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 use in 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 of 17 interdependent sub-modules that simulate the complications of diabetes (angina, myocardial infarction (MI), congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula edema, cataract, hypoglycaemia, ketoacidosis, 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 96 validation endpoints were simulated across 9 pivotal 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 1 and 1b) producing an R^2 statistic of 0.90 (Figure 1).
- For validation studies with duration of follow-up ≤5 years the CDM achieved R^2 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 R^2 of 0.72; for long-term 20-year validation to UKPDS in T2DM an R^2 of 0.92 was obtained; Figure 2.
- In the T2DM validation studies, model output showed a noteworthy lack of fit when predicting cardiovascular mortality for ACCORD and VADT.
- The ratios of observed to predicted events are summarised in boxplots shown in Figure 3 for studies with duration of follow-up of ≤5 years; ≤15 years and ≤30 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).

Table 1a. Outcomes studies in Type 1 Diabetes Mellitus

		Trial			CDM		
Trial (study follow-up)	**Endpoint**	**Intensive**	**Conventional**	**RR**	**Intensive**	**Conventional**	**RR**
DCCT[3] (5-6.5 years)	Retinopathy	23	91	0.275	28	91	0.345
	Neuropathy	7	28	0.292	8	30	0.323
	Microalbuminuria	55	103	0.586	72	105	0.768
	Albuminuria	9	9	1.130	6	10	0.610
DCCT/EDIC[4] (17-30 years)	CV events	25	38	0.633	38	43	0.853
	Retinopathy	153	356	0.420	200	211	0.923
	Nephropathy	66	178	0.360	101	83	1.182
	CVD	66	100	0.643	115	118	0.954
	ESRD	7	14	0.500	26	23	1.094

Table 1b. Outcomes studies in Type 2 Diabetes Mellitus

		Trial			CDM		
Trial (study follow-up)	**Endpoint**	**Intensive**	**Conventional**	**RR**	**Intensive**	**Conventional**	**RR**
UKPDS[5] (10 years)	MI	401	474	0.353	493	532	0.386
	Stroke	152	136	0.466	166	175	0.396
	CHF	82	90	0.380	156	167	0.390
	ESRD	16	21	0.318	5	7	0.298
	Cataracts	153	202	0.316	109	120	0.379
	All cause mortality	488	515	0.395	566	595	0.397
ACCORD Blood Pressure [6] (4.7 years)	Primary endpoint	208	237	0.880	188	223	0.845
	MI (non-fatal)	126	146	0.865	71	94	0.751
	Stroke (non-fatal)	34	55	0.620	25	38	0.676
	CHF	83	90	0.925	60	65	0.932
	CV Death	60	58	1.037	93	96	0.976
ACCORD Glucose [7] (4.7 years)	Primary endpoint	352	371	0.948	417	450	0.926
	MI	186	235	0.791	80	87	0.919
	Stroke	67	61	1.097	92	100	0.919
	CHF	135	173	0.780	122	130	0.938
	CV Death	152	124	1.225	245	263	0.931
ADVANCE [8] (5 years)	MI (non-fatal)	153	156	0.980	155	186	0.832
	Stroke (non-fatal)	214	209	1.024	161	171	0.936
	CV Death	253	289	0.875	208	215	0.969
	CHF	220	231	0.952	193	192	1.008
ASPEN [9] (4 years)	MI	96	133	0.720	128	171	0.741
	Stroke	72	75	0.958	48	50	0.961
	CV Death	75	75	0.990	60	72	0.826
VADT [10] (5.6 years)	Primary endpoint	235	264	0.897	235	274	0.864
	MI	64	78	0.827	48	60	0.806
	CHF	76	82	0.934	35	44	0.802
	Stroke	28	36	0.784	40	43	0.938
	Amputation	11	17	0.652	39	42	0.936
	CV Death	38	29	1.321	61	72	0.940
UKPDS [11] SU and insulin	MI	678	319	0.886	564	269	0.875
	Stroke	260	116	0.935	202	97	0.871
	All cause mortality	1162	537	0.902	1094	486	0.939
	Microvascular disease	429	429	0.417	398	239	0.695
UKPDS [11] metformin	MI	81	126	0.773	71	97	0.875
	Stroke	34	42	0.973	25	35	0.871
	All cause mortality	152	217	0.842	137	175	0.939
	Microvascular disease	66	78	1.017	50	86	0.695

RR=Relative Risk; MI=myocardial infarction; CHF=congestive heart failure; ESRD=end stage renal disease; CV=cardiovascular.

Figure 1. Scatterplot of observed versus predicted endpoints across all validation studies

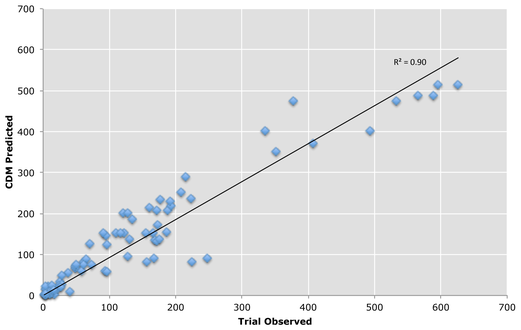


Figure 2 Scatterplot of observed versus predicted endpoints for Type 1 and Type 2 long-term studies

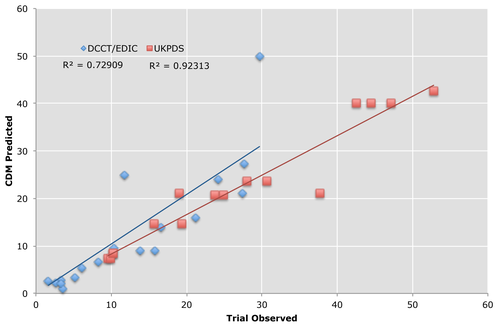
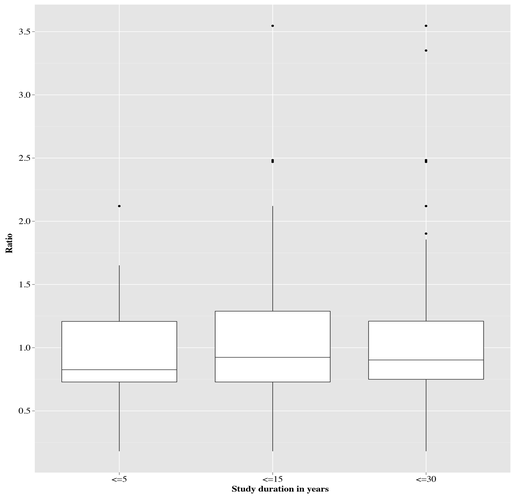


Figure 3. Ratio of observed to predicted endpoints stratified by duration of study



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 incidence and prevalence 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

[1] Palmer et al. Curr Med Res Opin 2004;20:S5–S26.
[2] Palmer et al. Curr Med Res Opin 2004;20:S27–40.
[3] The DCCT Research Group. Ann Intern Med 1995;122:561-8
[4] The DCCT/EDIC Research Group. Arch Intern Med. 2009;169(14):1307-1316
[5] UK Prospective Diabetes Study Group (UKPDS 33). Lancet 1998; 352:837–853
[6] The ACCORD Study Group. N Engl J Med 2010; 362:1575-1585
[7] The ACCORD Study Group. N Engl J Med 2008; 358:2545–2559
[8] The ADVANCE Collaborative Group. N Engl J Med 2008 358:2560–2572
[9] Knopp et al. Diabetes Care 2006; 29(7):1478-1485
[10] Duckworth et al. N Engl J Med 2009;360:129–139
[11] UKPDS 80. N Engl J Med 2008;359:1-13

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