PRM96

OPTIMIZING THRESHOLDS FOR A CLINICAL RECOGNITION ALGORITHM

Hays HD[1], Debes R[2], Sutariya B[3], Bozzette S[4]
[1]Cerner Research, Culver City, CA, USA, [2]Cerner Corporation, North Kansas City, MO, USA, [3]Cerner Research, North Kansas City, MO, USA, [4]Cerner Research and the University of California, San Diego, Culver City, CA, USA

OBJECTIVES: Cerner has developed the St John's Sepsis Alert, an evidence-based real-time algorithm that alerts clinicians to the presence of the Systemic Immune Response Syndrome or sepsis. Using simulation, we estimated the Alert's performance and determined the optimal cut-offs for ~17 included quantitative parameters (e.g., blood pressure). **METHODS:** We estimated the operating characteristics of the alert by applying its logic to 3 years of real-world data on adults from Cerner *Health Facts*, a time-stamped database extracted from electronic medical records. We evaluated the base-case and performed a 10,000-iteration uncertainty analysis. Each run used a different set of thresholds, each drawn randomly from the range of reasonable values using a Latin hypercube sampling design under the assumption of an independently distributed joint beta distribution. Each run provided a point on the Receiver Operator Characteristic curve. We constructed an extended dominance curve from the resulting point cloud and determined the optimal values as those associated with that curve. **RESULTS:** Data from ~69,000 hospitalizations with a 5% incidence of sepsis were available. Using baseline values for the Alert, we estimated a Sensitivity of 56%, Specificity of 90%, Positive Predictive Value of 22%, and Negative Predictive Value of 98%. The uncertainty analysis found that 10 sets of cut-offs dominated all the others. The C-statistics for these ranged from 67% to 75%, Sensitivity from 39% to 73%, Specificity from 96% to 76%, PPV 33% to 13%, NPV 95% to 98%, and the posterior probability of sepsis increased from 2.4- to 7-fold. The most accurate thresholds were not necessarily optimal for implementation; certain sets with only slightly lower C-statistics greatly decreased false positive rates. **CONCLUSIONS:** Simulation can usefully inform in the design of clinical algorithms prior to implementation. Examining a range of thresholds can identify statistical optimality and characterize trade-offs to deviating from it.

PRM97

EVALUATING THE COST-EFFECTIVENESS OF MULTICOMPONENT REHABILITATION GUIDELINES

Mewes JC, Steuten LMG, IJzerman MJ, van Harten WH
University of Twente, Enschede, The Netherlands

OBJECTIVES: The Dutch guideline for cancer rehabilitation recommends patients to engage in multicomponent interventions, i.e. several single interventions combined into a rehabilitation programme. To perform a health economic evaluation of this guideline, data on the cost-effectiveness of these multicomponent interventions is required. However, to date, the interventions´ (cost-)effectiveness is almost exclusively assessed for the single interventions, rather than for the multicomponent intervention, which challenges the health economic analysis of the multicomponent interventions. The objective of this study was to identify or develop a method that allows to deduct the cost-effectiveness of multicomponent interventions from published data of the single interventions. **METHODS:** We searched the literature for articles offering a method or ideas for the development of a method for assessing the cost-effectiveness of multicomponent interventions on the basis of data on the single interventions. The cost-effectiveness gap analysis method, which can be used for assessing the maximum cost of an intervention given a certain willingness-to-pay, was identified as suitable and was further developed to allow assessing if a multidimensional programmes is cost-effective, based on the (cost-)effectiveness data of the single interventions. **RESULTS:** Cost-effectiveness gap analysis was identified in the literature as being a suitable method, with further refinement. We suggested to first calculate the costs of all interventions. Given the effectiveness of one intervention it is then possible to estimate how much additional effectiveness a second (or any subsequent) intervention would have to provide so that the multicomponent intervention remains cost-effective, given a range of ceiling ratios. Recommendations for methods for estimating the additional effect of subsequent interventions were deducted from the literature identified. **CONCLUSIONS:** We suggest estimating the cost-effectiveness of the combined interventions as recommended in clinical guidelines by performing a refined cost-effectiveness gap analysis method.

PRM98

THE USE AND IMPACT OF VALUE OF INFORMATION ANALYSIS IN DECISION-MAKING

Chuang LH[1], Treur M[1], Heeg B[1], Van Hout B[2], Filonenko A[3]
[1]Pharmerit International, Rotterdam, The Netherlands, [2]Pharmerit International, York, UK, [3]Bayer Pharma AG, Berlin, Germany

OBJECTIVES: Along with uncertainty around reimbursement decisions, one should determine the worth of additional research to reduce the probability of making wrong decisions. Value of information analysis (VOI) provides an explicit framework to inform future research. The objectives of this research were to assess published evidence of VOI and to evaluate its impact on decision making and research agendas. **METHODS:** A literature review was conducted in MEDLINE and EMBASE to collect studies with VOI applications published until November 2012. Data extracted included study indication, year, country, sponsorship, type of VOI analysis, research impact and quality of the study. HTA guidelines of developed countries were checked and country experts were approached to discuss the relevance of VOI. **RESULTS:** One hundred studies with VOI applications were identified. Amongst these, cancer was the most popular indication (25%) and the majority had a UK perspective (49%). The number of publications gradually rose after 2005 but remained steady since 2009. Rarely, studies were sponsored by industry (8%). Expected value of perfect (parameter) information (EVP(P)I) was reported in 92% (59%) of the articles, respectively. Only 12% of articles reported expected value of sample information (EVSI) and 4% reported expected value of perfect implementation (EVPIM). Finally, no actual implication on future research had been reported. Only the UK and Netherlands recommend the use of VOI in the HTA guideline. However VOI is not a formal requirement in the manufacturer/sponsor submission of evidence to NICE or CvZ. All experts reported lack of influence of VOI in research decision. **CONCLUSIONS:** The application of VOI to inform HTA and research is limited. Even in the UK and Netherlands, where VOI analysis is recommended in the HTA guidelines.

PRM99

PREDICTION OF MORTALITY IN THE PRESENCE OF TIME-DEPENDED COVARIATES: AN APPLICATION FOR HEALTH ECOMONIC PROJECTIONS

Exuzides A, Colby C
ICON Late Phase & Outcomes Research, San Francisco, CA, USA

OBJECTIVES: We want to develop a parametric model to predict mortality for future patients with a disease that have specific demographic and clinical characteristics while considering patient trajectories over time for a set of biomarkers, which are critical predictors of disease progression. This is an important tool for many health economic projections. **METHODS:** In time-to-event studies, longitudinal measures are collected for important disease progression biomarkers. Using only the last available value of these measures in survival models discards important information from the longitudinal evolution. We used data from a 3-year observational study to estimate the covariate coefficients in a Cox-proportional hazards model in the presence of time-dependent biomarkers via SAS® PHREG. In addition, we applied a Weibull accelerated failure time model to estimate the scale/shape of a parametric survival distribution using SAS®LIFEREG, which, unlike PHREG, does not allow for direct incorporation of longitudinal measures. In developing the final prediction model, we combined the coefficients from PHREG and the scale/shape from LIFEREG to compute the probability of survival. **RESULTS:** By applying the Weibull model without considering patient trajectories over time, we predicted a 3-year survival rate of 55.1%. However, the hybrid combination approach of the Cox/Weibull model, predicted a more accurate 3-year survival rate of 46.7%, which fell within the confidence bounds of the original observational study. **CONCLUSIONS:** Ignoring the additional variability of patient trajectories over time, when modeling survival, can lead to biased estimates. We have implemented a hybrid approach by which we incorporated the impact of time-dependent biomarkers of the disease along with the scale/shape of a parametric survival distribution to more accurately project survival time in health economic modeling.

PRM100

MIXTURE SURVIVAL MODELING FOR HETEROGENEOUS PATIENT POPULATION

Qian Y[1], Kwon D[2]
[1]Amgen Inc., Thousand Oaks, CA, USA, [2]University of Miami, Miami, FL, USA

OBJECTIVES: It is not uncommon to have heterogeneous patient populations in clinical trials while lacking established biomarkers/factors to identify heterogeneity. In estimating average survival time, a critical component in economic models, extrapolation of limited trial data is often necessary and standard parametric survival models are regularly used without considering population heterogeneity. Our project was to introduce mixture modeling that incorporated population heterogeneity. **METHODS:** Heterogeneous survival data were simulated. Mixture models, besides standard survival models, were applied to address population heterogeneity via Bayesian inference, where clinical inputs (e.g., survival of one sub-population is longer than the other) can also be incorporated. The model fit was evaluated and the average survival was estimated. **RESULTS:** Two-hundred patient level survival data were simulated from a mixture of two exponentials with average survival of 3 (30% of patients) and 0.6 year respectively and overall average survival of 1.32 years. The simulation was run 100 times. For each dataset, Bayesian inference was based on 10000 iterations after 1000 burn-in. In one exercise, the standard approach, including exponential, Weibull and lognormal models, and a mixture of two exponentials were applied. The mixture model provided a good fit per DIC and the estimated proportion was 0.372 (SD: 0.13). The estimates for average survival were compared across methods (true mean: 1.32; exponential: 1.238 [SD: 0.142], Weibull: 1.260 [SD: 0.151], lognormal: 1.760 [SD: 0.311]; exponential mixture: 1.311 [SD: 0.178]). The extension to mixture models with different components (number or structure) could be implemented. **CONCLUSIONS:** The mixture modeling could potentially improve the estimates for average survival time in heterogeneous populations. Though this doesn't apply in every situation, heterogeneity should be considered based on clinical inputs, and tools that address heterogeneity from both clinical and statistical perspectives should continue to be developed to support survival modeling.

PRM101

A METHOD TO ESTIMATE DISEASE-STAGE-SPECIFIC SURVIVAL USING DATA OBTAINED FROM A PREVALENT COHORT

Sabatelli L
GLOB MOD, Barcelona, Spain

OBJECTIVES: Technical, ethical, and practical reasons may hamper efforts to understand how survival rates of treated and untreated individuals change as a result of disease progression. This is a rather general problem that concerns communicable and non communicable diseases alike. In certain instances, the only available survival information refers to prevalent (as opposed to incident) cohorts, where individuals are randomly selected and enrolled irrespectively of