Quantifying nonlinear effects in stochastic Markov simulation using UKPDS 68 and UKPDS 82 equations in type 2 diabetes modeling analysis with the IMS CORE Diabetes Model (CDM)

Introduction

Draining patient heterogeneity is adequately reflected in cost-effectiveness models is essential if the model’s output is to robustly inform on the expected changes in health benefit and costs associated with competing interventions.

Modeling cohorts in health economic evaluations using a “mean” model profile typically fail to capture the times of clinical events - higher risk patients will inevitably progress sooner than lower risk patients.

Previous studies using the CORE diabetes model (CDM) have demonstrated that incorporating parameter sampling (PS) within an analysis is crucial to capture nonlinear effects (NE) in cost-effectiveness modeling [1]. This is mostly undertaken when conducting probabilistic analysis but is also required to ensure that the point estimates predicted by a model are unbiased.

NE are, among other causes, driven by the degree through which the symmetric sampling of risk factors is translated into non-symmetrically distributed probabilities, for example, as generated by the model’s risk equations.

Methods

Objectives

This study sought to assess degree by which the incorporation of parameter sampling (PS) alters event rate predictions when utilizing either the UKPDS 68 (SU/INS) [2] or UKPDS 82 (SU) component risk equation in a set of selected validation studies conducted within the CDM.

The CDM is a recently validated lifetime simulation model designed to assess the health outcomes and economic consequences of interventional strategies in T1DM or T2DM. The CDM model incorporates a set of 17 interdependent sub-models that simulate the complications of diabetes (angina, myocardial infarction (MI), congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula edema, cataract, nephropathy, foot ulcer, amputation, pulmonary edema, depression) in addition to all-cause mortality.

The model is a first-order (annual) stochastic simulation with each submodule using time, state, and diabetes type dependent probabilities. Monte-Carlo simulations are performed at the individual patient level using tracker variables to accommodate complex interactions between individual complication sub-models.

Validation studies

A total of 51 validation simulations were performed to data from: the Diabetes Control and Complications Trial (DCCT) [8]; the UK Prospective Diabetes Study (UKPDS) 33 [7]; the UKPDS 80 model (a Nested study for Prevention of Coronary Heart Disease Endpoints in non-insulin dependent diabetes mellitus) [9]; the Veterans Affairs Diabetes Trial (VADT) [10]; the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [11]; the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [12,13].

Results

Figure 1 illustrates the impact that sampling cohort profiles have on predicted risk within the CDM (illustrated for 1st and 2nd myocardial infarction (MI) and mortality). Vertical lines demonstrate the event probability using a mean cohort profile: 1st MI = 0.049, 2nd MI = 0.041, death (with no history of prior complications) = 0.007; death (in year of diabetes related complication) = 0.189. The density plots are derived from cohorts of 1000 simulated patients.

Figure 2 shows the percentage increase in predicted risk with and without PS for the UKPDS intensive (INT) and standard (STD) cohorts simulated using UKPDS 68 and 82 risk equations.

Figure 3 demonstrates that the CDM model produced an R2 statistic of 0.876 and 0.791 in analysis with sampled cohort profiles for the UKPDS 68 and 82 risk equations, respectively. The findings from this study illustrate that PS has a significant impact on predicted risk of complications. The goodness of fit, as measured by the coefficient of determination, indicates that the external validity of the model declined with PS in simulations using UKPDS 68 and 82 risk equations.

Conclusions

The degree by which PS increased end point predictions was considerable stronger in UKPDS 82 risk equation predictions for MAC and ACM but lower for ACM when compared to UK 82 risk equations.

In the study the use of “mean” cohort risk was associated with a modest improvement in validation fit. Importantly, the validation studies used in this analysis were typically less than five years in duration, consequently, longer-term event rates may be significantly underestimated when PS is not utilized.

References

1. McEwan et al, ISPOR 16th Annual European Congress, Dublin, 2013 | PRM16
5. McEwan et al. ISPOR 16th Annual European Congress, Amsterdam, 8-12 November 2014 | PRM17

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