University of Utah School of Medicine, Salt Lake City, UT, USA,* [3]*F. Hoffmann-La Roche Ltd., Basel, Switzerland,* [4]*University Claude Bernard Lyon 1, Lyon, France*

OBJECTIVES: The literature provides little guidance on statistical methods for estimating parameters of Markov models using longitudinal data. We compared the commonly used naïve (based on raw data) and advanced approaches to estimate two model parameters: transition probabilities and hospitalisation rates. Both the naïve and advanced approaches were applied using data from the European Schizophrenia Cohort (EuroSC) to populate a Markov model in schizophrenia. **METHODS:** EuroSC is a 2-year observational study of patients with schizophrenia (n=1,208), with 5 visits at 6-month intervals. Patients were classified into 8 health states at each visit according to severity of symptoms assessed using the Positive and Negative Syndrome Scale (PANSS). For each health state, both model parameters (hospitalisation days and transition probabilities) were estimated based on raw data by pooling all time intervals (i.e. naïve approach). Similarly, for advanced methods, transition probabilities were estimated using multi-state models while hospitalisation days were estimated using two-part Generalised Estimating Equations (GEEs). Advanced methods adjusted for patient characteristics and included random effects to account for repeated measures. **RESULTS:** The naïve approach showed that the average number of hospitalisation days in a 6-month interval ranged from 4.20 in health state 1 to 19.43 in health state 8. Results from the two-part GEEs provided a range from 4.21 in health state 1 to 14.7 in health state 8. GEEs tended to provide narrower confidence intervals. With regards to transition probabilities, differences between the naïve approach and the multi-state model were mostly seen in the second decimal place. **CONCLUSIONS:** While the naïve approach is frequently used for its simplicity, it has a number of shortcomings including: not accounting for repeated measures and not allowing for adjustment of patient characteristics. To increase the robustness of results, we recommend using statistical models that recognise and account for the unique distributional characteristics of data.

PRM106

SURVIVAL ANALYSIS WITH COVARIATES IN COMBINATION WITH MULTINOMIAL ANALYSIS TO PARAMETRIZE TIME TO EVENT FOR MULTI-STATE MODELS

Feenstra TL[1], Postmus D[2], Quik EH[3], Langendijk H[4], Krabbe PFM[3]

[1]*University Medical Centre Groningen, Groningen, The Netherlands,* [2]*University Medical Center Groningen, Groningen, The Netherlands,* [3]*University of Groningen, University Medical Center Groningen, Groningen, The Netherlands,* [4]*UMCG, Groningen, The Netherlands*

OBJECTIVES: Recent ISPOR Good practice guidelines as well as literature encourage to use a single distribution rather than the latent failure approach to model time to event for patient level simulation models with multiple competing outcomes. Aim was to apply the preferred method of a single distribution on time to event in combination with a multinomial distribution on type of event for parameterizing the primary tumor component of a patient level head and neck cancer model. **METHODS:** Data on patients treated with radiation therapy as first line therapy for head and neck tumor at two university hospitals in The Netherlands between 25-02-1980–13-12-2010 was used (nUMCG=277 & nVUMC=736). Several distributions were tested for model fit, using QQ-plots, AIC, and simulated versus actual data plots to judge best fit. Covariates tested for inclusion were age, gender, tumor location dummies, nstage and tstage. The final model was applied in the patient simulation model. Multinomial regression with the same covariates and time of event added as a covariate was applied on type of event, distinguishing death, loco regional recurrence and metastasis as events. All analyses were performed in R. **RESULTS:** The LogNormal distribution showed best fit. The final model had the following coefficients for the location parameter (se in brackets): Intercept, 8.2 (0.38), Age -0.026 (0.0053), Tstage -0.38 (0.062), Nstage -0.21 (0.076), Locd1 -0.91 (0.22) , Locd2 -0.28 (0.15), Locd3 -0.72 (0.22). Locd refers to location dummies. The estimated value for Log(sd) was -0.44 (0.038). The multinomial model had age, tstage and time of event as significant covariates **CONCLUSIONS:** A disadvantage of this method is that a single distribution has to be fit to a time of event which is the result of different interacting stochastic processes. The resulting distributions showed acceptable fit and could be implemented straightforwardly in the patient level simulation model.