Mount Hood 2023 Challenges

(Type 1 diabetes)

Motivation:

The impact of model uncertainty on cost-effectiveness estimates of diabetes interventions is unknown. The aim of the Mt Hood 2023 challenges is to replicate the Mt Hood 2022 cost-effectiveness challenge set for an Asian Population. We recognise there is substantial intra-regional variation in population characteristics, potential responsiveness to treatment, and the costs and utilities attributed to diabetes and complication events. Nevertheless, the major aim of this challenge is to understand the variability in the predicted cost and effectiveness and incremental cost-effectiveness between models for a cohort with plausible biomarkers and who receive typical interventions and incur plausible costs within this region. This challenge examines the variation in cost-effectiveness of three categories of diabetes interventions for type 1 diabetes compared to traditional care: (1) intervention that reduces blood glucose levels [1]; (2) intervention that reduces blood glucose levels and risk of severe hypoglycaemia [1, 2], and (3) intervention that reduces blood glucose, LDL-cholesterol levels, and risk of hypoglycaemia [1-3]. Differences across model results will be used to understand the impact of model structures on cost-effectiveness estimates within this population.

To aid reporting, please note the information requested in the "Model Description" tab of the Excel file "2023 Mt Hood Asia Challenge Report_TYPE 1 DIABETES.xlsx". For this challenge we have included an additional request for information on whether your model uses ethnicity as a risk factor for diabetes-related complications and mortality, and if so, please report the risk ratios for ethnicity.

Challenge 1: Revisiting the reference simulation on risk factor progression with a new challenge design for type 1 diabetes

We will first ask groups to repeat the reference simulations for a standard patient that were performed in previous challenges and reported in the MT Hood model registry, taking into account the new design for treatment effects that are more relevant for type 1 diabetes. This will enable the simulated changes in risk factor values to be compared across models 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 2018 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 challenge in 2018); and (ii) allowing them to vary using equations or trajectories that are normally used in your simulation model. Treatment effects are assumed to be a constant displacement of risk factors from the usual time paths (i.e., a permanent shift in trajectories).

Challenge 2: Simulating effects of interventions on costs and effectiveness

In previous challenges, treatment costs and effects for type 1 diabetes were assumed to be the same as those for type 2 diabetes, which was not realistic. In this challenge, we assumed the following interventions, which are compared to the traditional care via multiple daily injections of insulin with self-monitoring of capillary blood glucose (MDI): (1) the continuous subcutaneous insulin infusion (CSII) to reduce HbA1c [1], (2) the automated insulin delivery system (AID) including a hybrid closed loop pump (HCL) and a continuous glucose monitoring device (CGM) to reduce HbA1c and risk of severe hypoglycaemia [1, 2], and (3) the lipid-lowering therapy to reduce LDL-cholesterol in addition to the traditional therapy [3]. The effectiveness of CSII and AID were assumed to be changes in HbA1c only and in both HbA1c and risk of hypoglycaemia, respectively, compared to MDI. Effectiveness of the lipid-lowering therapy was assumed to be a change in LDL-cholesterol compared to no therapy. The average treatment effect on risk factor values will be modelled by shifting the trajectory of HbA1c or LDL-cholesterol downward by a constant value. If your model does not simulate changes in LDL-cholesterol, please report this in the tab "Treatment effects and costs" of the Excel file "2023 Mt Hood Asia Challenge Report TYPE 1 DIABETES.xlsx

The treatment effect on the risk of hypoglycaemia will be modelled by reducing the annual risk of hypoglycaemia predicted in the simulation with the traditional therapy (i.e., baseline risk) by a constant proportion (see illustration in Figure 1).

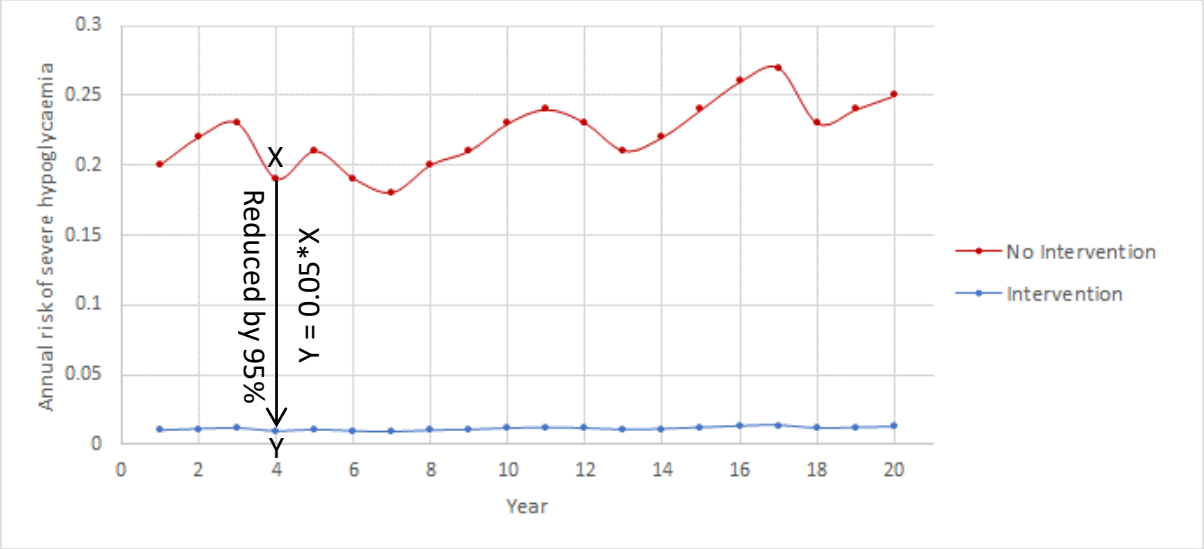

Figure 1. Method for simulating the treatment effect on risk of severe hypoglycaemia, assuming a risk reduction of 95% (i.e., risk ratio associated with the intervention compared to no intervention is 0.05)

If your model does not have a risk equation for severe hypoglycaemia, please use the following steps to calculate the risk of severe hypoglycaemia *in the traditional care arm (i.e., baseline treatment)* between the current age AGE and AGE + c (e.g., c is the cycle length), assuming that DISEASE_DURATION and A1c are diabetes duration and HbA1c at age AGE, respectively. The coefficients were based on a Gompertz proportional hazard model using age as time scale with an origin at age 18 years and fitted to part of the Swedish National Diabetes Register data. To simplify, the model included only four covariates: age in years, male (1 if male and 0 if female), HbA1c in % and disease duration in years.

(a) Calculate the cumulative hazard of severe hypoglycaemia at age AGE:

H(AGE) = (-1/0.07) * {exp[-0.07*(AGE - 18)] - 1} * exp(-7.61 + 0.07*AGE + 0.21*MALE + 0.16*A1c + 0.02*DISEASE_DURATION)

(b) Calculate the cumulative hazard of severe hypoglycaemia at age AGE + c:

H(AGE + c) = (-1/0.07) * {exp[-0.07*(AGE + c - 18)] - 1} * exp(-7.61 + 0.07*AGE + 0.21*MALE + 0.16*A1c + 0.02*DISEASE_DURATION)

(c) Calculate risk of severe hypoglycaemia between AGE and AGE + c:

Probability = 1 – exp{H(AGE) – H(AGE + c)}

If your model does not allow an integration of the above-mentioned steps, please report this in the tab "Treatment effects and costs" of the Excel file "2023 Mt Hood Asia Challenge Report TYPE 1 DIABETES.xlsx".

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

Evidence on disutility values associated with diabetes-related complications in Asian populations with type 1 diabetes is scarce. In this challenge, we use values estimated for European patients based on the reports of a literature review (noting the logical mismatch) (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 disutility values for certain health states (e.g., a raised BMI health state which is independent of BMI's effect on complication events) - please report these disutility values here. To simplify, 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 1 diabetes *		
		Utility/Disutility Values	Lower 95% CI	Upper 95% CI
Baseline utility value	Diabetes without complications	0.900[a]	0.880[a]	0.930[a]
	Major hypoglycemia event	-0.002[b]	-0.004[b]	-0.000[b]
	Major hyperglycemic event	–0.071[c]	-0.116[c]	-0.026[c]
Comorbidity	Excess BMI (each unit above 23 kg/m^2)	-0.005[b]	-0.009[b]	-0.001[b]
Retinopathy	Cataract			
	Moderate non-proliferative background diabetic retinopathy	-0.027[b]	-0.048[b]	-0.005[b]
	Vision-threatening diabetic retinopathy	-0.063[a]	-0.169[a]	0.044[a]
	Severe vision loss	-0.132[d]	-0.163[d]	-0.101[d]
Nephropathy	Proteinuria	-0.028[b]	-0.035[b]	0.09[b]
	Renal transplant	-0.053[e]	-0.077[e]	-0.029[e]
	Hemodialysis	-0.082[e]	-0.128[e]	-0.036[e]
Neuropathy	Peripheral vascular disease	-0.080[d]	-0.117[d]	-0.043[d]
	Neuropathy	-0.236[b]	-0.299[b]	-0.173[b]
	Foot ulcer	-0.083[a]	-0.271[a]	0.105[a]
	Amputation event	-0.117[b]	-0.225[b]	-0.009[b]
Cerebrovascular disease	Stroke	–0.291[a]	–0.475[a]	–0.108[a]
Coronary heart disease	Myocardial infarction	-0.146[c†]	-	-
	Ischemic heart disease	–0.181[a]	–0.331[a]	–0.031[a]
	Heart failure	-0.058[f]	-0.101[f]	-0.015[f]
	Percutaneous revascularization	+0.025[b]	-0.051[b]	0.101[b]
	Coronary revascularization	-0.079[b]	-0.218[b]	0.060[b]

* Compiled by An Tran-Duy (an.tran@unimelb.edu.au). Note that the 95% CIs were not reported in Hart et al (source: e) and Ahola et al (source: f) and were reconstructed based on t-values, p-values, sample sizes and/or standard errors where relevant.

† Based on disutility value associated with a macrovascular complication, as no value was available for myocardial infarction.

Source: [a] Solli et al 2010 based on EQ-5D-3L [4]; [b] Peasgood et al 2016 based on EQ-5D-3L [5]; [c] Hart et al 2003 based on EQ-5D-3L [6]; [d] Tabaei et al [7]; [e] Ahola et al 2010 based on 15D; [f] Coffey et al 2002 based on QWB-SA [8];. These are from studies in patients with type 1 diabetes from US, UK, Norway and Netherlands.

Abbreviations: QoL, quality of life; CI, confidence interval; BMI, body mass index.

Patient Baseline Characteristics

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values as listed in Table 2. If more specific ethnicity categories are available within the simulation model, please select an ethnicity which best matches the "East and South East Asian" ethnicity used for calculation of utilities. In all instances, please report the ethnic population named in your model for which your results are derived. 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 1 diabetes[a]**	
	Men	**Women**
Current age	28	28
Duration of diabetes	8	8
Current/former smoker	N	N
Ethnicity	Asian	Asian
HbA1c. %	8	8
Systolic Blood Pressure, mmHg	120	120
Diastolic Blood Pressure, mmHg	76	76
HDL Cholesterol, mmol/l	1.7	1.7
LDL Cholesterol, mmol/l	2.8	2.8
Triglycerides, mmol/L	0.7	0.7
Total Cholesterol, mmol/l	4.6[b]	4.6[b]
BMI	22.5	22.5
Albumin: creatinine ratio, mg/mmol	1.1	1.1
PVD	N	N
Micro or macro albuminuria (albuminuria >50)	N	N
Atrial fibrillation	N	N
eGFR (ml/min/1.73 m2)	143	143
Prior history of macrovascular disease	N	N
Prior history of microvascular disease	N	N

[a] Based on Luk et al 2014 (https://doi.org/10.2337/dc13-1336) and Tang et al 2019 (https://doi.org/10.2147/DMSO.S202193) and opinion of experts in endocrinology; [b] Calculated as HDL cholesterol + LDL cholesterol + 0.2*Triglycerides.

Costs

The perspective of the cost analysis is a representative Asian health care system. As there are no comprehensive studies on costs of complications in Asian patients with type 1 diabetes, in this challenge we used mean complication costs of Asian patients with type 2 diabetes obtained from the ADVANCE study cost calculator (Table 3). Please apply the same set of complication costs for both men and women.

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.

To simplify, 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 (US $)

	Year of Event	Cost in subsequent years	Source
Myocardial Infarction	9,804	6,623	[9]
Ischaemic Heart Disease	5,530	4,817	[9]
Heart Failure	5,194	6,262	[9]
Cerebrovascular Disease	4,091	5,357	[9]
Peripheral Vascular Disease	4,246	4,806	[9]
Neuropathy	3,643	4,612	[9]
Amputation	5,932	-	[9]
Renal Failure	2,653	3,804	[9]
Cataract	1,556	-	[9]
Retinopathy	3,971	4,858	[9]
Haemodialysis	11,775	20,027	[9]
Coronary revascularisation	8,707[a]	6,623[b]	[10]
Severe hypoglycaemia	1,378	0	[11]

[a] Average of the costs incurred by groups with high and low risk of mortality.

[b] Assuming the same cost as that of myocardial infarction.

Table 4. Mean intervention effects and costs (US $) (assume applied every year while patients are alive in the simulation)

Intervention	Mean relative effect compared to the traditional therapy (baseline)	Mean absolute annual cost ($)*
Intervention 1 (Continuous subcutaneous insulin infusion)	0.24% **point reduction** in HbA1c [12]	2,500
Intervention 2 (Integrated system of automated insulin delivery pump and continuous glucose monitoring device)	0.87% **point reduction** in HbA1c [13] and 95% **reduction** in the annual risk of severe hypoglycaemia [14-16]	6,000
Intervention 3 (Lipid-lowering therapy in addition to the traditional therapy)	1 mmol/L **reduction** in LDL-cholesterol [17]	300 + 1,500
Comparator (Tradition therapy, i.e., multiple daily injections)	-	1,500

* Based loosely on [12-21] and https://eshop.medtronic-diabetes.co/en/view/content

Challenge simulation

Step 1: Run a simulation using the baseline risk factors from Table 2 held constant over a 80-year period for type 1 diabetes, separately for males and for females. For models that do not support a time horizon of 80 years or longer, please use the longest possible duration and report this.

This simulation is similar to 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 for the first three interventions and then combination of intervention 2 and 3), separately for males and

females, that capture initial and permanent reductions in HbA1c and/or LDL-cholesterol values from time paths modelled in Step 1. Reductions from these risk factors should only be applied to post-baseline cycles, and baseline values should remain unchanged.

1. **Intervention 1**: 0.24% point reduction in HbA1c;
2. **Intervention 2:** 0.87% point reduction in HbA1c and 95% **reduction** in the annual risk of severe hypoglycaemia;
3. **Intervention 3:** 1 mmol/L (38.67 mg/dl) reduction in LDL-cholesterol
4. **Intervention 4:** Combination of Intervention 2 and Intervention 3 (i.e., 0.87% point reduction in HbA1c, 95% **reduction** in the annual risk of severe hypoglycaemia, and 1 mmol/L (38.67 mg/dl) reduction in LDL-cholesterol)

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 in Step 1 and estimate expected QALYs, assuming that decrements apply to the year of the 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 or weeks following 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 – Step 1,2&3").

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, e.g., 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 (see illustration in Figure 2).

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

Then, using the "Utility/disutility" values in Table 1, run the baseline simulation in Step 1 and simulations for four interventions in Step 2 using actual risk factors time paths to estimate the expected QALYs and calculate the incremental QALYs compared to the baseline (control).

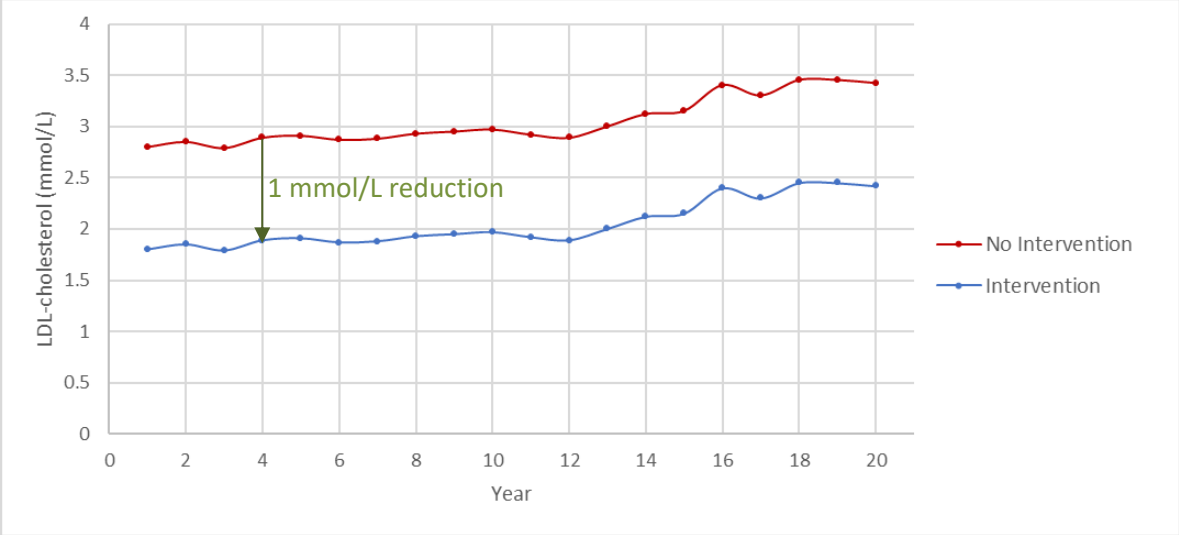

Figure 2. Method for simulating the treatment effect on LDL-cholesterol.

Extract the results and add to the accompanying Excel workbook (in tab labelled "Time paths & Outcomes – Step 4". 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 containing both 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: Estimate incremental QALYs, incremental costs and Incremental cost-effectiveness ratios (ICERs) for patients with no history of myocardial infarction

Re-run the simulation with two hypothetical interventions affecting HbA1c only (Intervention 1 in Table 4) and both HbA1c and risk of hypoglycaemia-cholesterol (Intervention 2 in Table 4). This is similar to the simulation in Step 2 but only the first two interventions are used and the cohort contains both males and females. Table 4 presents the relative effects of the interventions and the respective absolute 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 should be kept constant over time and not allowed to change over time (i.e., no drift over time).

Please apply the same effect and annual costs for both men and women over the whole simulation period. Costs of treatment are unchanged by the occurrence of complications. Assume that the interventions will have no effect on any risk factors other than HbA1c, and no effect on risks of any complications other than hypoglycaemia. Finally, assume adherence to each intervention to be 100% during the whole simulation period. Although the interventions are hypothetical, their effects are loosely based on the literature [12-16, 18-21] and https://eshop.medtronic-diabetes.co/en/view/content.

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 "Asian" perspective, using and reporting costs in US dollars ($) 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.

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, incremental costs and ICERs for patients with a history of myocardial infarction (optional)

Re-run the simulation in Step 5 but now for a cohort of patients with a history of myocardial infarction (MI). If your model requires a number of years since the event, please use 5 years since MI for all patients. Re-run for each of the four 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").

Summary of findings:

Compile a summary of your findings in the accompanying Excel spreadsheet (in tab labelled "Summary"). In this challenge the willingness-to-pay threshold is assumed to be $12,618 per QALY based on China´s GDP per capita in 2021 ($12,618; see https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=CN). Please complete the following.

A) Based on your results in Step 5, which intervention(s) were costs-effective at a $12,618 per QALY threshold?
B) Based on your results in Step 7, report which intervention(s) were costs-effective at a $12,618 per QALY threshold?
C) Summarize what you learnt from this challenge.

Submission:

Prior to the meeting, please submit the Excel spreadsheet ("GROUP_2023 Mt Hood Asia Challenge Report_TYPE 1 DIABETES.xlsx") to the Mount Hood challenge network at: mthood2016@gmail.com by **24 November 2023.** Please replace GROUP with your modelling group name before submission.

References

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