OPTIMIZING THRESHOLDS FOR A CLINICAL RECOGNITION ALGORITHM

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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 binned 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 Operating 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 >90,000 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 22%, and Negative Predictive Value of 98%. The uncertainty analysis found that thresholds can identify statistical optimality and characterize trade-offs to deviating from it.

EVALUATING THE COST-EFFECTIVENESS OF MULTICOMPONENT REHABILITATION GUIDELINES

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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 analysis 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 multicomponent intervention is cost-effective compared to the single interventions. RESULTS: Cost-effectiveness gap analysis was identified in the literature as being a suitable method, with further refinement. We simulated data 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.

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

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OBJECTIVES: Along with uncertainty around reimbursement decisions, one should determine the worth of additional research to reduce the probability of making erroneous 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 reimbursement. 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 unstructured interviews were performed 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 (EVPI) was reported in 92% (59%) of the articles, respectively. Only 1% (3%) reported expected value of sample information (EVSI) and 4% expected value of perfect implementation (EVPIF). Finally, no actual application 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 NICE. 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.

PREVENTION OF MORTALITY IN THE PRESENCE OF TIME-DEPENDENT COVARIATES: AN APPLICATION FOR HEALTH ECONOMIC PROJECTIONS

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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. Methods: Using a Cox-within-a-cox model, we added an accelerated failure time model to estimate the scale/shape of a parametric survival distribution using SAS®LIFEREG, which, unlike PHREG, does not allow for time-varying covariates. Experiments were conducted on simulated data of a parametric normal distribution, 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 normal distribution to more accurately project survival time in health economic modeling.

MIXTURE SURVIVAL MODELING FOR HETEROGENEOUS PATIENT POPULATION

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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 health economic evaluation 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 survival model was 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 and evaluated. The model fitting time-to-event 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 1000 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: 0.138]. 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.

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

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OBJECTIVES: Technical, ethical, and practical reasons may hamper efforts to collect survival data. When data are not available, we would like to use data as a stage of a disease 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