Long-term validation of the IMS CORE Diabetes Model in Type 1 and Type 2 diabetes

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Background and Aim
• The CORE Diabetes Model (CDM) is an extensively validated simulation model designed for both for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) studies [1,2].
• Validation to external published studies is an ongoing and important part of demonstrating model credibility; importantly, many of these studies have a relatively short period of follow-up.
• The CDM is widely used to estimate long-term clinical outcomes in diabetes patients, therefore the aim of this study was to validate the CDM to contemporary outcomes data; particularly those with a 20-30 year time horizon.

Methods
• The CDM is a lifetime simulation model designed to assess the health outcomes and economic consequences of interventions in T1DM or T2DM.
• The model structure comprises 17 interconnected sub-modules that simulate the complications of diabetes (anxiety, myocardial infarction (MI), congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula edema, cataract, hypoglycaemia, ketosis, lactic acidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcer, amputation, pulmonary edema and depression) in addition to all-cause mortality.
• The model is a fixed-time increment (annual) stochastic simulation with each sub-module 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-modules.
• A total of 95 validation endpoints were simulated across 9 predesigned type 1 and type 2 outcomes studies (Table 1a and 1b).
• Results were stratified by duration of study follow-up (long-term defined as > 15 years follow-up); for long-term results simulation cohorts representing baseline DCCT and UKPDS cohorts were generated and intensive and conventional treatment arms were defined in the CDM.
• Predicted versus observed macrovascular and microvascular complications and all cause mortality were assessed using the coefficient of determination (R2) goodness of fit measure.

Results
• Across all validation studies predicted events from the CDM are contrasted with observed study events (Table 1a and 1b) producing an R² statistic of 0.90 (Figure 1).
• For validation studies with duration of follow-up <15 years the achieved R² values of 0.9 and 0.88 for T1DM and T2DM respectively.
• In T1DM, validating to 30-year DCCT/EDIC outcomes data resulted in an R² of 0.73, for long-term 20-year validation to UKPDS in T2DM an R² of 0.52 was obtained (Figure 2).
• In the T2DM validation studies, model output showed a noteworthy lack of fit when predicting cardiovascular morbidity and mortality.
• The ratio of observed to predicted events are summarized in bar charts shown in Figure 3 for studies with duration of follow-up of <5 years; 15 years and 630 years. Overall variability in the ratio of observed to expected events increased with study follow-up: SD=0.41, 0.58 and 0.56 respectively.

Conclusion
• Projecting the long-term clinical consequences associated with alternative therapeutic options is an essential part of health technology assessments.
• This study supports the CDM as a credible tool for predicting both the absolute number of clinical events and projecting the future treatment consequences associated with managing patients with diabetes.
• Where long term (>20 years) data exist, for example DCCT and UKPDS, this study demonstrates the CDM is capable of reproducing consistent event rates with those observed in the respective trials.
• With increasing prevalence and incidence of diabetes worldwide this is of particular importance for healthcare decision-makers for whom the robust evaluation of alternative healthcare policies and therapeutic options is essential.

Acknowledgments
The IMS CORE Diabetes Model is owned and maintained by IMS Health.

References

Table 1a: Outcomes studies in Type 1 Diabetes Method

<table>
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<tr>
<th>Study</th>
<th>Validation Period</th>
<th>Endpoint</th>
<th>CDM Predicted</th>
<th>Conventional</th>
<th>CDM Predicted</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS[8]</td>
<td>10 years</td>
<td>MI</td>
<td>216</td>
<td>254</td>
<td>0.944</td>
<td>0.947</td>
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<td></td>
<td></td>
<td>Stroke</td>
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<td>113</td>
<td>0.913</td>
<td>0.915</td>
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<tr>
<td></td>
<td></td>
<td>CHF</td>
<td>30</td>
<td>35</td>
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</table>

Table 1b: Outcomes studies in Type 2 Diabetes Method

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<th>Study</th>
<th>Validation Period</th>
<th>Endpoint</th>
<th>CDM Predicted</th>
<th>Conventional</th>
<th>CDM Predicted</th>
<th>Conventional</th>
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</thead>
<tbody>
<tr>
<td>DCCT[9]</td>
<td>6.5 years</td>
<td>MI</td>
<td>7</td>
<td>10</td>
<td>0.542</td>
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<td></td>
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<tr>
<td></td>
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<td>CHF</td>
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<td>12</td>
<td>0.565</td>
<td>0.565</td>
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</tbody>
</table>

Table 2: Scatterplot of observed versus predicted endpoints across all validation studies

Figure 1. Scatterplot of observed versus predicted endpoints for T1DM and T2DM studies

Figure 2. Scattered of observed versus predicted endpoints by duration of study