Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

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To cite this article: Stefanie Maxion-Bergemann, Silke Walleser, Elvira Müller, Sean F Dinneen, Samy Suissa, Hans Hauner, Andrew D Morris & Rito Bergemann (2006) Diabetes Mel l it us Model (DMM): internal validation of a computer simulation model for type 1 and type 2 diabetes, Journal of Medical Economics, 9:1-4, 69-82, DOI: 10.3111/200609069082

To link to this article: https://doi.org/10.3111/200609069082

Published online: 01 Dec 2008.

Diabetes Mellitus Model (DMM): internal validation of a computer simulation model for type 1 and type 2 diabetes

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The aim of the analysis described in this paper was to confirm the internal validity of the Diabetes Mellitus Model (DMM), which is an epidemiological simulation model for the prediction of short- and long-term complications of diabetes. For the validation, mean values and confidence intervals (CIs) of simulated event rates (ERs) were calculated. The expected ERs were derived from publications. Internal validity of the DMM was defined as an agreement (overlap) between the model outputs and the published data allowing for a range of 25% deviation from the original data.

The results of the validation process revealed coherence between mean simulated ERs and expected ERs for most of the examined events. A fit of the range of CIs within the range of expected ERs can be observed for macular oedema in type 1 and type 2 diabetes, for retinopathy in type 1 diabetes, and for amputation and diabetic foot syndrome in type 2 diabetes. With the exception of end-stage renal disease, the CIs and ranges of the other events overlap significantly, supporting the view that the model can be considered as internally valid.

These results substantiate the DMM as an internally valid diabetes model that predicts complication rates consistent with observed rates. The DMM is a valuable tool for medical decision-making. Further research is required to provide external validation of the model.

Key words: computer simulation model, diabetes, internal validation

Accepted for publication: 10th February 2006

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Introduction

In recent years, the use of computer-simulated disease models has increased[1]. In a simulation model, the main clinical characteristics of a specific disease and its influencing factors are described, and evidence from several sources is gathered to provide insight into the nature and development of the disease. Modelling techniques are useful in chronic diseases such as diabetes mellitus that are associated with serious and burdensome long-term clinical complications. Simulation models can widen the scope of clinical trials and facilitate simultaneous evaluation of the long-term effects of various treatment scenarios easily and economically[2], in lieu of long-term clinical trials. It has been reported previously that models provide important information for clinical practice and are valuable tools in medical decision-making[3]. In the field of health policy, models are incorporated into regulatory processes and governmental decision-making[4]. The need for diabetes mellitus simulation models in the field of economic analysis has been clearly identified[5]. To meet this need, a new diabetes mellitus simulation model, the Diabetes Mellitus Model (DMM), has been developed, which is able to predict the short- and long-term outcomes both of type 1 and type 2 diabetes separately over a course of 10 years[6].

To serve its purpose, confirmation of the validity of this model is essential. Four steps are recommended for the validation process.

(1) The structure of the model should be comprehensible to experts.
(2) The model should reproduce the outcomes observed in the studies used to estimate its parameters (internal validation).
(3) The model's predictions should be compared with results from studies not used in its construction to ensure that it meets with the 'real world' situation (external validation).
(4) The model should be used to predict outcomes for new treatment programmes and the predictions compared with the outcomes when the programme is implemented.

The aim of the analysis described in this paper was to confirm the internal validity of the DMM (point 2 of the validation process). To this end, we examined whether the predictions of the model with respect to specific long-term clinical trial endpoints are comparable with the data from the studies that provided the input parameters for the model. Point 1 of the validation process is already complete and a panel of experts established structural validity of the model[6,7]. Point 3 is currently underway.

Research design and methods

The Diabetes Mellitus Model

The DMM is a Markov model, with memory, that was developed to predict a broad range of short- and long-term outcomes of types 1 and 2 diabetes over the course of 10 years. Among various demographic (e.g. age, duration of diabetes, gender), physiological (e.g. haemoglobin A1c (A1c), systolic blood pressure (SBP), albumin excretion rate) and lifestyle (e.g. smoking) input parameters, the main determinant of events is the level of A1c, which is simulated over time and takes a predefined target A1c into account.

The DMM applies the method of global microsimulation. As such, up to 100,000 hypothetical patients can be generated by the model and are assigned demographic and disease-specific characteristics based on settings predefined by the user. The model updates the values of the various input parameters of each patient in yearly cycles and calculates event rates (ERs; events/100 patients, cumulative up to 10 years) for diabetes outcomes based on these variables and the underlying risk equations.

Twenty events and mortality are simulated in the model, including hypoglycaemia, ophthalmic disorders, neuropathy, renal disease, and cardiovascular and cerebrovascular complications. The simulation of events is based on risk equations (see Appendix A) that calculate probabilities of diabetes outcomes for each patient. These probabilities are updated each year, taking changes in a simulated patient's health state over time into account.

The basis of the underlying calculations is published data, mainly from the UK Prospective Diabetes Study (UKPDS)[8,9], the Diabetes Control and Complications Trial (DCCT)[10] and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[11]. The DMM aggregates the data from these studies and extrapolates the results regarding diabetes-related complications for up to 10 years.

The DMM's structure and formula are described elsewhere[6,7,12]. A scientific panel of experts in the field of diabetes established the structural validity and ensured that the main relevant input parameters and outcomes were included in the model. Internal consistency, described as the correct implementation of the model formula and risk equations into the program[13], has been ensured by continuous checking for program errors and by recalculating the model formula with another software program. Validation of the DMM simulation process, through validation of the random number generators that are used to generate patients and their health states, has been confirmed and is published elsewhere[14,15].

Internal validation of the DMM

The objective of the internal validation process of the DMM was to examine whether the outcomes produced by the model (simulated ERs) are consistent with the outcomes from the main publications (expected ERs) on which the model was based. Expected ERs were derived from these publications, and simulated ERs were obtained from the DMM simulation. The validation process then compared the mean and confidence interval (CI) of the simulated ER with the expected mean ER and range calculated for each event.

Comparison between model-simulated ERs and expected ERs determined from reference publications was conducted for the most important events simulated in the DMM for the type of diabetes for which study data were available. For type 1 diabetes, the events validated were non-proliferative and proliferative retinopathy, macular oedema (MO), end-stage renal disease (ESRD), diabetic foot syndrome (DFS) and amputation. For type 2 diabetes, MO, blindness, DFS, amputation, ESRD, myocardial infarction (MI), angina pectoris, heart failure and stroke were validated.

Definition of population characteristics at

baseline

In the DMM, the simulation population at baseline (start of simulation) is defined by a profile of input parameters encompassing specific demographic and physiological characteristics. For the internal validation process a profile was defined, which represents as closely as possible the characteristics of the populations observed in the reference publications on which the DMM was based. This allows for a comparison of the outputs from the model with the results of the reference publications. Occasionally, however, the reference publications did not contain all the information needed to define the baseline population characteristics. The WESDR was one such case, and in this instance the WESDR paper by Moss et al[16] provided the additional information needed. For some characteristics it was necessary to make a number of assumptions and calculations, which are described below and summarised in Table 1.

Definition of target A1c

For the definition of profiles used in the DMM, it is necessary to define a target A1c value that patients in the model aim for. This target influences the course of A1c over simulation time. For definition of the profiles used for the internal validation, since target A1c values were not available from the reference publications, certain assumptions were necessary. For type 1 diabetes, the baseline values given in the published studies were used as the target A1c values; the assumption would, therefore, be that the A1c remains essentially unchanged for all 10 years of the simulation. For type 2 diabetes, the target A1c for patients from WESDR (who show a 2% increase of A1c over 10 years of simulation time) was defined as baseline A1c – 1%. For the profiles based on the UKPDS, the target A1c was estimated using the median A1c values over 10 years, as listed in the reference publication (UKPDS 33)[8].

Definition of baseline systolic blood pressure

For the population characteristics based on the UKPDS, the baseline SBP value for hypertensive and non-hypertensive patients was estimated based on the general baseline SBP in the reference publications (UKPDS 33, 38)[8,9]. In the WESDR publications, no specific information was available for mean SBP values at baseline, therefore SBP values and percentage of hypertensive patients at baseline were estimated from the stratified data documented in the reference publication, with the method of weighted means applied.

Calculation of expected event rates

Type 1 diabetes

For type 1 diabetes, 10-year mean expected ERs for MO and ESRD could be derived directly from the reference publications. For all other events, the expected mean ERs were calculated based on the annual hazard rate (HR) of an event.

From this annual HR, the probability for an event after 10 years (P_{10} year) was calculated and then multiplied by 100 to obtain the mean 10-year incidence rate per 100 patients (see Appendix B). These incidence rates were defined as the expected ER. The range of expected ERs was defined as ±25% about the mean value, based on advice from the panel of experts.

Type 2 diabetes

For MO and DFS in type 2 diabetes, expected ERs were based on the WESDR. Therefore, the procedure was the same as for WESDR for type 1 diabetes as described above. For expected

Table 1. Profile characteristics (for haemoglobin A1c and systolic blood pressure (SBP) values and hypertension (HT) prevalence), expected event rates (ERs) and sources for events validated

Event	Type 1 diabetes					Type 2 diabetes				
	Source	Profile			Expected	Source	Profile			Expected
		A1c, % (mean ± SD)	SBP[a] with	% HT	ER (±25%)		A1c, % (mean ± SD)	SBP[a] with	% (range) HT	ER
Non-proliferative retinopathy	Klein *et al* 1998[17] (Tables 1, 2 and 6)	10.6 ± 2	112/178	14.1	74.95		NDA			
Proliferative retinopathy	Klein *et al*, 1998[17] (Tables 1, 2 and 6)	10.6 ± 2	112/178	14.1	27.95		NDA			
Macular oedema	Klein *et al*, 1998[17] (Tables 1, 2 and 6)	10.6 ± 2	111/178	15.5	20.1	Moss *et al*, 1999[11] (Table 1); Klein *et al*, 1995[18] (Table 4)	Baseline: 10.97 ± 1.5; Target: 9.97 ± 1.5	121/178	44.56	18.45
Blind in one eye	NDA					UKPDS 33[8]; UKPDS 38[9]; Moss *et al*, 1998[16]	Baseline: 7.1 ± 1.5; Target (int/conv): 5.5 ± 0.5/7.6 ± 0.5	130/140	30	3.08–18.57
End-stage renal disease (dialysis, transplantation)	Moss *et al*, 1999[11] (Table 1); Klein *et al*, 1999[19] (Table 4)	10.0 ±2.1	112/173	18.3	14.40	UKPDS 33[8]; UKPDS 38[9]; WESDR[19] (Table 4)	Baseline: 7.1 ± 1.5; Target (int/conv): 5.5 ± 0.5/7.6 ± 0.5	130/140	30	0.66–14.4
Amputation	Moss *et al* 1999[11] (Tables 1 and 2)	10.8 ± 2.1	105/150	18.3	5.19	Moss *et al*, 1999[11] (Tables 1 and 3); UKPDS 33[8]; UKPDS 38[9]	Baseline: 9.6 ± 1.5; Target: 8.6 ± 1.5	121/179	73.2	1.18–7.23

Table 1 (Continued). Profile characteristics (for haemoglobin A1c and systolic blood pressure (SBP) values and hypertension (HT) prevalence), expected event rates (ERs) and sources for events validated

Event	Type 1 diabetes					Type 2 diabetes				
	Source	Profile			Expected	Source	Profile			Expected
		A1c, % (mean ± SD)	SBP[a] with	% (±25%) HT	ER with		A1c, % (mean ± SD)	SBP[a]	% with HT	ER (range)
Diabetic foot syndrome	Moss *et al*, 1999[11] (Table 1); Moss *et al*, 1992[20] (Table 3)	12.7 ± 1.5	112/178	21	22.08	Moss *et al*, 1999[11] (Table 1); Moss *et al*, 1992[20] (Table 4)	Baseline: 11.24 ± 1.5; Target: 10.24 ± 1.5	121/178	46.5	24.22
Myocardial infarction (non-fatal)			NDA			UKPDS 33[8]; UKPDS 38[9]; UKPDS 35[21]; UKPDS 36[22]	Baseline 7.1 ± 1.5; Target (int/conv): 5.5 ± 0.5/7.6 ± 0.5	130/140	30	7.07–9.24
Angina pectoris			NDA			UKPDS 33[8]; UKPDS 38[9]	Baseline: 7.1 ± 1.5; Target (int/conv): 5.5 ± 0.5/7.6 ± 0.5	130/140	30	6.77–7.76
Heart failure			NDA			UKPDS 33[8]; UKPDS 38[9]; UKPDS 35[21]; UKPDS 36[22]	Baseline: 7.1 ± 1.5; Target (int/conv): 5.5 ± 0.5/7.6 ± 0.5	130/140	30	2.91–5.13
Stroke (non-fatal)			NDA			UKPDS 33[8]; UKPDS 38[9]; UKPDS 35[21]; UKPDS 36[22]	Baseline: 7.1 ± 1.5; Target (int/conv): 5.5 ± 0.5/7.6 ± 0.5	130/140	30	4.21–7.76

SD, standard deviation; int/conv, intensively/conventionally controlled groups; NDA, no data available

[a]Normotensive patients/hypertensive patients, in mmHg.

mean simulated ER and the expected ER was based on the calculated expected ER based on

ERs based on the UKPDS studies, the incidence rates (events/1,000 patient-years) as published for intensively and conventionally controlled groups were used. In light of the large size of the two treatment groups, weighted means of events/1,000 patient-years were calculated and subsequently used to define the range of expected ERs.

Simulation of event rates

For each event, 40 simulation runs were carried out, each with a different baseline population of 1,000 diabetes patients. This resulted in 40 ERs (events/100 patients) after 10 years from which mean values and 95% CIs for the simulated ERs were computed.

Definition of validity

Internal validity of the DMM was evaluated for each event by comparing the simulated ERs (mean and CI) with the expected ERs (mean and range). An event was termed 'internally valid' if the simulated ER CI fell within or overlapped with the expected ER range.

Results

The range of expected ERs from the publications and the CI of simulated ERs are depicted in Figure 1 for type 1 and type 2 diabetes. The expected ERs refer to the estimated mean derived from the publications with a range of ± 25%. The CI of the simulated ERs is based on the mean of the simulated ERs and should overlap with the range of expected ERs. The results for each of the endpoints depicted are described in detail below.

Type 1 diabetes

Retinopathy

A total fit of the simulated ER CIs within the range of expected ERs was observed for non-proliferative retinopathy (CI 75.0–76.5 vs. expected ER range 56.2–93.7 events/100 patients), with a mean simulated ER of 75.75 events/100 patients versus a mean expected ER of 74.95 events/100 patients. Proliferative retinopathy also showed a total fit (CI 24.9–26.9 vs. expected ER range 21.0–34.9 events/100 patients) as did MO (CI 17.2–22.7 vs. expected ER range 16.1–26.8 events/100 patients) (Figure 1A).

End-stage renal disease

The largest difference between the simulated and expected mean ERs was observed for ESRD in type 1 diabetes (8.79 vs. 14.4 events/100 patients). This was also the only event for which there was no overlap between the simulated ER CI and the range of expected ERs (6.95–10.63 vs. 10.8–18 events/100 patients) (Figure 1A).

Diabetic foot syndrome

For DFS which (refers to the diagnosis of sores and ulcers, based on medical history questionnaires[20]), the simulated range fell completely within the expected ER range, where the CI was 14.5–22.1 events/100 patients compared with a range of expected ERs of 16.6–27.6 events/100 patients, with mean ERs of 18.3 vs. 22.1 events/100 patients, respectively (Figure 1A).

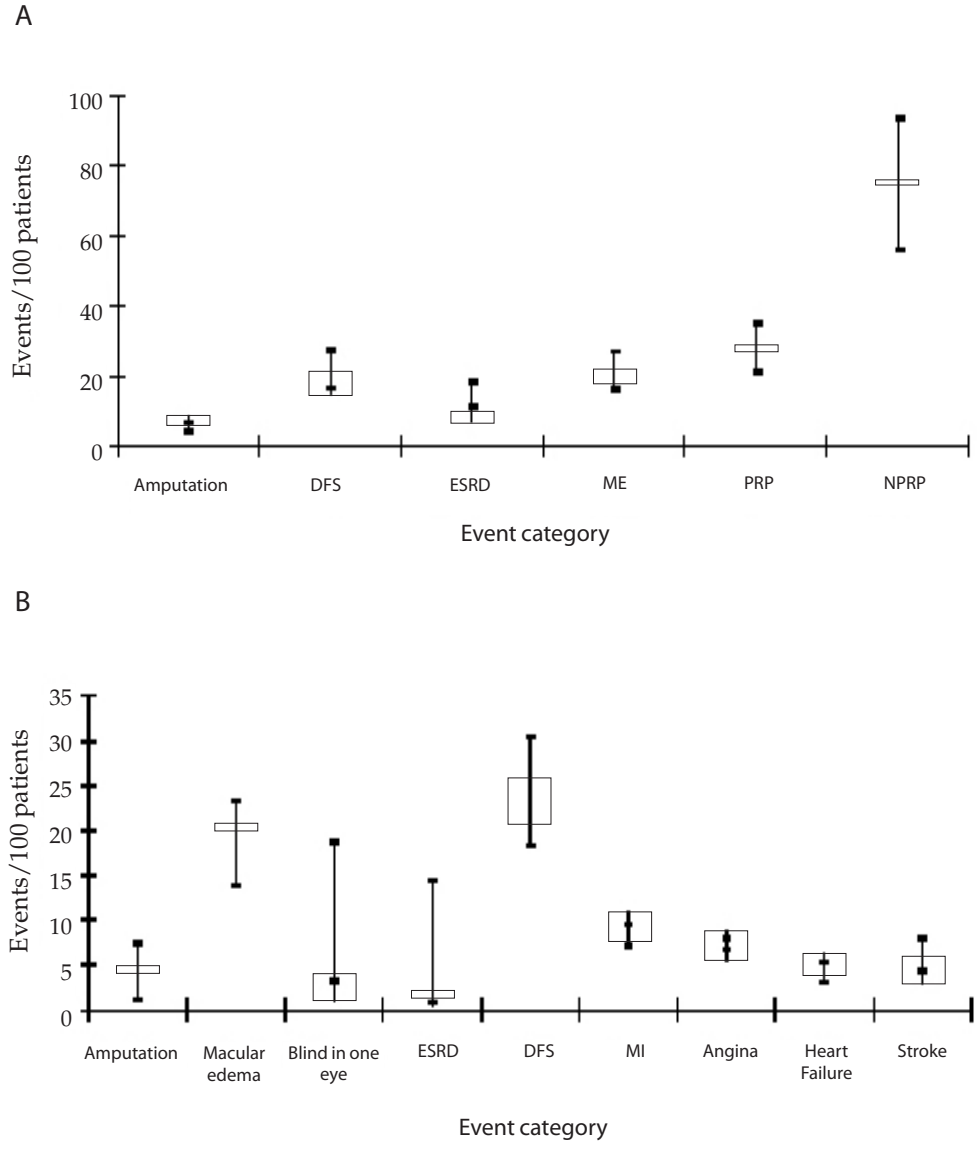
Amputation

For amputation, the model CI extended beyond the range of expected ERs, with a CI of 4.5–8.0 vs. an expected ER range of 3.9–6.5 events/100 patients (Figure 1A).

Type 2 diabetes

Except for MO and DFS, comparison of the

Figure 1. Comparison of model output (simulated event rates) with expected event rates for major events in patients with (A) type 1 diabetes and (B) type 2 diabetes. Bars indicate confidence intervals (CIs) of simulation, lines indicate ranges of expected event rates.



DFS, diabetic foot syndrome; ESDR, end-stage renal disease; ME, macular oedema; PRP, proliferative retinopathy; NPRP, non-proliferative retinopathy; MI, myocardial infarction.

the annual HR of an event.

Macular oedema

For MO, the simulated ER CI showed a total fit within the range of expected ERs (19.1–20.5 vs. 13.8–23.1 events/100 patients; mean ERs being 19.83 vs. 18.45 events/100 patients for simulated and expected ERs, respectively) (Figure 1B).

Diabetic foot syndrome

For DFS, the simulated ER range showed a total fit within the expected ER range, with a simulated ER CI of 19.8–26.1 and an expected ER range of 18.2–30.3 events/100 patients. Mean values were 22.97 and 24.22 events/100 patients, respectively (Figure 1B).

End-stage renal disease

In contrast to type 1 diabetes, the simulated ER CI and expected ER range overlapped for ESRD in type 2 diabetes (0.56–1.8 vs. 0.66–14.4 events/100 patients, respectively) (Figure 1B). Although this overlap covered only a short range of events, the differences between the lower boundaries of the ranges were quite small, whilst the differences between the upper boundaries were much larger; consequently, a substantial proportion of the simulated CI overlapped with the range of expected ERs for ESRD (Figure 1B).

Cardiovascular events

The model CI was not a total fit within the expected ER range for MI. However, the two ranges did overlap to a large degree. The simulated ER CI upper boundaries extended beyond those of the range of expected ERs, whilst the lower boundaries were relatively similar (7.2–10.93 and 7.07–9.24 events/100 patients for simulated ER CI and range of expected ERs, respectively) (Figure 1B). For angina, the simulated ER CI upper and lower boundaries both extended beyond those for the range of expected ERs (5.57–8.79 vs. 6.77–7.76 events/100 patients).

Blindness

For blindness, a similar situation to that with ESRD was observed, with a substantial proportion of the simulated ER CI overlapping with the range of expected ERs (CI 1.2–3.9 vs. expected ER range 3.1–18.6 events/100 patients).

Amputation

A total fit of the simulated ER CI within the range of expected ERs was also observed for amputation (4.1–5.1 vs. 1.2–7.2 events/100 patients) (Figure 1B).

Discussion

The purpose of this analysis was to demonstrate internal validity for the DMM, which was defined as the simulated ER CI falling within or overlapping with the expected ER range. On the basis of this definition for internal validity, it can be concluded that all of the long-term clinical outcomes evaluated in the DMM are internally valid for type 2 diabetes. The same can be said for the simulation of long-term clinical outcomes in type 1 diabetes, with the exception of ESRD.

The lack of internal validity for ESRD simulation in type 1 diabetes using the DMM may be due in part to the data source used to construct this simulation in the model. The simulation of ESRD in type 1 diabetes in the DMM is based on the WESDR[19], where the 10-year incidence of ESRD was 14.4%. Expert opinion suggests that this rate is extraordinarily high, and recent studies have shown an impressive reduction in the incidence of diabetic nephropathy (probably owing to improved management of diabetes and hypertension)[23], suggesting that the incidence of ESRD in type 1 diabetes may be much lower today. This was accounted for in the risk equation for ESRD in the DMM, and as a consequence simulated ERs in the model will always be systematically lower compared with WESDR data since the model does not

aim to reproduce the outcomes from the source publication. As such, the definition of internal validity used in this evaluation is not applicable to ESRD in type 1 diabetes.

The highest degree of internal validity (i.e. total fit of the simulated ER CI within the range of expected ERs) was found for MO in type 1 and type 2 diabetes, non-proliferative and proliferative retinopathy in type 1 diabetes, and amputation and DFS in type 2 diabetes. The lower simulated mean ER compared with the expected mean ER seen for DFS in type 1 diabetes can be explained in part by the fact that a high probability (0.07) for 'sores or ulcers' was reported at baseline in the study population from which the expected ER was derived. This probability was higher for groups with a longer duration of diabetes at baseline. Consequently, extrapolation of the 4-year incidence to a 10-year incidence led to higher expected ERs compared with simulated ERs. Also, the influence of diabetes duration in the model for this event was derived from a different source that assumes a smaller risk for diabetes duration, further contributing to the difference between expected ERs and simulated ERs for these complications.

When interpreting the results of this internal validation, it is important to remember that a number of factors may influence the overlap between the simulated ER CI and the expected ER range. The first factor to consider is the limited range of the simulated ER CI relative to the expected ER range for ESRD in type 2 diabetes. This can be explained by the two different studies used for the simulation of events: the UKPDS and the WESDR[19]. The WESDR is an observational study with published data for the subgroup of patients with type 1 diabetes. It describes high cumulative incidences for ESRD of 14% after 10 years which suggest that the population is rather poorly controlled with respect to blood sugar levels and blood pressure. In contrast, the UKPDS is a randomised controlled study in newly diagnosed type 2 diabetes, where part of the study population was intensively controlled; therefore, the A1c and blood pressure values were better controlled and thus lower risks for long-term complications were observed relative to the WESDR. The net result of this is a large difference in expected ERs calculated from these studies, with the UKPDS accounting for the lower range and the WESDR accounting for the upper end of the range. Since the risk equation in the DMM for ESRD includes more risk factors based on UKPDS data than on WESDR data, the model's mean simulated ER and its CI will, therefore, only cover the lowest part of the expected ER range.

The degree of overlap between simulated event CIs and the range of expected ERs is also influenced to a large extent by the baseline characteristics of the simulated populations defined at the start of the simulations. The baseline characteristics of the simulated population were defined to represent as closely as possible the study populations from the publications that the model simulations are based on. However, in the publications from which baseline population characteristic profiles were constructed, only limited data were available. For example, normal distribution had to be assumed for age and duration of diabetes, since only the mean (± standard deviation) was available from the

published studies. Also, many baseline parameters were not documented for the specific subpopulation under study and had to be derived from other publications that were not sources for the model. In addition, there were instances where data for subgroups defined at baseline were missing (e.g. SBP in hypertensive vs. non-hypertensive groups). Consequently, it was necessary to make a number of estimations and assumptions when defining the profiles for the internal validation, which contribute to uncertainty.

Because of the DMM's simulation methodology (Monte Carlo simulation), the uncertainty around the simulated ER reflected in its associated CI depends on both the number of contributing factors included in the risk equation for that event and the probability of the occurrence of that event. Thus, the greater the number of contributing factors included, the higher the variance in the model between simulation runs, and the larger the CIs of all the model runs. Variance between model simulation runs will also increase with decreasing probability of an event. Both of these factors will contribute to broader CIs. For some input parameters (e.g. age), the model assumes a distribution from which values are selected according to a random number generator. This second order uncertainty is also reflected in the CIs of the simulated ERs.

Finally, the set-up of the simulation itself has an influence on the variation of the simulation results. The number of patients and iterations also contribute to the variation. For the presented validation, 1,000 patients per simulation and 40 iterations were used. Increase of either number would have positively influenced the results, i.e. led to smaller CIs.

Therefore, when interpreting the results of this internal validation, all of these issues regarding the DMM simulation methodology need to be considered because they influence the simulated ER CIs and, therefore, their degree of fit within the range of expected ERs. These CIs are a measure of the confidence of the model results and its virtual population and do not necessarily reflect the confidence around ERs of the model's underlying study populations.

The question of how best to estimate uncertainty in the DMM, or indeed any simulation model, is an area where further research is required. An extended approach to the one presented here, for example, could account for the difference in risks by increasing the number of simulated patients for events that occur only rarely. How this issue can be addressed in detail is beyond the scope of this paper and requires further investigation.

In conclusion, based on the four essential validation steps defined at the start of this paper, the first two steps have now been fulfilled and the internal validity of the DMM has been proven. However, as the DMM reflects evidence from clinical trials, certain factors (e.g. healthcare setting factors) that influence diabetes outcomes are not considered and generalisability is still limited. Therefore, the next step in the process of continuous improvement of the DMM is external validation, where simulated ERs are compared with expected ERs derived from data that were not used for construction of the model. External validation determines the applicability of a simulation model to the 'real world' and provides insight into necessary adaptations of

the model assumptions and calculations to real-world conditions. Whilst the validation process is still ongoing, the data to date suggest that the DMM is a valid model for the prediction of long-term clinical outcomes both in type 1 and type 2 diabetes.

Acknowledgement

Development and realisation of the DMM was supported by a grant from Sanofi-Aventis Pharma, Bridgewater, USA.

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Appendix A

Based on published studies, each parameter–outcome relationship was mathematically described[8–11]. All input parameters (x) influencing one model outcome (event) are incorporated in an event- and diabetes-type specific risk equation. Each risk equation calculates the probability of an event (P_{event}) per patient and updates it each simulation year. P_{basic} is calculated as follows:

$P_{basic} = 1\text{-}e\ ([\ln (1\text{-}CI/100)]/t[\text{years}])$

where CI=cumulative incidence defined as the absolute rate of events per 100 patients, t=observed time in years, ln=natural logarithm and e=exponential function.

Appendix B

The average annual hazard rate (HR) for an event was calculated using the following formula:

$P_{event} = P_{basic/A1c} * RR_{X(1)} * RR_{X(2)} * ... RR_{X(n)}$

where P_{event} is the individual probability of an event (conditional probability), $RR_{X(n)}$ is relative risk fuction per parameter (risk function can be: linear $[a_{11} * x_{11} + b_{11}]$ or exponential $[a_{11} * \exp(b_{11} x_{11})]$ where a_{11}, b_{11} are regression coefficients) and x_n are actual values for risk factors (e.g. blood pressure).