

2022 Mount Hood Malmo Diabetes Challenges

Motivation:

The impact of model uncertainty on cost-effectiveness estimates of diabetes interventions is unknown. The aim of Mt Hood 2022 challenges is to examine the variation in cost-effectiveness estimates associated with two categories of diabetes interventions: a reduction in a patient's blood glucose levels and a reduction in weight. This variation will provide an estimate of model uncertainty, which will provide the basis for a publication. The challenge is broken into two components and they applicable to both type 2 and type 1 modelling groups.

Challenge 1: Revisiting the reference simulation

We will also ask groups to repeat the reference simulations for a standard patient that were in previous challenges and reported in the MT Hood model registry. This will enable model simulations to be compared across time and these values will be used to update the model registry: <https://www.mthooddiabeteschallenge.com/registry>. Previous reference simulations have often assumed that risk factors are held constant over time which is often unrealistic. Since the last Mt Hood challenge several risk factor time path equations have been published (eg <https://onlinelibrary.wiley.com/doi/10.1111/dme.14656>). Hence we ask all modelling groups to run the reference simulations under two scenarios: (i) risk factor values held constant (which was the assumption from the previous challenge); and (ii) allowing them to vary using equations or trajectories that are normally used in your simulation model. Treatment effects will assume to be a constant displacement from the usual time path.

Challenge 2: Simulating costs and cost-effectiveness

Following the 2018 Mt Hood Quality of life Challenge, the challenge employs average values or characteristics of patients enrolled in RCTs of common diabetes therapies. The average treatment effect of each category of intervention will be modelled by permanent reduction in HbA1c and body mass index. The results from this exercise will provide an indication of what factors influence the cost-effectiveness of these interventions. The challenge will also examine how the estimated incremental QALYs, incremental costs and ICERs vary for a cohort of patients with a history of myocardial infarction and following the inclusion of unrelated future medical costs.

Model Inputs:

Utility Values

The challenge uses the health utility values from the 2018 Mt Hood Quality of life Challenge for type 2 diabetes and newly added health utility values for type 1 diabetes (Table 1). It will be adequate to use point estimates and not model second order uncertainty if the model allows it.

If you require additional utility weights for health states not listed, please add utility values you currently use. Please document your sources and assumptions in the “Utility values” tab in the accompanying Excel spreadsheet.

For the challenge, please apply disutility values only to complication events described in the instructions as far as possible. If this is not possible and your model **requires** you to apply additional disutilities for certain health states (e.g. a raised BMI health state which is independent of BMI's effect on complication events) - please report these disutilities here. Please also keep baseline utilities constant across all ages as set out in instruction table 1. Where possible, please do not change baseline utilities by age. However, if your model requires you to do so – please report this in the Excel sheet.

Note: please make sure to avoid confusion with utility/disutility terminology in loading the models and in reporting results. The “Utility/Disutility Values” column in Table 1 reports “utility” only for diabetes without complication (which is positive). The remaining items (all negative) are disutility and are incremental.

Based on the 2018 Mt. Hood challenge conference call on September 5, 2018, two suggestions were made for the Quality of Life challenge, including:

- 1) The additive quality-of-life (QoL) model is recommended when populating the health utility values into the simulation model. As shown in Table 1 below, if a subject has experienced two different complications belonging to 2 different categories of disease (e.g., stroke [in the category of cerebrovascular disease] and myocardial infarction [in the category of coronary heart disease]), the health utility value will be reduced by 0.219 which is the sum of individual decrement for these 2 complications (i.e., $0.164+0.055$). However, if a subject has experienced two or more complications within the same category of disease (e.g., myocardial infarction [in the category of coronary heart disease] and congestive heart failure [in the category of coronary heart disease]), the health utility value will be reduced by 0.108 (the decrement for heart failure) which is the largest decrement of these two complications. If the additive QoL model is not feasible in your model, please document your assumptions how the health utility values are populated in your model.
- 2) The utility decrement and its 95% confidence interval for renal transplant was assumed to be half of those for hemodialysis.

Table 1. Utility values by categories of diseases/complications

Disease category	Complication level provided in Mt. Hood QoL challenge	Type 2 diabetes ^a			Type 1 diabetes [*]		
		Utility/Disutility Values	Lower 95% CI	Upper 95% CI	Utility/Disutility Values	Lower 95% CI	Upper 95% CI
Baseline utility value	Diabetes without complications	0.785	0.681	0.889	0.900 ^b	0.880 ^b	0.930 ^b
Acute metabolic disorder	Minor hypoglycemia event	-0.014	-0.004	-0.004			
	Major hypoglycemia event	-0.047	-0.012	-0.012	-0.002 ^c	-0.004 ^c	-0.000 ^c
	Major hyperglycemic event				-0.071 ^d	-0.116 ^d	-0.026 ^d
Comorbidity	Excess BMI (each unit above 25 kg/m ²)	-0.006	-0.008	-0.004	-0.005 ^c	-0.009 ^c	-0.001 ^c
Retinopathy	Cataract	-0.016	-0.031	-0.001			
	Moderate non-proliferative background diabetic retinopathy	-0.040	-0.066	-0.014	-0.027 ^c	-0.048 ^c	-0.005 ^c
	Moderate macular edema	-0.040	-0.066	-0.014			
	Vision-threatening diabetic retinopathy	-0.070	-0.099	-0.041			
	Severe vision loss	-0.074	-0.124	-0.025			
Nephropathy	Proteinuria	-0.048	-0.091	-0.005			
	Renal transplant ¹	-0.082	-0.137	-0.027	-0.053 ^e	-0.077 ^e	-0.029 ^e
	Hemodialysis	-0.164	-0.274	-0.054	-0.082 ^e	-0.128 ^e	-0.036 ^e
	Peritoneal dialysis	-0.204	-0.342	-0.066			
Neuropathy	Peripheral vascular disease	-0.061	-0.090	-0.032			
	Neuropathy	-0.084	-0.111	-0.057	-0.236 ^c	-0.299 ^c	-0.173 ^c
	Active ulcer	-0.170	-0.207	-0.133	-0.125 ^c	-0.226 ^c	-0.023 ^c
	Amputation event	-0.280	-0.389	-0.170	-0.117 ^c	-0.225 ^c	-0.009 ^c
Cerebrovascular disease	Stroke	-0.164	-0.222	-0.105	-0.291 ^b	-0.475 ^b	-0.108 ^b
Coronary heart disease	Myocardial infarction	-0.055	-0.067	-0.042			
	Ischemic heart disease	-0.090	-0.126	-0.054	-0.181 ^b	-0.331 ^b	-0.031 ^b
	Heart failure	-0.108	-0.169	-0.048	-0.058 ^f	-0.101 ^f	-0.015 ^f
	Percutaneous revascularization				+0.025 ^c	-0.051 ^c	0.101 ^c
	Coronary revascularization				-0.0787 ^c	-0.218 ^c	0.060 ^c

Source: ^a Beaudet et al. 2014 [1]; ^b Solli et al 2010 based on EQ-5D-3L [2]; ^c Peasgood et al 2016 based on EQ-5D-3L [3]; ^d Hart et al 2003 based on EQ-5D-3L [4]; ^e Ahola et al 2010 based on 15D; ^f Coffey et al 2002 based on QWB-SA [5]; Abbreviations: QoL, quality of life; CI, confidence interval; T2DM, type 2 diabetes; BMI, body mass index. ¹The utility decrement and its 95% confidence interval for renal transplant was assumed to be the half of those for haemodialysis.

* Compiled by An Tran-Duy (an.tran@unimelb.edu.au) on behalf of the COSMO-T1D modelling group. Note that the 95% CIs were not reported in Hart et al (source: d) and Ahola et al (source: e) and were reconstructed based on t-value, p-value, sample size and/or standard error where relevant.

Patient Baseline Characteristics

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values as listed in Table 2. Any other baseline patient characteristics that your model may require can be sourced from publicly available literature (but please document this including sources in “Baseline Characteristics” tab in the accompanying Excel spreadsheet).

Table 2: Patient Baseline Characteristics

Patient Characteristics	Type 2 diabetes ^a		Type 1 diabetes ^b	
	Men	Women	Men	Women
Current age	66	66	37	37
Duration of diabetes	8	8	22	22
Current/former smoker	N	N	N	N
Ethnicity	White	White	White	White
HbA1c. %	7.5	7.5	8.1	8.1
Systolic Blood Pressure, mmHg	145	145	127	127
Diastolic Blood Pressure, mmHg	80	80	73	73
Total Cholesterol, mmol/l	5.2	5.2	4.8	4.8
HDL Cholesterol, mmol/l	1.3	1.3	1.6	1.6
LDL Cholesterol, mmol/l	3.0	3.0	2.7	2.7
Triglycerides, mmol/L	2.0	2.0	1.2	1.2
BMI	28	28	25	25
Albumin: creatinine ratio	14.2	14.2		
PVD	N	N	N	N
Micro or macro albuminuria (albuminuria >50)	N	N	N	N
Atrial fibrillation	N	N	N	N
eGFR (ml/min/1.73 m ²)	70	70	96	96
WBC (x10 ⁹ /l)	7	7		
Heart rate (bpm)	79	79		
Haemoglobin (g/dl)	14	14		
Prior history of macrovascular disease	N	N	N	N
Prior history of microvascular disease	N	N	N	N

Source: ^a[ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline](#); see Appendix 1 for summary table; ^b Tran-Duy et al 2020 [6]

Costs

The perspective of the cost analysis is the health care system in the United Kingdom. Table 3 shows mean complication costs of diabetic patients obtained from UK literature. Please apply the same set of complication costs for both men and women and for both type 2 and type 1 diabetes individuals.

Please apply costs only to complication events described in the instructions as far as possible. To give example, if your model usually incorporates increased costs from raised BMI increases independently of complication events which occur, please turn this off if possible. If not possible to model costs only for complication events, then please report any additional costs.

Additionally, please keep baseline costs in the absence of complications constant across all ages as set out in instruction table 3, apart from for step 7 of Challenge 2 – where costs of unrelated medical expenditure vary by age. If possible, please do not otherwise change baseline costs by age. However, if your model requires you to do so – please report this in the excel spreadsheet.

Table 3 Complication costs (£, 2017-18 prices)

	Fatal cost	Non-fatal cost	Cost in subsequent years	Source
Ischemic heart disease/Angina	6,070	14,001	3,550	Alva et al. 2015 [7]
Myocardial infarction	3,318	9,518	3,424	Alva et al. 2015 [7]
Heart failure	2,825	5,650	4,277	Alva et al. 2015 [7]
Coronary revascularisation	-	8,302	3,550	Keng et al. 2021 [8] & Alva 2015 [7]
Stroke	6,463	10,755	3,534	Alva et al. 2015 [7]
Amputation	9,825	15,153	5,328	Alva et al. 2015 [7]
Blindness	0	4,247	2,206	Alva et al. 2015 [7]
Haemodialysis	0	43,359	43,359	Davies et al. 2012 [9] as cited in Ramos et al. 2019 [10]
Renal failure / transplant	10,289	20,578	20,578	NHS Blood and Transplant 2009 [11]
Ulcer	0	7,076	1,072	Kerr et al. 2014 [12]
Peripheral vascular disease	0	4,698	1,010	Baxter et al. 2016 as cited in Ramos et al. 2019
Cataract operation	0	2,636	178	Davies et al. 2012 [9], 2016 [13] as cited in Ramos et al. 2019 [10]
Neuropathy	0	29	29	Davies et al. [13] as cited in Ramos et al. 2019 [10]
Gangrene treatment	0	3,694	0	Davies et al. [13] as cited in Ramos et al. 2019 [10]
Retinopathy laser treatment	0	1,176	0	Davies et al. 2012 [9] as cited in Ramos et al. 2019 [10]
Peritoneal Dialysis	0	32,556	32,556	Davies et al. 2012 [9] as cited in Ramos et al. 2019 [10]
Severe hypoglycaemia (req. med. assistance)	0	1,470	0	Evans et al. 2017 [14] as cited in Ramos et al. 2019 [10]
Severe hypoglycaemia (req. non med. assistance)	0	433	0	Evans et al. 2017 [14] as cited in Ramos et al. 2019 [10]
Non-severe hypoglycaemia	0	4	0	Evans et al. 2014 [15] as cited in Ramos et al. 2019 [10]
Cost in the absence of complications		1,990		Alva et al. 2015 [7]

Table 4 Mean Intervention effect costs (£, 2017-18 prices) (assume applied every year while patients are alive in the simulation)

Intervention	Mean effect	Mean annual cost (£)
Blood glucose intervention 1:	0.5% point reduction in HbA1c & no effect on BMI	12
Blood glucose intervention 2:	0.9% point reduction in HbA1c &) 1-unit increase in BMI (kg/m ²) increase in BMI	320
Blood glucose intervention 3:	1.5% point reduction in HbA1c & 1-unit reduction in BMI	3810

Challenge simulation

Step 1: Run a simulation using the baseline risk factors from Table 2 held constant over a 40-year period for type 2 diabetes and a 70-year period for type 1 diabetes, separately for males and for females

This simulation should match both the 2018 Mt Hood challenge and the reference case simulations which are on the Mt Hood website: (<https://www.mthooddiabeteschallenge.com/refsim>). Ensure the costs and health outcomes are **not discounted** for this challenge.

Extract the results and enter input values in a transparent manner in the accompanying Excel workbook in tab labelled “Time paths & Outcomes” (modify the workbook to fit your outcomes if necessary, but please try to preserve the basic structure). Do not forget to include traces (risk factor time paths) for input values of all the above risk factors; rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.), and life-expectancy.

For microsimulation models, please ensure that the number of replications is sufficient to generate stable results.

Step 2: Reference simulation of common treatment effects

Re-run the simulation with four individual interventions (one-at-a-time and then all combined), separately for males and females, that capture initial and permanent reductions in common risk factors from time paths modelled in Step 1. Reductions from these interventions should only be applied to post-baseline cycles and baseline values should remain unchanged.

- (i) 0.5%-point reduction in HbA1c;
- (ii) 10mm Hg reduction in Systolic Blood Pressure;
- (iii) 0.5 mmol/l (19.33 mg/dl) reduction in LDL Cholesterol
- (iv) 1-unit reduction in BMI (kg/m²)
- (v) All 4 of the interventions above applied simultaneously#

Extract the results and add to the accompanying Excel workbook (in tab labelled “Time paths & Outcomes”. Report outcomes and inputs in a transparent manner. Do not forget to include traces (numerical or curves) for input values of all the above risk factors; cumulative rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.) and life expectancy.

Step 3: Estimate incremental QALYs, separately for males and females

Using the “Utility/disutility” values in Table 1 run the baseline simulation and estimate expected QALYs, assuming that decrements apply to the year of the event and are similarly applied to each subsequent year. However, if temporary events/states such as hypoglycaemia are modelled, it is likely that these decrements only apply to the year of the event. If so, please document this.

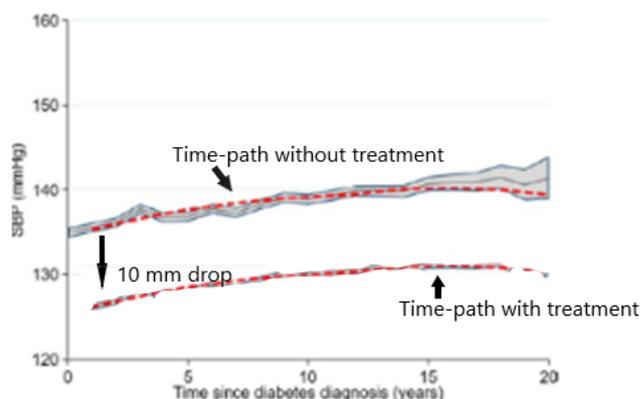
Run each of the four interventions listed in Step 2 to estimate the expected QALYs and calculate the incremental QALYs compared to the baseline (control). Extract the results and add to the accompanying Excel workbook (in tab labelled “Time paths & Outcomes”).

Be sure to report incremental QALYs so that a negative value indicates worse QALYs (not inverting to account for a positive value indicating more disutility)

Step 4: Reference simulation of common treatment effects when risk-factor time-paths are NOT held constant

The simulation in step 1 does not capture the drift that can occur in many risk factors over time eg. the gradual increase in HbA1c. To understand what impact change in risk factors may have on incremental benefits the second component of this challenge is to redo the four simulations outlined in step 2 using the actual risk factor time paths or assumptions regularly used in your model. Please assume that treatment effects are permanent vertical displacements from the trajectories without intervention time-paths.

As an example consider the blood pressure treatment simulation – the treatment will permanently reduce SBP 10 mm Hg below the projected trajectory of SPB without treatment. Similarly, please allow all risk factors that are normally projected in your model to vary. So, when simulating the blood pressure lowering intervention allow HbA1c, LDL, BMI and other risk factors to follow the time-path predicted by your model without any treatment effect.



Extract the results and add to the accompanying Excel workbook (in tab labelled “Time paths & Outcomes”). Report outcomes and inputs in a transparent manner. Do not forget to include traces (numerical or curves) for input values of all the above risk factors; cumulative rates (or counts) of all major health states in the model (e.g. MI; stroke; renal failure, etc.), QALYs and life expectancy.

Challenge 2: Simulating costs and cost-effectiveness of hypothetical interventions

Challenge two involves a cost-effectiveness evaluation on a hypothetical cohort of the male and female patients that have been simulated in the first challenge. For this challenge assume that there are equal numbers of females & males. Groups are asked to report overall cost-effectiveness results for the cohort in the remaining challenges.

Step 5: Simulate three glucose lowering interventions

Re-run the simulation with three hypothetical interventions affecting blood glucose and BMI that capture initial and permanent reductions in common risk factors from time paths modelled in Step 1. Table 4 presents the effects of the interventions and respective annual costs.

It is important in each simulation that all risk factors are kept constant between simulations and limit variation to the intervention effects and costs as per instructions in the steps below. This includes assumptions around biomarker evolution; i.e. HbA1c and BMI should be kept constant over time and not allowed to change over time (i.e., drift).

Please apply the same effect and annual costs for both men and women over the whole simulation period. These costs are unchanged by the occurrence of complications. Assume that the interventions will not have an effect on any other risk factors than HbA1c and BMI. Finally, assume adherence to each intervention to be 100% during the whole simulation period. Although the interventions are hypothetical, their effect size is based on a recent meta-analysis of glycaemic drugs [<https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.1307>] and their costs on the British National Formulary (BNF).

To estimate QALYs, use the utility values from Table 1 and follow the same assumptions as in Step 3. Estimate non-intervention costs (complications and management) by applying the costs from Table 3. Document any additional health states and/or costs used beyond those in Table 3.

The main outputs required are:

- incremental QALYs,
- incremental costs and
- incremental cost-effectiveness ratios

Report the above for the overall cohort of 50:50 males/females Conduct these simulations from a UK perspective, using and reporting costs in UK currency (£) and **setting the discount rate to 3.5%** for QALYs and costs prior to running the simulations.

Please use the minimum number of loops to reach convergence for the main outputs of interest. Report the number of loops used in each simulation.

Extract the results and add to the accompanying Excel workbook (in tab labelled “costs & ICERs”). Do not forget to include traces (numerical or curves) for input values of HbA1c and BMI risk factors.

Be sure to report incremental QALYs and costs of each intervention relative to no intervention so that a negative value indicates worse QALYs for the intervention compared to no intervention (not inverting to account for a positive value indicating more disutility)

Step 6: Estimate incremental QALYs and incremental costs for patients with a history of myocardial infarction (optional)

Re-run the simulation for a cohort of patients with a history of prior myocardial infarction again using the mean intervention costs provided in Table 4. If your model requires a number of years since the event, please use 5 years for all patients. Re-run for each of the blood glucose interventions, estimate the expected incremental QALYs and incremental costs, and calculate ICERs for each intervention compared to no intervention. Extract the results and add to the accompanying Excel workbook (in tabs labelled "Costs & ICERs").

Step 7: Estimate the ICERs for each intervention including estimates of future unrelated medical costs (optional)

Re-run Step 5 with the addition of unrelated medical costs (Table 5). These can be added to your model as annual costs unrelated to complications. These costs are assumed to remain unchanged by the occurrence of complications. Table shows separate costs by age group and sex, these should be included where possible. If this is not possible, collapse to mean values where required and make a note of this.

Table 5 Total annual expenditure on unrelated medical cost (£, 2017-18 prices)

	Men	Women
Aged 65-69	1,737	1,659
Aged 70-74	2,085	1,989
Aged 75-79	2,742	2,565
Aged 80-84	3,189	2,962
Aged 85+	3,694	3,339

Source: Briggs et al 2018 [16]

Extract incremental QALYs and incremental costs, and calculate ICERs for each intervention compared to no intervention and add to the accompanying Excel workbook (in tab labelled "Costs & ICERs"). **Again please report overall results for the cohort (which will be the results that will be focused on in the challenge).** Groups can also report subgroups if they wish to further explain their results.

Summary of findings:

Compile a summary of your findings in the accompanying Excel spreadsheet (in tab labelled "Summary"). Please complete the following.

- A) Based on your results in Step 5, which intervention(s) were costs-effective at a £20,000 per QALY threshold?
- B) Based on your results in Step 7, report which intervention(s) were costs-effective at a £20,000 per QALY threshold?
- C) Provide an overview of what you learnt from this challenge.

Submission:

Prior to the meeting, please submit the Excel spreadsheet ("MH MALMO CHALLENGE – ICER challenge_GROUP") to Mount Hood at: mthood2016@gmail.com by **12 September 2022**. Please replace GROUP with your modelling group name before submission.

APPENDIX 1

ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline <https://doi.org/10.1111/j.1464-5491.2005.01596.x>

Table 1 Baseline characteristics of randomized patients (*n* = 11 140)

Characteristic	Mean (SD) or %
Mean age, years	66 (6)
Female, %	43
Mean duration of diabetes, years	8 (6)
Prior vascular disease	
History of major macrovascular disease, %	32
History of major microvascular disease, %	10
Other major risk factors	
Current smokers, %	14
Mean total cholesterol, mmol/l	5.2 (1.2)
Mean HDL cholesterol, mmol/l	1.3 (0.4)
Mean triglycerides, mmol/l	2.0 (1.5)
Mean albumin : creatinine ratio, µg/mg	14.2 [6.4–38.1]*
Mean body mass index, kg/m ²	28 (5)
Mean waist circumference, cm	99 (13)
Blood pressure control	
Mean systolic blood pressure, mmHg	145 (22)
Mean diastolic blood pressure, mmHg	81 (11)
History of hypertension, %	69
Current blood pressure lowering therapy, %	75
ACE inhibitors, %	43
Angiotensin-receptor blockers, %	5
Beta-blockers, %	24
Calcium antagonists, %	31
Thiazide/thiazide-like diuretics, %	14
Other diuretics, %	11
Other blood pressure lowering drugs, %	12
Glucose control	
Mean haemoglobin A _{1c} concentration, %	7.5 (1.5)
Diet-only treated diabetes, %	9
Current oral hypoglycaemic, %	91
Sulphonylurea, %	71
Metformin, %	61
Thiazolidinediones, %	4
Glinides, %	2
Acarbose, %	9
Current insulin†, %	1
Other major current treatments	
Aspirin or other anti-platelet, %	47
Lipid-lowering therapy, %	35

*Median and interquartile range presented as the distribution is highly skewed.

†Not prescribed as permanent or long-term therapy.

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