Electronic Supplementary Material 1

Comparing the Cohort and Micro-Simulation Modeling Approaches in Cost-Effectiveness Modelling of Type 2 Diabetes Mellitus (T2DM): A Case Study of the IHE Diabetes Cohort Model and the Economics and Health Outcomes Model of T2DM

Journal: Pharmacoeconomics

Michael Willis[1]

Adam Fridhammar[1]

Jens Gundgaard[2]

Andreas Nilsson[1]

Pierre Johansen[2]

[1]The Swedish Institute for Health Economics, Lund, Sweden

[2]Novo Nordisk A/S, Søborg, Denmark

Corresponding author:

Michael Willis, PhD

The Swedish Institute for Health Economics

Box 2017

SE-220 02 Lund

Email: mw@ihe.se

Table of Contents

1. The IHE Diabetes Cohort Model (IHE-DCM) v. 4.3.0

IHE-DCM was developed to estimate the cost-effectiveness of treatment interventions for T2DM using the cohort (representative patient) approach. IHE-DCM (v. 4.3.0) can be run with one intervention and up to twelve comparator arms, supporting the comparison of multiple treatment strategies at once. It can be run either deterministic or with probabilistic sensitivity analysis (to account for second-order uncertainty in underlying parameters).

IHE-DCM uses Markov health states that capture important microvascular and macrovascular complications and premature mortality resulting from T2DM, which is illustrated in Figure 1. The cycle length is one year, and the time horizon is user-definable (up to 40 years). The model is flexible as most model parameters are defined by the user on the input sheet.

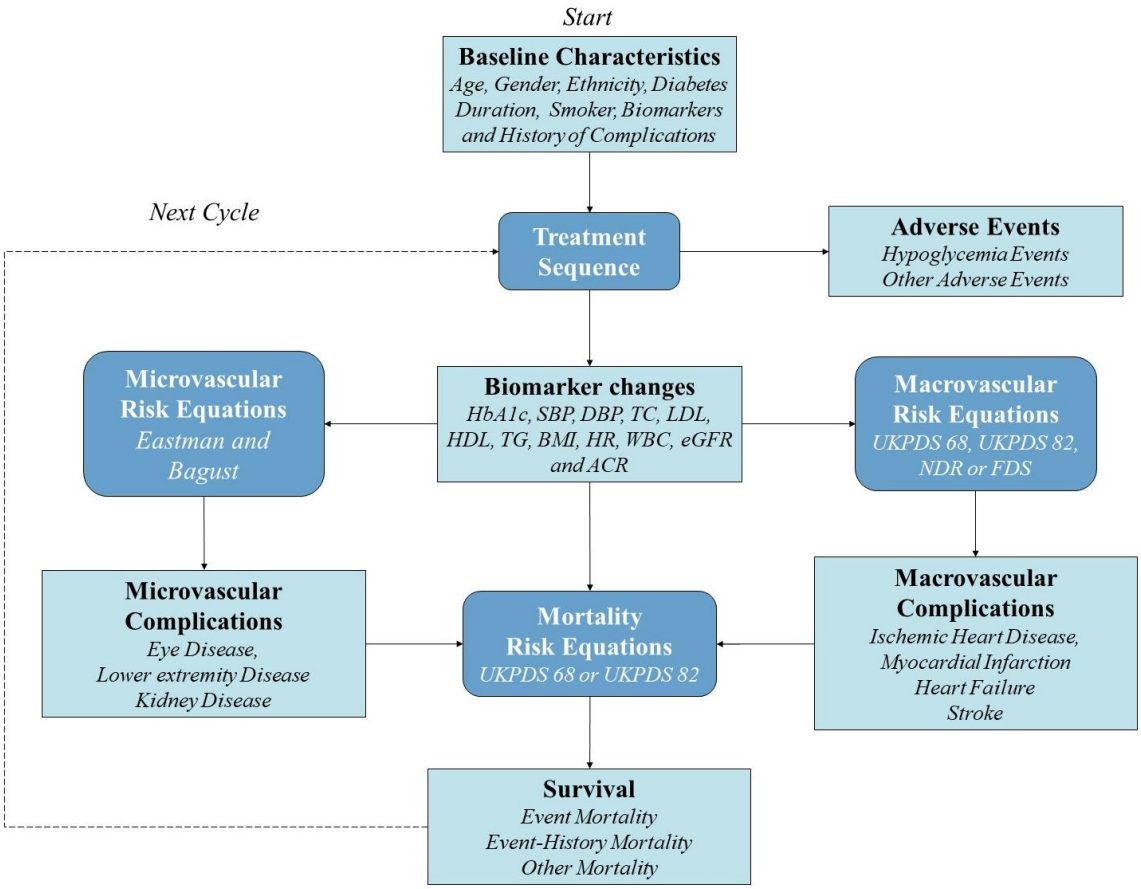
The model was constructed in Microsoft® Excel 2013 with the aid of the built-in Visual Basic for Applications (VBA) and requires no plugins or external programs to use. To ensure the flexibility necessary to model many different applications, the model contains many user-definable parameters, including baseline characteristics of the cohort, choice of risk equations, treatment algorithms, unit costs and quality-adjusted life-years (QALY) weights. The baseline characteristics of the cohort are demographics (e.g., age and gender), biomarkers (e.g., HbA1c and blood pressure), and pre-existing complications (e.g., microalbuminuria and stroke).

At the start of the simulation, a cohort of hypothetical patients is defined from user-defined baseline characteristics and cloned for study arm. Each cohort is assigned a unique treatment algorithm. The treatment algorithms allow for modification of doses and addition of new medications when the initial treatment regime does not achieve adequate HbA1c control. Medication to control blood pressure, blood lipids and overweight may also be applied. Treatment effects are modeled as absolute changes applied at simulation start or, for treatment intensification, during the year of it occurs in combination with annual drifts for each treatment line). The evolution of biomarkers is simulated annually until the predefined time horizon is reached. Adverse events, including up to three severities of hypoglycemia (e.g., moderate, and severe) and up to five user definable events are applied using an annual event rate. A hazard ratio of 1.43 sourced form the Diabetes Control and Complications Trial [1] is applied to the hypoglycemic event rates to each 1% point decrease from corresponding HbA1c. Development and progression of complications and mortality are simulated next to the evolution of biomarkers. Risk equations govern the progression of the cohort between different health states.

The macrovascular and microvascular health states were selected to capture the most important complications for T2DM. To make the cohort approach feasible, the sets of micro- and macrovascular health states were divided into two separate Markov sub-models. The 120 microvascular health states express the possible combinations of eye disease, kidney disease, and lower extremity amputation states. The transition probabilities are sourced from the [2] and Bagust et al.[3] and are applied individually to each microvascular health state. The 100 macrovascular health states combine stages of ischemic heart disease, myocardial infarction, stroke and heart failure. The user can choose form a set of four macrovascular risk prediction equations including United Kingdom Prospective Diabetes Study (UKPDS) 68 [4], UKPDS 82 [5], Swedish National Diabetes Registry (NDR) [6], and Australian Freemantle Diabetes Study (FDS) [7], which are applied individually to each macrovascular health state. The user can choose between two sets of mortality equations, either the UKPDS 68 [4], or the UKPDS 82 [5] which are applied individually across 600 combination of the macrovascular health states, ischemic heart disease, myocardial infarction, stroke and heart failure and the microvascular health states, amputation and end-stage renal disease.

Unit costs and QALY weights, matching current treatment, distribution of health states and adverse events, are applied to the cohort in each cycle. Model outcomes include mean survival, expected Life-Years (LYs), Quality-Adjusted LYs (QALYs), and direct costs. The outcomes are combined to compute incremental cost-effectiveness ratios (ICERs) and Cost-Effectiveness Acceptability Curves (CEACs), among other outcomes.

ESM Figure 1: Schematic Overview – IHE-DCM



2. The Economics and Health Outcomes models of T2DM (ECHO-T2DM) v. 3.5.1

ECHO-T2DM is a stochastic (2nd order uncertainty) micro-simulation model in which cohorts of individual hypothetical patients are created and simulated over time using Monte Carlo (1st order uncertainty) techniques [8]. The cycle length is one year and the time horizon is user-definable. ECHO-T2DM is programmed in R with Excel® front- and back-end interfaces for inputting in the simulation scenarios and exporting simulation results, respectively. Seed values can be used to allow replication of simulation results. The structure of ECHO-T2DM is depicted in Figure 2.

Cohorts of hypothetical T2DM patients are generated at baseline by randomly assigning a vector of key descriptive covariates including age, sex, duration of disease, ethnicity, smoking status, HbA1c, systolic blood pressure (SBP), lipids values, body mass index (BMI), heart rate, eGFR, white blood cell count and history of pre-existing micro- and macrovascular disease from probabilistic distributions. Correlation between the initial biomarkers is used to account for observed patterns of risk factor clustering in creating the baseline population [9].

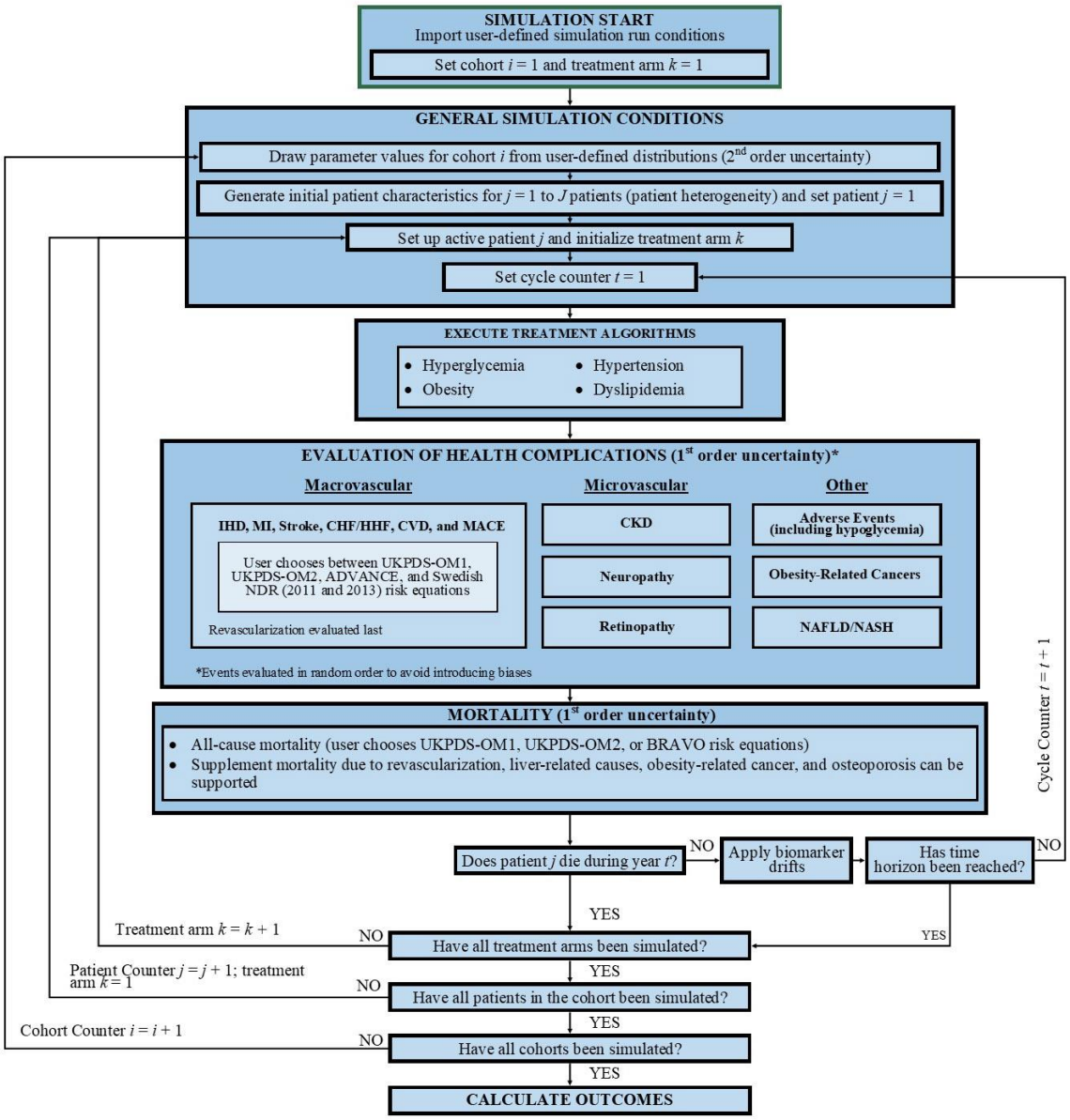
The user defines an anti-hyperglycemic treatment intervention profile and up to 10 treatment comparator profiles (supporting multiple comparison analysis). Patients are assigned at baseline one of these anti-diabetes treatment regimens and a treatment algorithm steers anti-diabetes treatment over time. Each treatment has a user-defined profile, which can modify HbA1c, SBP, BMI, blood lipid values, eGFR, and heart rate during the first year of use. A user-defined drug-specific annual biomarker drift is supported, thereafter. When a pre-specified maximum treatment duration is reached or when medication fails to meet pre-specified HbA1c levels, new medications (including insulin) are added according to user-defined sequences and the original treatment may be continued or discontinued. Adverse events are modelled explicitly and can lead to decreased patient adherence (which can in turn precipitate treatment changes). A hazard ratio of 1.43 sourced form the Diabetes Control and Complications Trial [1] is applied to the hypoglycemic event rates to each 1% point decrease from corresponding HbA1c

The model also allows for the treatment of related co-morbid conditions, including overweight, hypertension, and dyslipidemia. The user defines treatment sequences for hypertension, dyslipidemia, and obesity. Overt hypertension and dyslipidemia are treated at user-defined thresholds and treatment of these co-morbidities can be escalated. Treatment contraindications disallow treatments according to user-defined criteria, such as the development of user-specified co-morbidities (e.g., CHF).

Health and economic outcomes are represented as Markov health states that represent the development and consequences of key micro- and macrovascular complications and mortality, which are then simulated for a user-defined time horizon stochastically using transition probabilities that depend on time-dependent patient-level covariates. Patients transition on an annual basis separately in each of three parallel sets of increasingly severe microvascular health states (nephropathy, neuropathy, and retinopathy) and can suffer six types of macrovascular complications (IHD, MI, CHF, stroke, CVD, and MACE). The transition probabilities were derived from the NIH model,[2, 10] DiDACT,[3] and the CDC model of chronic kidney disease [11, 12] for microvascular events. The user can choose between five sets of macrovascular risk equations, including UKPDS 68 [4], UKPDS 82 [5], ADVANCE [13], and two sets from the Swedish NDR [14, 6]. Mortality rates are generated using either the UKPDS 68, UKPDS 82, or BRAVO risk equations [4, 5, 15], The user-modifiable covariates driving the transition probabilities include demographics (e.g., age, sex, ethnicity), biomarkers (e.g., HbA1c, SBP, BMI, and lipids), and disease history (e.g., MI, stroke, CHF).

Model outcomes include mean survival, expected Life-Years (LYs), Quality-Adjusted LYs (QALYs), time-to-rescue (years), and direct costs (separately by event and state costs). The outcomes are combined to compute incremental cost-effectiveness ratios (ICERs), Net Monetary Benefits (NMBs), and Cost-Effectiveness Acceptability Curves (CEACs), among other outcomes.

ESM Figure 2: Schematic Overview ECHO-T2DM Model



3. Differences Between IHE-DCM and ECHO-T2DM

IHE-DCM and ECHO-T2DM share several key features. However, the models also differ in a number of ways that are relevant to interpreting cost-effectiveness results. Where possible, the models were standardized for this cross-validation analysis to better identify differences due to the cohort vs. micro-simulation approach but which make the analyses somewhat artificial. These differences and standardizations as well as remaining post-standardization are described below and summarized in Table 2.

Model differences that were eliminated via standardization

- Neuropathy health states
  - Like ECHO-T2DM, IHE-DCM features symptomatic neuropathy, PVD, and lower extremity amputation, though unlike ECHO-T2DM the costs and QALY consequences are reported collectively and not individually. ECHO-T2DM additionally includes foot ulcer in the neuropathy submodule, which is not part of IHE-DCM.
  - While it is not possible to deactivate foot ulcer in ECHO-T2DM to match IHE-DCM, we were able to minimize the impact by setting the associated unit costs and QALY disutility weights to 0. As foot ulcer is associated with an increased risk of LEA and is risk factor for the development of CHF in the UKPDS 82 risk prediction equations, simulated development of foot ulcers in ECHO-T2DM will have indirect effects on costs and QALYs and thus the standardization is not complete.
- Kidney health states
  - IHE-DCM features the conventional nephropathy health states first modeled in the NIH Model [10, 2], consisting of no neuropathy, microalbuminuria, macroalbuminuria, and then ESRD. ECHO-T2DM features a newer CKD-based structure, which combines these health states into the CKD health stages advocated by the NKF/KDOQI[16] (i.e., stages 0, 1, 2, 3A, 3B, 4, 5, and ESRD), which is driven in part by the trajectory of eGFR over time. This can lead to differences in outcomes (and inactivating kidney disease to circumvent is considered here in scenarios analysis).
  - To minimize between-model differences, unit costs and QALY disutility weights for kidney outcomes were set to 0.
- Macrovascular and mortality risk prediction equations
  - The models each contain multiple sets of macrovascular and mortality risk prediction equations, some overlapping (UKPDS 68 [4], UKPDS 82 [5], and Swedish NDR risk equations by Kialdaliri et al.[6]) and others unique (Australian FDS [7] for IHE-DCM and ADVANCE [17] and Swedish NDR risk equation by Zethelius et al.[18] for ECHO-T2DM).
  - The UKPDS 82 risk prediction equations [5] were used for both models in this analysis.
- Risk adjustment for SBP
  - Each model contains power functions to link the risk of selected retinopathy outcomes and micro-and macroalbuminuria with HbA1c. ECHO-T2DM also includes power functions to link the risk of PDR, micro- and macroalbuminuria with SBP which is not captured in IHE-DCM
  - To standardize the models, the SBP power function in ECHO-T2DM has been set to have no impact on the risk prediction of micro-and macroalbuminuria.
- Progression of Biomarkers
  - Both models support annual changes for all biomarkers (e.g., HbA1c, SBP, and lipids). However, ECHO-T2DM also supports non-linear HbA1c trajectories for HbA1c from UKPDS

68. Additionally, eGFR evolution is hard-coded at the values included in the CDC Model of CKD,[11] which depends on current eGFR level as well as albuminuria status.

  - To standardize the models, an annual linear increase of 0.14 was assumed for HbA1c in both models and a linear decline for eGFR was estimated from the CDC CKD model for IHE-DCM to minimize (though not eliminate) between-model differences (some differences involving non-linearities in eGFR evolution in the CDC model remain, which will directly impact the risk of macrovascular outcomes and mortality in the UKPDS 82 risk prediction equations).

- Insulin Treatment Profile
  - IHE-DCM does not distinguish between insulin and non-insulin treatments. ECHO-T2DM includes a specific insulin treatment profile allowing for, among other things, the ability to titrate dose freely to match patient needs for glycemic control.
  - To standardize the models, the ECHO-T2DM simulations were run by fixing the insulin doses (eliminating the ability to titrate doses freely).
- Treatment of hypertension, dyslipidemia, and obesity
  - ECHO-T2DM assigns relative risk multipliers for a number of micro-and macrovascular events for patients designated to receive treatment with statins, angiotensin-converting-enzyme inhibitor (ACE) inhibitors, and Angiotensin II Receptor Blockers (ARBs).
  - No treatment for other disease managements were included in the simulations for IHE Diabetes Cohort and ECHO-T2DM.
- Unit Costs for Complications
  - IHE-DCM distinguishes unit costs by event costs and annual costs (applied the year in which the complication occurs) while ECHO-T2DM distinguishes unit costs by costs for the year in which the event occurs and follow-up costs for all later years. To standardize the models, the annual follow-up cost in ECHO-T2DM is deducted from the event costs in IHE-DCM to produce a first-year cost aligned with ECHO-T2DM.
  - IHE-DCM includes separate costs for 1st and 2nd events of MI, stroke, and LEA, not supported in ECHO-T2DM. ECHO-T2DM supports separate costs for fatal and non-fatal macrovascular events, not supported in IHE-DCM. To standardize the models, the same costs for 1st and 2nd events, as well as fatal and non-fatal events are applied.
- QALY Disutility Weights
  - Similar to unit costs, IHE-DCM support separate QALY disutility weights for 1st and 2nd MI and stroke. To standardize the models, the same disutility weights is applied for 1st and 2nd events.

<u>Remaining model differences</u>

- Risks for CKD (micro-and macroalbuminuria and ESRD)
  - IHE-DCM estimates the risk of micro-and macroalbuminuria solely based on transition probabilities sourced from the NIH model developed by Eastman et al.[2] ECHO-T2DM models the risk of microalbuminuria with transition probabilities that varies by eGFR level derived by adjusting UKPDS data[19] using NHANES % persistent disease data.[11, 12, 20] The risk of macroalbuminuria is also sourced from UKPDS data[19] but the risk does not vary by eGFR. As the risk of micro-and macroalbuminuria is different in the models, some variation in estimated number of events is anticipated and while cost and QALY disutility weights have been set to zero for micro-and macroalbuminuria there is an indirect link between albuminuria and the risk of CHF, MI, stroke, and mortality in UKPDS 82 risk equations.
  - Additionally, in ECHO-T2DM it is theoretically possible to reach ESRD (based on eGFR thresholds) without a prior diagnosis of macroalbuminuria (though all patients developing

ESRD are then assigned a history of both micro-and macroalbuminuria). Nephropathy in IHE-DCM model is strictly linear and progressive, in contrast.

- IHE-DCM estimate risk of ESRD based on transition probabilities sourced from the NIH Model[2] while ESRD in ECHO-T2DM is directly linked with current eGFR and is defined as eGFR<15 for more than one year. As the risk of ESRD is different in the models, some variation in estimated number of events is anticipated and as ESRD increase the risk of death some bias in the mortality risk is also anticipated.

- Risk for MI and Stroke events for patients with MI and/or Stroke history at baseline
  - The UKPDS 82 risk prediction equations includes separate equations for 1st and 2nd events for MI and stroke. As the UKPDS trial recruited patients that were effectively history-free at baseline, 1st events in the trial were generally also 1st events overall and 2nd events in the trial were generally 2nd events overall. For hypothetical patients simulated without a history of MI or stroke history at baseline, risks for both IHE-DCM and ECHO-T2DM are sourced from the 1st event prediction equations.
  - IHE-DCM and ECHO-T2DM differ in their handling of event risks for patients simulated with a history of MI and/or stroke at baseline, however, which is important when applying the UKPDS risk equations (based on a newly diagnosed, CV-free population) in alternative patient populations (with at least some patients with MI or stroke history at baseline). Importantly for cost-effectiveness analysis, the timing (and even number) of previous events is seldom known, so time at risk (a key component of the UKPDS 82 equations) for 2nd events is also not known. For a hypothetical patient with a history of an event (MI or stroke) at baseline:
    - IHE-DCM assigns risk using the risk equation (MI and/or stroke) for 2nd events. An assumption is made that assigns time at risk as time since simulation start (i.e., time since baseline), though the true timing likely preceded study baseline.
    - ECHO-T2DM, in contrast, matches event number in the trial (ignoring baseline history) with event number in the simulation, which ignores the baseline history (and may lead to underestimated risk) but properly assigns time at risk. As the UKPDS risk predictions are well known to overestimate the risk of macrovascular complications in contemporary patient populations, in some cases substantially [21-25]. this may not be a significant source of bias.

4. Complete Input Data

ESM Table 1: Unit Costs and QALYs

	Unit Costs (CAN$ 2018)		QALY Disutility Weights				
			Reference Case[d]		Expanded Reference Case		
	First Year Costs[c]	Annual Follow-up	Mean	SE	Mean	SE	Source for Expanded Reference Case
Baseline	--	--	0.785	0.000	1.027	0.027	Bagust et al.[26]
Patient Characteristics							
Age (per 10 Years)	--	--	0.000	0.000	-0.002	0.000	Bagust et al.[26]
Female	--	--	0.000	0.000	-0.093	0.009	Bagust et al.[26]
Duration of DM (per 10 Years)	--	--	0.000	0.000	-0.016	0.001	Bagust et al.[26]
Macrovascular							
MI	19,807	3,097	-0.090	0.000	-0.041	0.010	CADTH[27]
IHD	6,199	3,579	-0.055	0.000	-0.041	0.010	CADTH[27]
CHF	18,119	5,080	-0.108	0.000	-0.064	0.016	CADTH[27]
Stroke	26,979	3,743	-0.164	0.000	-0.052	0.013	CADTH[27]
PVD	132	132	-0.061	0.000	-0.061	0.015	Bagust et al.[26]
Microvascular							
Symptomatic neuropathy	919	1,152	-0.084	0.000	-0.084	0.014	Bagust et al.[26]
Diabetic Foot Ulcer[a]	0	0	0.000	0.000	-0.170	0.019	Bagust et al.[26]
1st LEA[b]	41,849	5,732	-0.280	0.000	-0.272	0.029	CADTH[27]
2nd or Subsequent LEA[b]	41,849	5,732	-0.280	0.000	-0.272	0.029	CADTH[27]
ME	835	73	-0.040	0.000	-0.040	0.010	Fenwick et al.[28]
ME & Blindness in 1 Eye	3,314	2,362	-0.074	0.000	-0.050	0.012	CADTH[27]
PDR	643	73	-0.070	0.000	-0.070	0.018	Fenwick et al.[28]
ME & PDR	835	73	-0.070	0.000	-0.070	0.018	Fenwick et al.[28]
PDR & Blindness in 1 Eye	3,314	2,362	-0.074	0.000	-0.050	0.012	CADTH[27]
ME, PDR & Blindness in 1 Eye	3,314	2,362	-0.074	0.000	-0.050	0.012	CADTH[27]
BDR	643	73		0.000	-0.040	0.010	Fenwick et al.[28]
Blindness	3,314	2,362	-0.074	0.000	-0.050	0.012	CADTH[27]
Microalbuminuria[a]	0	0	0.000	0.000	0.000	0.000	Assumption
Macroalbuminuria[a]	0	0	0.000	0.000	-0.048	0.022	Bagust et al.[26]

	Unit Costs (CAN$ 2018)		QALY Disutility Weights				
			Reference Case[d]		Expanded Reference Case		
	First Year Costs[c]	Annual Follow-up	Mean	SE	Mean	SE	Source for Expanded Reference Case
Stage 1 CKD	0	0	0.000	0.000	0.000	0.000	Assumption
Stage 2 CKD	0	0	0.000	0.000	0.000	0.000	Assumption
Stage 3A CKD	0	0	0.000	0.000	-0.050	0.000	Hoerger et al.[12]
Stage 3B CKD	0	0	0.000	0.000	-0.050	0.000	Hoerger et al.[12]
Stage 4 CKD	0	0	0.000	0.000	-0.070	0.000	Hoerger et al.[12]
Stage 5 CKD (no ESRD)	0	0	0.000	0.000	-0.070	0.000	Hoerger et al.[12]
ESRD	0	26,398	-0.184	0.000	-0.263	0.000	CADTH[27]
Obesity							
Per 1 BMI > 25	--	--	-0.006	0.000	-0.006	0.010	Bagust et al.[26]

a. Set to zero to standardize the models b. Figures divided by 12 to enter as Monthly costs in ECHO-T2DM c. Applied as event cost in IHE-DCM with annual subtracted from event costs not to double count first year costs in IHE-DCM d. Sourced from the Mt. Hood Challenge Instructions [29]; BMI body mass index, BDR background diabetic retinopathy, CADTH Canadian agency for drugs and technologies in health, CHF congestive heart failure, ESRD end-stage renal disease, IHD ischemic heart disease, LEA lower extremity amputation, ME macular edema, MI myocardial infarction, PDR proliferative diabetic retinopathy, PVD peripheral vascular disease

ESM Table 2: Insulin Rescue Treatment Profiles for Expanded Reference Case

Treatment	Basal		Basal and Bolus	
	Mean	SE	Mean	SE
ΔHbA1c, %[a]	-1.196	0.095	-2.224	0.357
ΔBMI, kg/m^2 [a]	0.735	0.111	1.605	0.487
Rates of adverse events, per patient year of exposure:				
Non-Severe Hypoglycemia [a]	1.980	2.170	10.280	13.700
Severe Hypoglycemia [a]	0.005	0.190	0.042	0.037
Corresponding HbA1c [a]	8.800	--	8.800	--
Treatment Costs (CAN$)				
Drug	1,000	--	1,600	--
Test strips	500	--	1,900	--

[a] Sourced from Willis et al.[30]

5. Additional Results for Reference Case

ESM Table 3: Cost and Disutility Drivers Reference Case (Males)

Cost Drivers	IHE-DCM			ECHO-T2DM		
	Intervention	Control	Difference	Intervention	Control	Difference
Costs Drivers						
Treatment	39,770	15,298	24,472	36,292	13,806	22,486
MI	7,555	8,999	-1,444	6,726	7,873	-1,148
IHD	8,081	8,708	-627	4,816	5,186	-369
CHF	5,756	6,070	-314	4,433	4,619	-186
Stroke	9,745	12,173	-2,427	7,045	8,646	-1,602
PVD	--	--	--	324	298	26
Retinopathy	182	345	-163	124	237	-114
CKD	502	926	-424	0	0	0
Neuropathy	--	--	--	318	418	-100
Amputation follow-up	--	--	--	2,019	1,939	80
Lower Extremity Disease*	7,459	7,702	-243	6,780	6,725	56
Hypoglycemia	0	0	0	0	0	0
Total Costs	79,051	60,221	18,829	66,216	47,093	19,123
Disutiltiy Drivers						
MI	0.060	0.070	-0.011	0.049	0.057	-0.008
IHD	0.190	0.205	-0.014	0.108	0.116	-0.008
CHF	0.142	0.148	-0.007	0.063	0.065	-0.002
Stroke	0.094	0.118	-0.024	0.117	0.145	-0.027
PVD	--	--	--	0.157	0.145	0.013
Retinopathy	0.025	0.047	-0.021	0.021	0.038	-0.017
CKD	0.004	0.006	-0.003	0.000	0.000	0.000
Neuropathy	--	--	--	0.025	0.033	-0.008
Amputations event	--	--	--	0.092	0.088	0.004
Lower Extremity Disease	0.297	0.295	0.002	--	--	--
Hypoglycemia	0.000	0.000	0.000	0.000	0.000	0.000
Excess Weight	0.194	0.280	-0.086	0.183	0.262	-0.079
Survival **	-		-0.479	-		-0.559
Total Disutility Avoided with Intervention			0.642			0.692
Health Outcomes (Discounted)						
LY's	15.908	15.298	0.610	14.990	14.277	0.713
QALY's	11.482	10.839	0.642	10.952	10.260	0.692
Survival at End of Year 40	1.6%	1.4%	0.2%	0.8%	0.7%	0.1%
Net Monetary Benefits			13,293			15,452
Incremental Cost Per QALY Gained			29,309			27,654

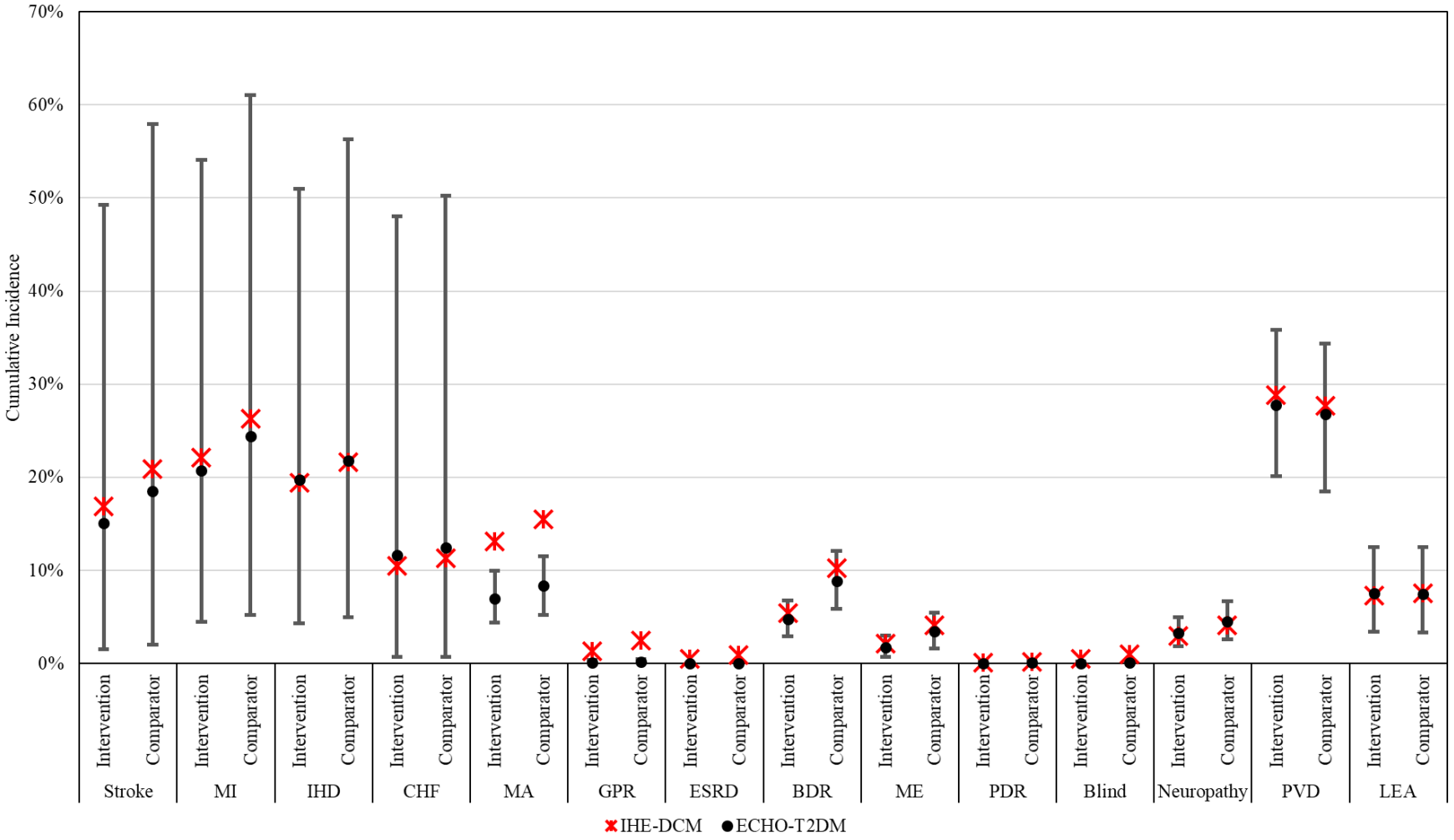
*Note: this is the outcome measure for IHE Cohort Model. Individual components are calculated separately for ECHO-T2DM, but we calculate this ex post as PVD + amputation + neuropathy for comparison purposes ** For consistency with the other disutility measures, only the disutility associated with survival differences is reported (with the value of one intervention naturalized to 0).

ESM Table 4: Cost and Disutility Drivers Reference Case (Females)

Cost Drivers	IHE-DCM			ECHO-T2DM		
	Intervention	Control	Difference	Intervention	Control	Difference
Costs Drivers						
Treatment	42,630	16,582	26,048	39,979	15,445	24,535
MI	8,033	8,574	-541	7,660	8,056	-396
IHD	5,449	6,082	-632	3,102	3,442	-340
CHF	6,145	6,634	-488	4,695	5,051	-356
Stroke	7,010	9,004	-1,994	5,337	6,751	-1,414
PVD	--	--	--	317	298	18
Retinopathy	206	398	-192	148	292	-144
CKD	575	1,091	-516	0	0	0
Neuropathy	--	--	--	368	500	-133
Amputation follow-up	--	--	--	2,149	2,168	-19
Lower Extremity Disease*	7,266	7,769	-503	7 025	7,266	-241
Hypoglycemia	0	0	0	0	0	0
Total Costs	77,315	56,134	21,181	67,945	46,302	21,643
Disutiltiy Drivers						
MI	0.062	0.066	-0.003	0.057	0.059	-0.002
IHD	0.128	0.143	-0.015	0.069	0.077	-0.007
CHF	0.151	0.162	-0.011	0.067	0.071	-0.005
Stroke	0.066	0.086	-0.020	0.091	0.115	-0.024
PVD	--	--	--	0.153	0.145	0.009
Retinopathy	0.028	0.053	-0.025	0.024	0.045	-0.021
CKD	0.004	0.008	-0.004	0.000	0.000	0.000
Neuropathy	--	--	--	0.029	0.039	-0.010
Amputations event	--	--	--	0.098	0.099	-0.001
Lower Extremity Disease	0.285	0.290	-0.006	--	--	--
Hypoglycemia	0.000	0.000	0.000	0.000	0.000	0.000
Excess Weight	0.208	0.303	-0.095	0.202	0.293	-0.091
Survival **	-		-0.369	-		-0.430
Total			0.548			0.583
Health Outcomes (Discounted)						
LY's	17.052	16.582	0.470	16.468	15.920	0.548
QALY's	12.453	11.906	0.548	12.137	11.554	0.583
Survival at End of Year 40	1.9%	1.7%	0.2%	1.1%	1.0%	0.2%
Net Monetary Benefits			6,199			7,518
Incremental Cost Per QALY Gained			38,680			37,109

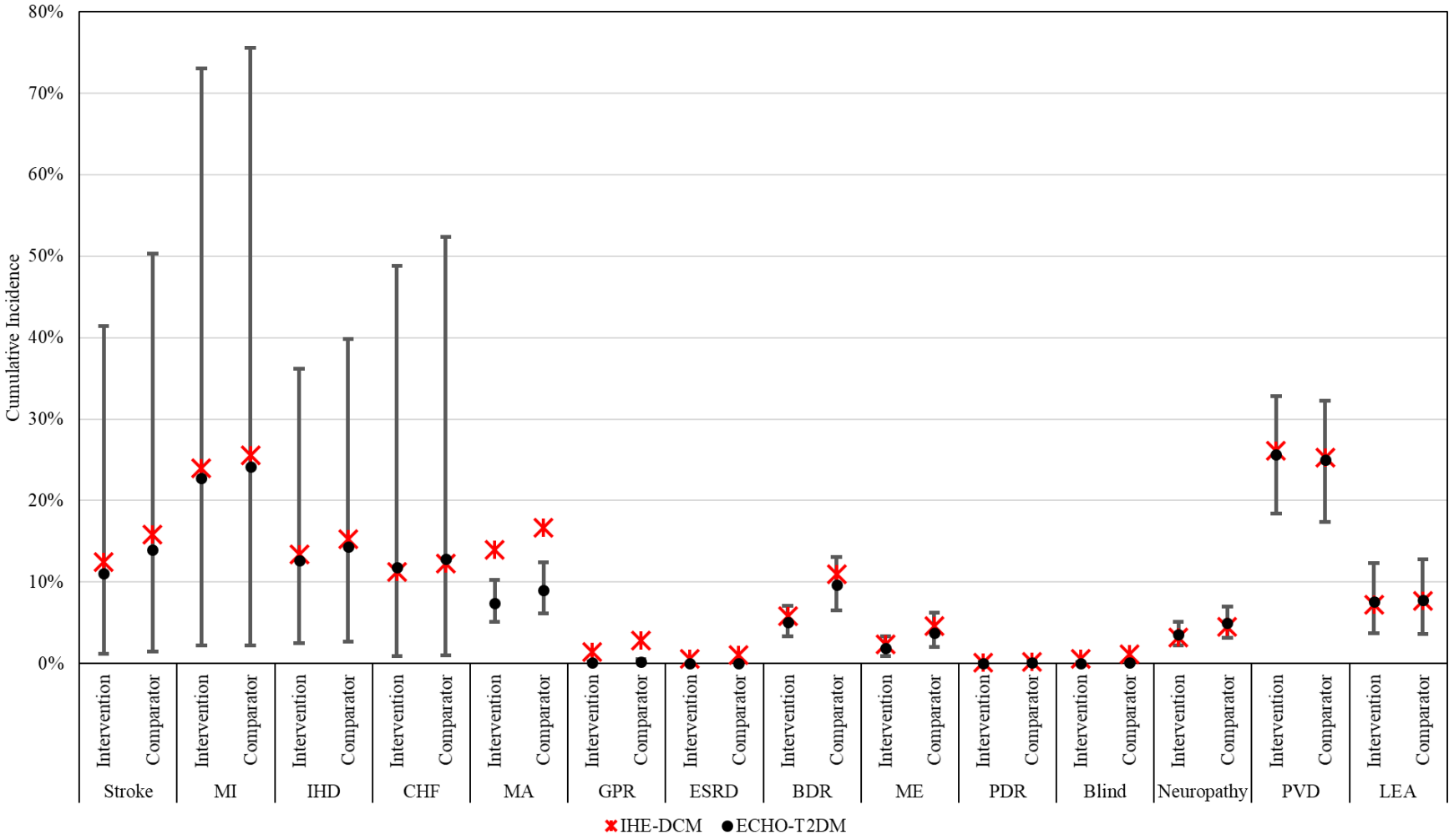
*Note: this is the outcome measure for IHE Cohort Model. Individual components are calculated separately for ECHO-T2DM, but we calculate this ex post as PVD + amputation + neuropathy for comparison purposes ** For consistency with the other disutility measures, only the disutility associated with survival differences is reported (with the value of one intervention naturalized to 0).

ESM Figure 3: Cumulative Incidences and Confidence Intervals (95%) – Reference Case (Males)



BDR background diabetic retinopathy, CHF congestive heart failure, ESRD end-stage renal disease, GPR gross proteinuria (macroalbuminuria), IHD ischemic heart disease, LEA lower extremity amputation, MA microalbuminuria, ME macular edema, MI myocardial infarction, PDR proliferative diabetic retinopathy, PVD peripheral vascular disease

ESM Figure 4: Cumulative Incidences and Confidence Intervals (95%) – Reference Case (Females)



BDR background diabetic retinopathy, CHF congestive heart failure, ESRD end-stage renal disease, GPR gross proteinuria (macroalbuminuria), IHD ischemic heart disease, LEA lower extremity amputation, MA microalbuminuria, ME macular edema, MI myocardial infarction, PDR proliferative diabetic retinopathy, PVD peripheral vascular disease

6. Additional Results for Expanded Reference Case

ESM Table 5: Overview of Key Results for all Expanded Reference Case Scenarios

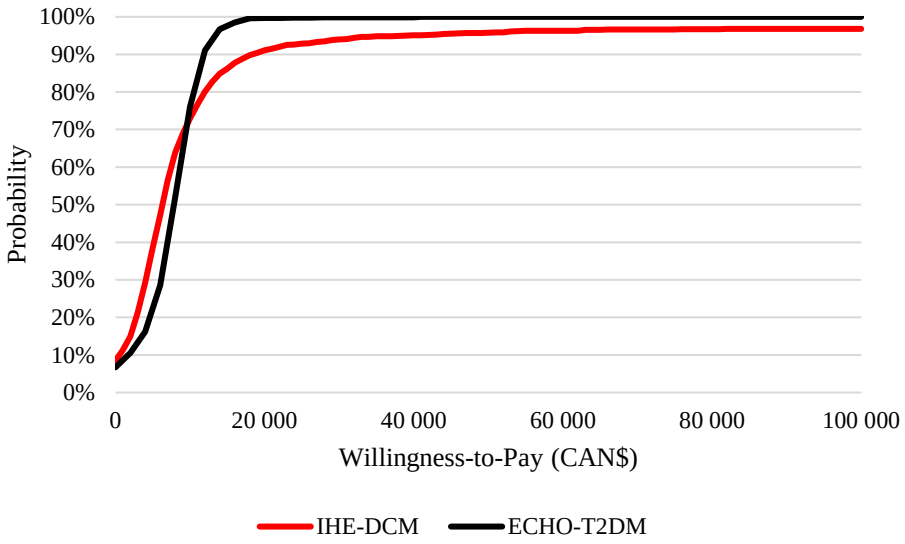
	Description	Model	Total Costs (CAN$)			Total Life-Year			Total QALYs			ICER	NMB
			Intervention	Comparator	Differences	Intervention	Comparator	Differences	Intervention	Comparator	Differences		
BC	Base Case	ECHO-T2DM	76 410	71 312	5 098	11.15	10.55	0.6	8.98	8.26	0.72	7 059	31 009
		IHE-DCM	84 266	80 547	3 719	13.17	12.71	0.46	10.97	10.29	0.67	5 542	29 834
1	HbA1c target of 8.5%	ECHO-T2DM	74 123	67 233	6 890	11.04	10.34	0.7	9.08	8.28	0.8	8 628	33 038
		IHE-DCM	84 955	77 374	7 581	13.1	12.62	0.49	11.16	10.53	0.62	12 160	23 590
2	Higher HbA1c drift for Comparator	ECHO-T2DM	76 265	72 466	3 799	11.2	10.59	0.61	8.98	8.16	0.82	4 636	37 171
		IHE-DCM	84 266	83 090	1 175	13.17	12.7	0.47	10.97	10.13	0.84	1 408	40 578
3	Intensification after year 3	ECHO-T2DM	65 031	61 422	3 609	10.8	10.59	0.21	8.96	8.74	0.22	16 551	7 294
		IHE-DCM	78 272	74 760	3 512	12.84	12.64	0.19	10.95	10.72	0.22	15 678	7 689
4	Model applied "as intended"	ECHO-T2DM	73 740	68 176	5 564	11.25	10.67	0.58	8.56	7.83	0.74	7 555	31 259
		IHE-DCM	84 385	80 665	3 720	13.17	12.71	0.46	10.93	10.25	0.67	5 531	29 911
5	No PSA (2nd order uncertainty)	ECHO-T2DM	74 203	67 874	6 329	11.86	11.04	0.82	9.59	8.7	0.89	7 081	38 366
		IHE-DCM	79 396	74 452	4 944	13.89	13.47	0.42	11.57	10.97	0.6	8 204	25 187
6	Early disease	ECHO-T2DM	105 874	102 286	3 589	18.39	17.64	0.74	14.78	13.84	0.94	3 804	43 574
		IHE-DCM	111 433	110 732	700	21.52	20.99	0.53	17.7	16.86	0.84	834	41 298
7	Late disease	ECHO-T2DM	60 628	56 131	4 497	6.91	6.44	0.46	5.38	4.86	0.52	8 595	21 662
		IHE-DCM	76 100	71 357	4 743	8.59	8.22	0.37	6.98	6.51	0.47	10 054	18 844

	Description	Model	Total Costs (CAN$)			Total Life-Year			Total QALYs			ICER	NMB
			Intervention	Comparator	Differences	Intervention	Comparator	Differences	Intervention	Comparator	Differences		
8	Alternative QALY decrements for key outcomes	ECHO-T2DM	75 775	70 751	5 025	11.01	10.43	0.59	8.88	8.18	0.71	7 113	30 296
		IHE-DCM	84 266	80 547	3 719	13.17	12.71	0.46	10.99	10.31	0.68	5 485	30 185
9	HbA1c lowering only	ECHO-T2DM	76 420	70 373	6 047	10.84	10.79	0.04	8.67	8.43	0.24	24 846	6 122
		IHE-DCM	85 696	80 155	5 542	12.86	12.82	0.04	10.64	10.38	0.26	21 021	7 640
10	Rebound of treatment effects following discontinuation	ECHO-T2DM	79 538	72 415	7 123	11.06	10.66	0.4	8.68	8.23	0.45	15 832	15 373
		IHE-DCM	91 435	84 708	6 727	13.2	12.71	0.5	10.24	9.92	0.32	21 099	9 214
11	Discontinuation of treatments	ECHO-T2DM	86 779	75 633	11 146	11.24	10.38	0.86	9.07	8.11	0.96	11 671	36 605
		IHE-DCM	99 965	89 115	10 851	13.18	12.71	0.47	11.01	10.29	0.72	15 095	25 091
12	Lower Insulin Cost	ECHO-T2DM	69 244	62 808	6 436	11.15	10.55	0.6	8.98	8.26	0.72	8 913	29 670
		IHE-DCM	77 326	70 852	6 474	13.17	12.71	0.46	10.97	10.29	0.67	9 648	27 079
13	Higher treatment costs	ECHO-T2DM	83 930	71 312	12 618	11.15	10.55	0.6	8.98	8.26	0.72	17 473	23 488
		IHE-DCM	92 821	80 547	12 274	13.17	12.71	0.46	10.97	10.29	0.67	18 291	21 279
14	Lower treatment costs	ECHO-T2DM	68 890	71 312	-2 422	11.15	10.55	0.6	8.98	8.26	0.72	Dominates	38 529

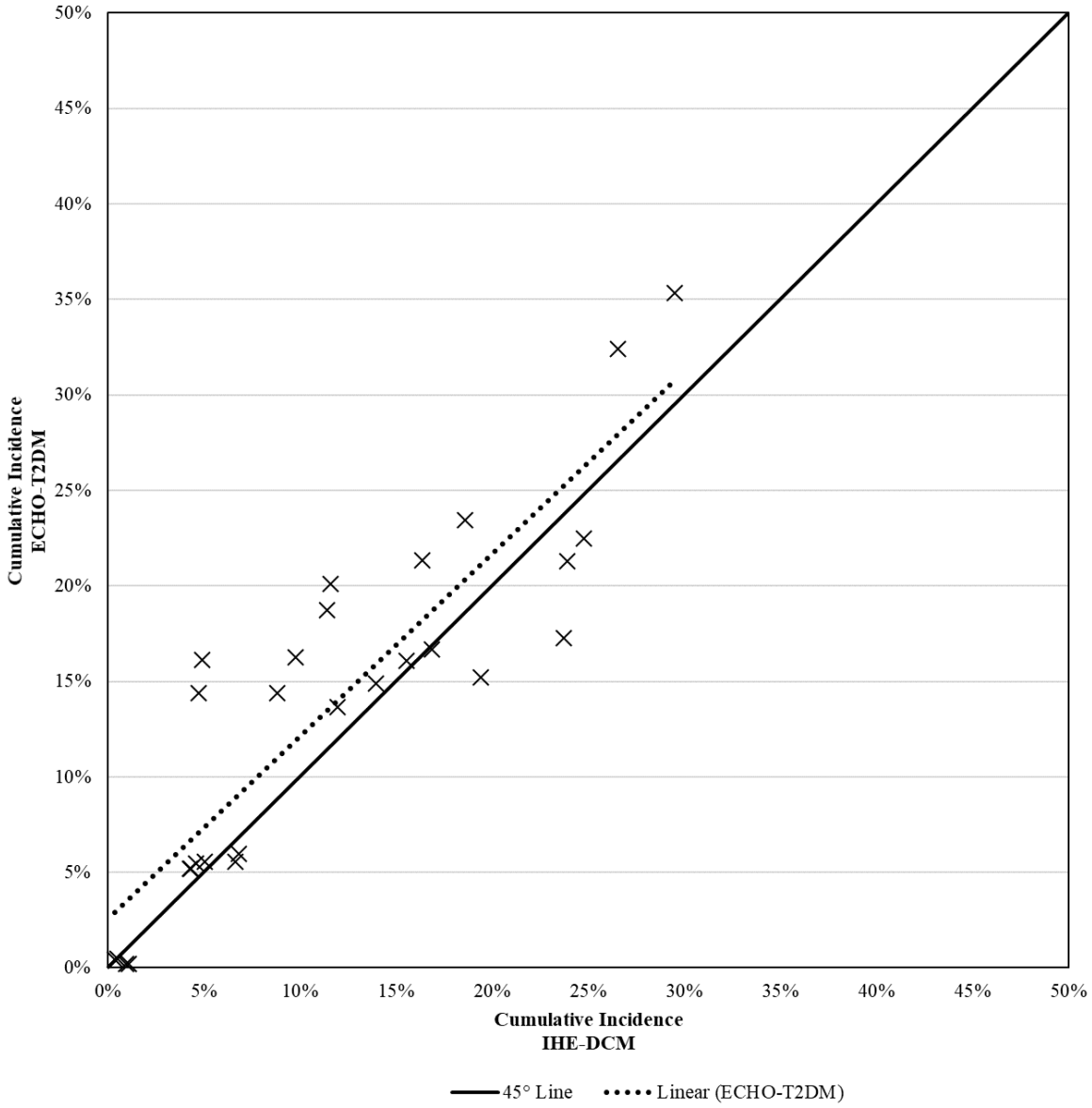
	Description	Model	Total Costs (CAN$)			Total Life-Year			Total QALYs			ICER	NMB
			Intervention	Comparator	Differences	Intervention	Comparator	Differences	Intervention	Comparator	Differences		
		IHE-DCM	75 711	80 547	-4 835	13.17	12.71	0.46	10.97	10.29	0.67	Dominates	38 389
15	No modelling of CKD	ECHO-T2DM	75 012	68 938	6 074	12.77	12.32	0.44	10.16	9.55	0.62	9 853	24 750
		IHE-DCM	80 382	76 633	3 749	13.97	13.65	0.32	11.61	11.03	0.57	6 536	24 932
16	Deterministic Cohort model	ECHO-T2DM	76 410	71 312	5 098	11.15	10.55	0.6	8.98	8.26	0.72	7 059	31 009
		IHE-DCM	79 396	74 452	4 944	13.89	13.47	0.42	11.57	10.97	0.6	8 204	25 187
17	Female subgroup	ECHO-T2DM	76 011	70 755	5 256	11.31	10.71	0.6	8.58	7.88	0.7	7 486	29 851
		IHE-DCM	83 015	78 981	4 034	13.3	12.86	0.45	10.49	9.85	0.64	6 277	28 103
18	Males subgroup	ECHO-T2DM	75 391	70 496	4 895	10.8	10.21	0.59	9.16	8.42	0.74	6 602	32 176
		IHE-DCM	85 794	82 421	3 373	12.97	12.5	0.47	11.37	10.67	0.7	4 844	31 445
	Averages Across Scenarios	ECHO-T2DM	--	--	**5 614**	--	--	**0.56**	--	--	**0.68**	**10 042**	**28 486**
		IHE-DCM	--	--	**4 576**	--	--	**0.42**	--	--	**0.6**	**9 773**	**25 551**

CKD chronic kidney disease, ICER incremental cost-effectiveness ratio, NMB net monetary benefits, PSA probabilistic sensitivity analysis, QALY quality-adjusted life-years, SC scenario

ESM Figure 5: Cost-Effectiveness Acceptability Curves for Base Case, by Model



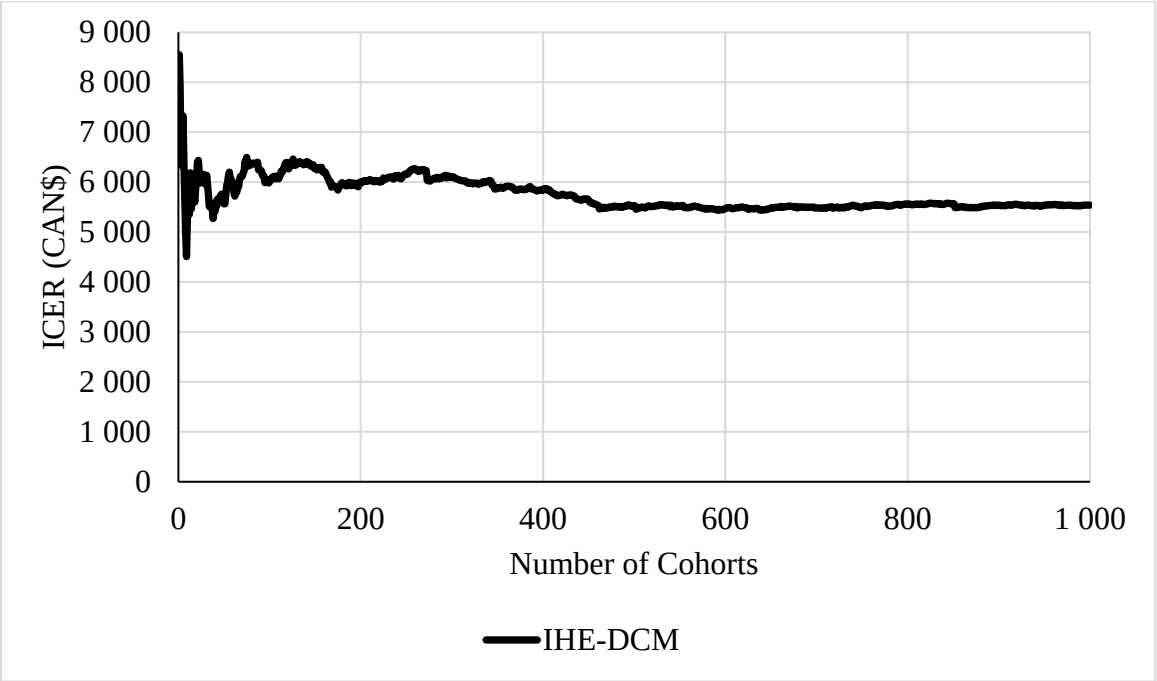
ESM Figure 6: Base Case Cumulative Incidence Rates, by Complication and Model



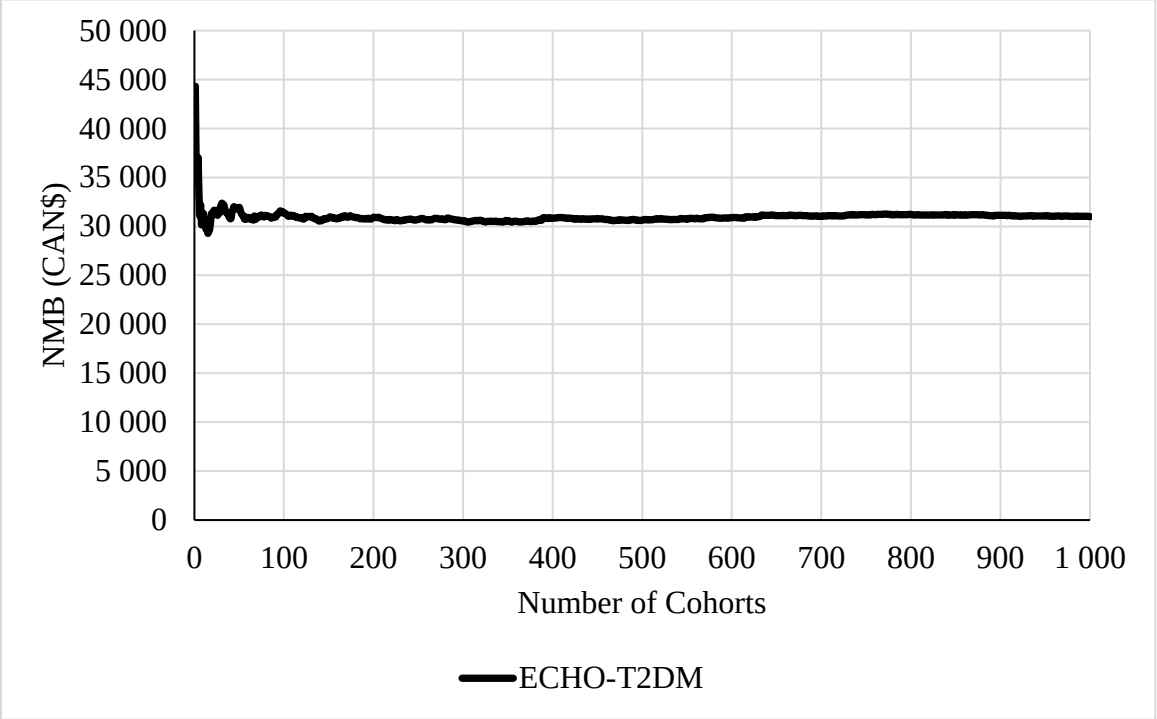
Each point represents the cumulative incidence of a micro-or macrovascular complication. The dotted line indicates the linear regression of the cumulative incidences in ECHO-T2DM

ESM Figure 7: Convergence Plots

(A) Base Case ICER Convergence Plot for IHE-DCM

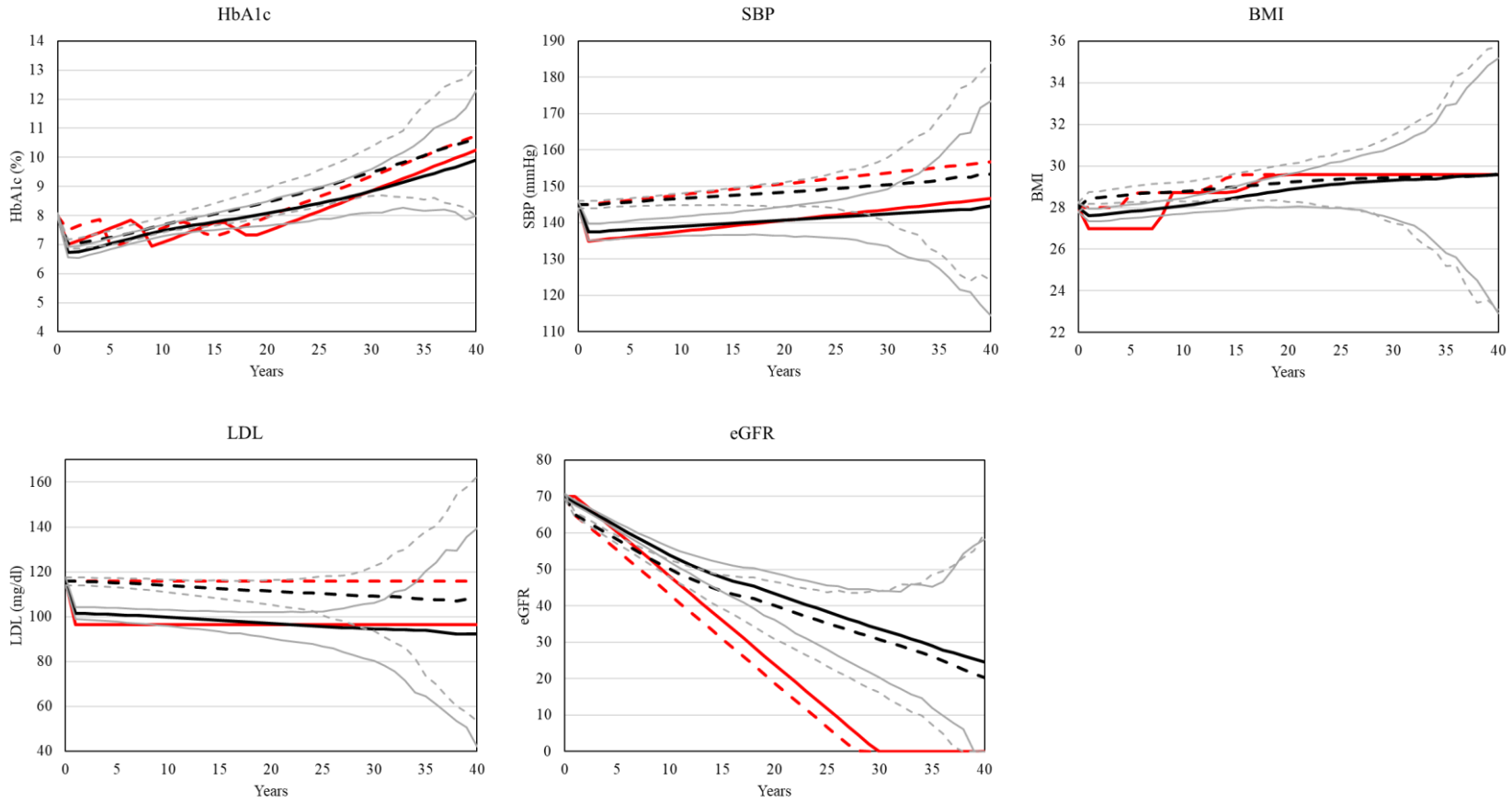


(B) Base Case NMB Convergence Plot for ECHO-T2DM*



*1,000 patients per cohort

ESM Figure 8: Biomarker Evolution in Expanded Reference Case, by Model



ESM References

1. DCCT. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. Am J Med. 1991;90(4):450-9.

2. Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Zbrozek AS, Dong F et al. Model of complications of NIDDM. I. model construction and assumptions. Diabetes care. 1997;20(5):725-34.

3. Bagust A, Hopkinson PK, Maier W, Currie CJ. An Economic Model of the Long-Term Health Care Burden of Type II Diabetes. Diabetologia. 2001;44(12):2140-55. doi:10.1007/s001250100023.

4. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to Estimate the Lifetime Health Outcomes of Patients with Type 2 Diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004;47(10):1747-59. doi:10.1007/s00125-004-1527-z.

5. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925-33. doi:10.1007/s00125-013-2940-y.

6. Ahmad Kiadaliri A, Gerdtham UG, Nilsson P, Eliasson B, Gudbjornsdottir S, Carlsson KS. Towards renewed health economic simulation of type 2 diabetes: risk equations for first and second cardiovascular events from Swedish register data. PloS one. 2013;8(5):e62650. doi:10.1371/journal.pone.0062650.

7. Davis WA, Knuiman MW, Davis TM. An Australian cardiovascular risk equation for type 2 diabetes: the Fremantle Diabetes Study. Internal medicine journal. 2010;40(4):286-92. doi:10.1111/j.1445-5994.2009.01958.x.

8. Willis M, Johansen P, Nilsson A, Asseburg C. Validation of the Economic and Health Outcomes Model of Type 2 Diabetes Mellitus (ECHO-T2DM). PharmacoEconomics. 2017;35(3):375-96. doi:10.1007/s40273-016-0471-3.

9. Brown JB, Russell A, Chan W, Pedula K, Aickin M. The Global Diabetes Model: User Friendly Version 3.0. Diabetes research and clinical practice. 2000;50 Suppl 3:S15-46.

10. Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Copley-Merriman C, Maier W et al. Model of complications of NIDDM. II. analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. Diabetes care. 1997;20(5):735-44.

11. Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P et al. A health policy model of CKD: 1. Model construction, assumptions, and validation of health

consequences. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(3):452-62. doi:10.1053/j.ajkd.2009.11.016.

12. Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P et al. A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(3):463-73. doi:10.1053/j.ajkd.2009.11.017.

13. Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil. 2011;18(3):393-8. doi:10.1177/1741826710394270.

14. Zethelius B, Eliasson B, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Cederholm J. A New Model for 5-year Risk of Cardiovascular Disease in Type 2 Diabetes, From the Swedish National Diabetes Register (NDR). Diabetes research and clinical practice. 2011;93(2):276-84. doi:10.1016/j.diabres.2011.05.037.

15. Shao H, Fonseca V, Stoecker C, Liu S, Shi L. Novel Risk Engine for Diabetes Progression and Mortality in USA: Building, Relating, Assessing, and Validating Outcomes (BRAVO). PharmacoEconomics. 2018. doi:10.1007/s40273-018-0662-1.

16. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713-35. doi:10.1053/j.ajkd.2014.01.416.

17. Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2011;18(3):393-8. doi:10.1177/1741826710394270.

18. Zethelius B, Eliasson B, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Cederholm J. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). Diabetes research and clinical practice. 2011;93(2):276-84. doi:10.1016/j.diabres.2011.05.037.

19. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63(1):225-32. doi:10.1046/j.1523-1755.2003.00712.x.

20. Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P et al. Supplementary Item S1, Hoerger et al, AJKD, “A Health Policy Model of CKD”. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(3).

21. Kengne AP, Patel A, Colagiuri S, Heller S, Hamet P, Marre M et al. The Framingham and UK Prospective Diabetes Study (UKPDS) Risk Equations Do Not Reliably Estimate the Probability of Cardiovascular Events in a Large Ethnically Diverse Sample of Patients With

Diabetes: The Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Study. Diabetologia. 2010;53(5):821-31. doi:10.1007/s00125-010-1681-4.

22. van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. Diabetes care. 2009;32(11):2094-8. doi:10.2337/dc09-0745.

23. McEwan P, Bennett H, Ward T, Bergenheim K. Refitting of the UKPDS 68 risk equations to contemporary routine clinical practice data in the UK. PharmacoEconomics. 2015;33(2):149-61. doi:10.1007/s40273-014-0225-z.

24. Tao L, Wilson EC, Griffin SJ, Simmons RK. Performance of the UKPDS outcomes model for prediction of myocardial infarction and stroke in the ADDITION-Europe trial cohort. Value in Health. 2013;16(6):1074-80. doi:10.1016/j.jval.2013.06.001.

25. van Dieren S, Beulens JW, Kengne AP, Peelen LM, Rutten GE, Woodward M et al. Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review. Heart (British Cardiac Society). 2012;98(5):360-9. doi:10.1136/heartjnl-2011-300734.

26. Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health economics. 2005;14(3):217-30. doi:10.1002/hec.910.

27. CADTH. Therapeutic Review New Drugs for Type 2 Diabetes: Second-Line Therapy Recommendations Report 2017 Contract No.: 1c.

28. Fenwick EK, Xie J, Ratcliffe J, Pesudovs K, Finger RP, Wong TY et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. Investigative ophthalmology & visual science. 2012;53(2):677-84. doi:10.1167/iovs.11-8992.

29. Mt Hood Diabetes Challenges. Challenge Session Final instructions. https://www.mthooddiabeteschallenge.com/challenge-sessions. Accessed December 2019.

30. Willis M, Asseburg C, Nilsson A, Johnsson K, Kartman B. Multivariate Prediction Equations for HbA1c Lowering, Weight Change, and Hypoglycemic Events Associated with Insulin Rescue Medication in Type 2 Diabetes Mellitus: Informing Economic Modeling. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2017;20(3):357-71. doi:10.1016/j.jval.2016.10.004.