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Long-term validation of the 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).
- In T1DM, validating to 30-year outcomes data resulted in an R^2 of 0.67; for long-term 20-year validation to UKPDS in T2DM an R^2 of 0.98 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 ratio of observed to predicted events are summarised in boxplots shown in Figure 3 for studies with duration of follow-up of ≤5 years; >5 and ≤10 years and >10 years. Overall variability in the ratio of observed to expected events increased with study follow-up; SD=0.3, 0.5 and 0.8 respectively).
- 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.

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 years)	Retinopathy	8	24	0.35	7	24	0.27
	Neuropathy	17	41	0.41	3	10	0.30
	Microalbuminuria	21	28	0.77	16	27	0.59
	Albuminuria	2	3	0.59	3	2	1.13
DCCT/EDIC[4] (30 years)	Retinopathy	21	50	0.42	26	28	0.93
	Gross Proteinuria	25	9	2.78	13	11	1.21
	Angina, stroke or MI	3	5	0.63	5	6	0.84
	CV Death	9	14	0.64	15	16	0.96
	ESRD	1	4	0.25	3	3	1.12

Table 1b. Outcomes studies in Type 2 Diabetes Mellitus

		Trial			CDM		
Trials and follow-up	**Endpoint**	**Intensive**	**Conventional**	**RR**	**Intensive**	**Conventional**	**RR**
UKPDS[5] (10 years)	MI	401	474	0.35	493	532	0.39
	Stroke	152	136	0.47	166	175	0.40
	CHF	82	90	0.38	156	167	0.39
	ESRD	16	21	0.32	5	7	0.30
	Cataracts	153	202	0.32	109	120	0.38
	All cause mortality	488	515	0.40	566	595	0.40
ACCORD Blood Pressure [6] (4.7 years)	Primary endpoint	208	237	0.88	188	223	0.84
	MI (non-fatal)	126	146	0.87	71	94	0.75
	Stroke (non-fatal)	34	55	0.62	25	38	0.68
	CHF	83	90	0.92	60	65	0.93
	CV Death	60	58	1.04	93	96	0.98
ACCORD Glucose [7] (4.7 years)	Primary endpoint	352	371	0.95	417	450	0.93
	MI	186	235	0.79	80	87	0.92
	Stroke	67	61	1.10	92	100	0.92
	CHF	135	173	0.78	122	130	0.94
	CV Death	152	124	1.22	245	263	0.93
ADVANCE [8] (5 years)	MI (non-fatal)	153	156	0.98	155	186	0.83
	Stroke (non-fatal)	214	209	1.02	161	171	0.94
	CV Death	253	289	0.88	208	215	0.97
	CHF	220	231	0.95	193	192	1.01
ASPEN [9] (4 years)	MI	96	133	0.72	128	171	0.74
	Stroke	72	75	0.96	48	50	0.96
	CV Death	75	75	0.99	60	72	0.83
VADT [10] (5.6 years)	Primary endpoint	235	264	0.90	235	274	0.86
	MI	64	78	0.83	48	60	0.81
	CHF	76	82	0.93	35	44	0.80
	Stroke	28	36	0.78	40	43	0.94
	Ampitation	11	17	0.65	39	42	0.94
	CV Death	38	29	1.32	61	72	0.94
UKPDS [11] SU and insulin	MI	678	319	0.89	564	269	0.87
	Stroke	260	116	0.93	202	97	0.87
	All cause mortality	1162	537	0.90	1094	486	0.94
	Microvascular disease	429	429	0.42	398	239	0.70
UKPDS [11] metformin group	MI	81	126	0.8	71	97	0.88
	Stroke	34	42	1.0	25	35	0.87
	All cause mortality	152	217	0.84	137	175	0.94
	Microvascular disease	66	78	1.02	50	86	0.70

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

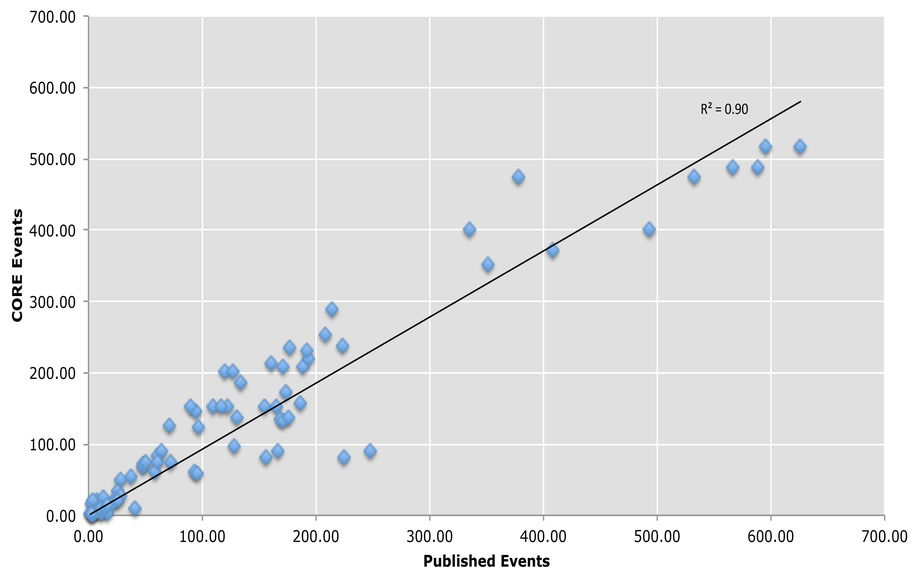


Figure 2 Scatterplot of observed versus predicted endpoints for Type 1 and Type 2 long-term studies

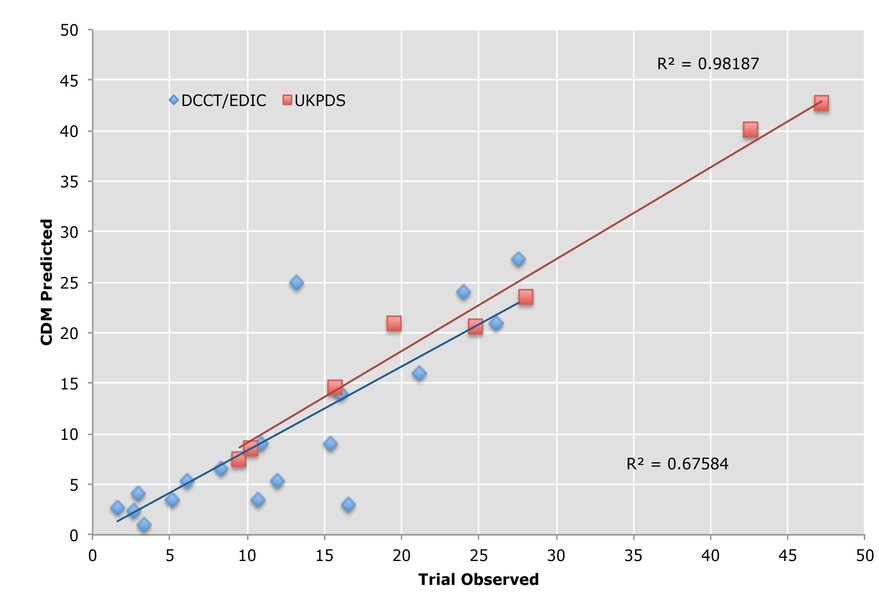
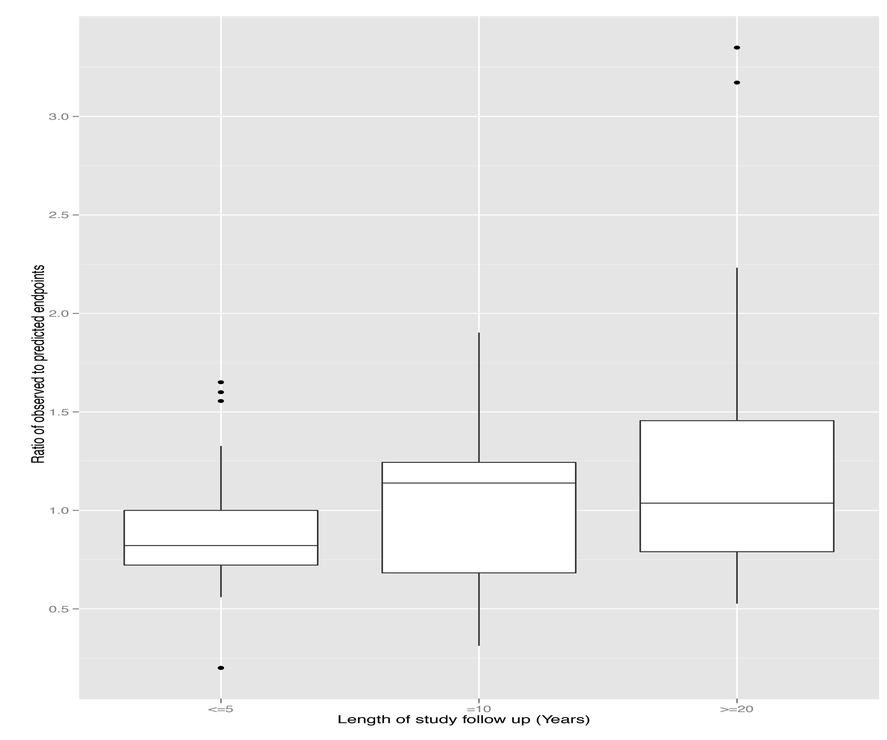


Figure 3. Ratio of observed to predicted endpoints stratified by duration of study



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.

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Acknowledgments

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