PHM15

HEMATOLOGICAL DISORDERS—Methods and Concepts

POSITIVE INVESTMENT INTERVAL (PII) AND PAYBACK PERIOD (PP) OFFER DIFFERENT INTERPRETATIONS IN HEALTH TECHNOLOGY INVESTMENT DECISIONS: PII IS A MATTER OF BEING AND PP IS A MATTER OF TURNING BENEFICIAL—A CASE OF HEMOPHILIA A

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OBJECTIVES: Investment views have been more or less neglected in economic evaluations. Fortunately, investments can be efficiently and easily assessed by evaluating the most uncertain feature of investment—Time—from two perspectives. The innovation, Positive Investment Interval (PII), its estimation and interpretation are presented here in relation to Payback Period (PP) with a safety example of Hemophilia A (HA), where the best safety is achieved using plasma/albumin-free methods (PFM). METHODS: PII estimates the interval when safety costs are compensated by the treatment costs of adverse events (AE). PP, on the other hand, estimates the time when the safety costs become compensated by the AE treatment costs. RESULTS: Both PII and PP are acceptable if the effectiveness of treatment options is equal. PII estimates the interval when investment to safety offers positive margin. In simple terms, PII is interval when no security threats should occur, if more risky treatment is used. Mathematically, PII compares the incremental costs of new minus old therapy (e.g., safety costs) to the incremental AE costs of old minus new therapy in a given interval (e.g., annual budgeting period). PP is the reversed version of PII. Stochastic PII can be presented in an AE costs-safety costs plane. In HA case, when base-case PIs for annual PFM Advate vs. non-PFM Kogenate investment were 1–7 years depending on patient’s weight, age, and treatment modality, were PPs 2–11 months. Longer PII, the better and shorter PP, the better. Thus, PII > PP is usually a potentially good and beneficial investment depending on the expected time horizons of possible AE or other patient security risks. CONCLUSION: PII is related to e.g., safety need as time and, thus, it has hands-on interpretation for political debate. PII can be compared to the time intervals of emerging security problems—not just to the probability of problem.

PHM16

PHARMACOKINETIC-PHARMACODYNAMIC-PHARMACOECONOMIC (P3) MODELING TO INFORM PHARMACOGENOMIC TRIAL DESIGN AND RISK MANAGEMENT

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OBJECTIVES: Our objective is to develop a quantitative, model-based protocol simulation approach for evaluating the clinical and economic effects of adverse drug outcomes related to genetic variation at early stages of drug or test development, using warfarin pharmacogenomics as a case-study. METHODS: We implemented a previously published (Hamberg et al. (2007)) population pharmacokinetic/pharmacodynamic (PK/PD) model of warfarin distribution and effect that incorporates the effects of genetic variation in the CYP2C9 and VKORC1 genes and other relevant demographic variables. We simulated outcomes (INR distribution) of a non-pharmacogenomic-based warfarin dosing protocol, and plan to simulate various pharmacogenomic-based dosing protocols and then integrate these results with pharmacoeconomic simulation models. RESULTS: INRs were modeled for 500 simulated patients using the same patient demographics (median and range) as those reported in the Hamberg analysis. The 5 mg/daily INR nomogram of Kovacs et al. (2003) was simulated. Baseline INRs were uniformly distributed over a range of 0.9 to 1.3. The INR at day 6 after initiation of therapy ranged from 0.97 to 10.31 with a median of 3.61. Median INR grouped by CYP2C9 expression ranged from 3.17 for *1*1 patients to 5.29 for *3*3 patients. INR variations are linked to the risks of bleeding and stroke, and ultimately to the pharmacoeconomic outcomes of costs and quality-adjusted life years. CONCLUSION: P3-cubed (P3) modeling will be feasible only when sufficient population PK/PD data are available and valid long-term linkages can be made. It may serve as a tool to explore the robustness of such linkages and probe alternative therapeutic scenarios. Although our findings are preliminary to date, P3-modeling may provide a useful quantitative framework to help inform pharmacogenomic trial design, regulatory decisions, and potentially clinical guidelines and reimbursement policies.

PHM17

RECOMBINANT ACTIVATED FACTOR VII (RFVIIA) VS. ACTIVATED PROTHROMBIN COMPLEX CONCENTRATE (APCC) FOR ON-DEMAND TREATMENT OF JOINT BLEEDS IN HEMOPHILIACS WITH INHIBITORS: A SYSTEMATIC REVIEW AND BAYESIAN META-REGRESSION SURVIVAL MODEL WITH TIME-DEPENDENT COVARIATES

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OBJECTIVES: The recent FENOC 2006 comparative trial reported comparable efficacy for RFVIIa and APCC in the treatment of joint bleeds in hemophiliacs with inhibitors. A literature-based Bayesian meta-regression analysis was carried out to place these results within the context of earlier, non-comparative studies and to identify key variables influencing treatment efficacy. METHODS: A systematic search of the literature identified 15 studies reporting usable and relevant data, which were pooled in a Bayesian random-effects survival model. A repeating Gompertz hazard function was selected to model an initial increase in the hazard of bleed resolution after each injection, followed by a decrease until the next injection was administered. Model covariates included medication type and the combination of the time-
dependent covariate dose and medication type. Efficacy was assumed identical for each subsequent injection. RESULTS: The systematic review revealed that different regimens were applied across pre-FENOC studies. Furthermore the Bayesian analysis demonstrated that medication type, alone or combined with dosage, had a significant influence on modelled efficacy. Using a standard treatment regimen of one 90 µg/kg rFVIIa injection every 3 hours, the model estimated that at 12, 24, and 36 hours the probability of bleed resolution was 76%, 94%, and 99%, respectively. In contrast, using a standard regimen of one 75 IU/kg APCC injection every 12 hours, the probability of bleed resolution at the corresponding times was 40%, 60%, and 79%, respectively. CONCLUSION: The present Bayesian meta-regression suggests that, despite the outcome of the FENOC study, on-demand treatment with rFVIIa may be associated with a faster time to joint bleed resolution than APCC using the standard treatment regimens specified. Future research should include time-independent confounding factors (e.g., efficacy rating scale method, efficacy rater, treatment setting, bleed severity).

**BEST-WORST CASE SCALING IN DISCRETE CHOICE EXPERIMENTS: AN APPLICATION IN A RARE DISEASE POPULATION**

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OBJECTIVES: Although discrete choice experiments are increasingly being used in health care applications to elicit preferences, their use has been limited in diseases with low prevalence because it is challenging to design a statistically and clinically meaningful study with a small sample of respondents. This study used best-worst case scaling to enhance the design of a discrete choice experiment eliciting physician preferences related to the care of patients being treated for hemophilia with inhibitors. METHODS: Thirty hematologists provided data on factors having an impact on their treatment decisions by completing a survey instrument via face-to-face interviews at a scientific meeting. To increase the amount of useful information obtained from each respondent, best-worst scaling was used. Specifically, each choice task was structured so that respondents provided input on and ranked three scenarios from most to least preferred. This innovative method had not previously been used in discrete choice modeling. RESULTS: With the increase in data due to the applied best-worse scaling method, an aggregate multinomial logit model established stable parameter estimates while obtaining a ‘consensus’ view of hematologists’ preferences. In substantive terms, the time required to stop bleeding was the most important factor affecting treatment decisions [relative importance (RI) = 16.3%]. Physicians also preferred treatments that resulted in quick pain relief [RI = 12.9%]. CONCLUSION: This example indicates that best-worst case scaling can effectively be used in discrete choice experiments involving aggregate multinomial logit modeling. This method can enhance and increase the use of discrete choice experiments to elicit preferences from relatively small numbers of physicians or patients with rare diseases, or when few respondents are available.

**VALUE OF TRANSFUSION-FREE LIVING IN MDS: RESULTS OF HEALTH UTILITY INTERVIEWS WITH MDS PATIENTS**

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OBJECTIVES: To elicit how MDS patients value transfusion independence (TI), reduced transfusions (RT) and transfusion-dependence (TD). METHODS: Forty-seven MDS patients were interviewed, US (n = 8), France (n = 9), Germany (n = 9) and the UK (n = 21), to elicit the utility value of TI, RT and TD. Health states (HS), based on literature, focus groups and validated by a