9th Mount Hood Diabetes Conference
Quality of Life Challenge

Motivation:

The purpose of this challenge is to examine the magnitude of impact of different aspects of quality of life on incremental health economics outcomes associated with common diabetes interventions. To ensure the simulations are relevant to common economic evaluations, the challenge will employ the average values for characteristics of patients enrolled in RCTs of common diabetes therapies. The average treatment effects will be modelled by permanent reductions in common risk factors including: (i) HbA1c; (i) systolic blood pressure; (iii) LDL cholesterol; and (iv) body mass index. Simulations will be undertaken for both men and women with the same characteristics.

This challenge is intended to form the basis of publication centred around understanding the elasticity of incremental estimated QALYs with respect to utility weights in diabetes models; i.e. the degree to which changes in utility weights affect QALYs.

The exercise will allow us to assess this by looking at what factors, and to what extent, have the greatest influence on incremental QALYs associated with common interventions used to treat people with diabetes.

An Excel spreadsheet accompanying these instructions (MH9 CHALLENGE – QOL.xlsm) is provided for the documentation of inputs and simulated outcomes.

Model Description:

We acknowledge that different models incorporate utilities in different ways (e.g. some assume additive effect, while others assume a multiplicative effect). The purpose of this exercise is **not** to standardize how health state utilities are incorporated into models, but to look at the sensitivity of changes in utilities for common health states and QALY outcomes in models as they are currently used in practice.

For transparency it would be useful to describe how utilities are incorporated into different diabetes models. Please provide the following information in the accompanying Excel spreadsheet (in tab labelled "Model Description"). These will be used to form a table in the manuscript.

(i) What health states have a utility in your model;

(ii) What values are typically assumed for each health state (provide point estimates and/or ranges). If these have varied over time, what values were used in the most recent published economic evaluation that involved a QALY simulation of the model. Please provide references of the source of the utilities where available.

(iii) In 150 words (or less) succinctly describe how quality of life is modelled (e.g. are changes in utilities assumed to have an additive or multiplicative effect on QALY outcomes).

Model Inputs:

Utility Values

To examine the effect of different assumptions regarding quality of life's impact on outcomes, we will run the same simulation with a variety of different assumptions regarding the utility associated with health states (such as diabetes-related complications). These values have been chosen to reflect high/low and average values from the literature. Utility values (Figure 1) from a recent systematic review (Beaudet et al., 2014) should be used for this challenge. In this challenge, it would be adequate to use point estimates and not model 2nd order uncertainty.

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

Figure 1: Utility values used to populate model

Table 3 – Preferred utility values for modeling complications associated with T2DM.

Parameter	Proposed reference	Proposed utility value	95% CI	Range of candidate values
T2DM without complication	Clarke et al. [21]	0.785	0.681–0.889	0.690–0.940
Myocardial infarction	Clarke et al. [21]	−0.055	−0.067 to −0.042	−0.059 to −0.007
Ischemic heart disease	Clarke et al. [21]	−0.090	−0.126 to −0.054	−0.090 to −0.027
Heart failure	Clarke et al. [21]	−0.108	−0.169 to −0.048	−0.108 to −0.051
Stroke	Clarke et al. [21]	−0.164	−0.222 to −0.105	−0.164 to −0.070
Severe vision loss	Clarke et al. [21]	−0.074	−0.124 to −0.025	−0.070 to −0.012
Amputation event	Clarke et al. [21]	−0.280	−0.389 to −0.170	−0.280 to −0.063
Peripheral vascular disease	Bagust and Beale [22]	−0.061	−0.090 to −0.032*	−0.186 to −0.061
Proteinuria	Bagust and Beale [22]	−0.048	−0.091 to −0.005*	One reference identified
Neuropathy	Bagust and Beale [22]	−0.084	−0.111 to −0.057*	−0.247 to −0.050
Active ulcer	Bagust and Beale [22]	−0.170	−0.207 to −0.133*	−0.206 to −0.016
Excess BMI (each unit above 25 kg/m^2)	Bagust and Beale [22]	−0.006	−0.008 to −0.004*	−0.006 to −0.002
Hemodialysis	Wasserfallen et al. [23]	−0.164	−0.274 to −0.054*	One reference identified
Peritoneal dialysis	Wasserfallen et al. [23]	−0.204	−0.342 to −0.066*	One reference identified
Renal transplant	Kiberd and Jindal [26]	0.762	0.658–0.866	0.762–0.820
Cataract	Lee et al. [32]	−0.016	−0.031 to −0.001*	One reference identified
Moderate nonproliferative background diabetic retinopathy	Fenwick et al. [24]	−0.040	−0.066 to −0.014†	One reference identified
Moderate macular edema	Fenwick et al. [24]	−0.040	−0.066 to −0.014†	One reference identified
Vision-threatening diabetic retinopathy	Fenwick et al. [24]	−0.070	−0.099 to −0.041†	−0.070 to −0.012
Major hypoglycemia event	Currie et al. [18]	−0.047	−0.012‡	−0.020–0.005‡
Minor hypoglycemia event	Currie et al. [18]	−0.014	−0.004‡	−0.031 to −0.001‡

CI, confidence interval; T2DM, type 2 diabetes mellitus.
* Estimated from the standard error values provided.
† Estimated from the interquartile range values provided.
‡ Disutilities converted into annual values.

Source: Table 3 from Beaudet et al. "Review of utility values for economic modeling in type 2 diabetes." Value in Health 17.4 (2014): 462-470
https://www.valueinhealthjournal.com/article/S1098-3015(14)00054-0/pdf

Patient Baseline Characteristics

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values as listed in Table 1. 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).

If possible, please email the covariate, covariate value, and suggested source in advance to Michelle Tew (michelle.tew@unimelb.edu.au), who can cumulate responses and redistribute to the groups to ensure greater standardization. This should be provided within 1 week of challenge instruction dissemination.

Table 1: Characteristics of a representative patient to be used in the simulations

Patient Characteristics	**Men**	**Women**
Current age	66	66
Duration of diabetes	8	8
Current/former smoker	N	N
HbA1c %	7.5	7.5
Systolic Blood Pressure mmHg	145	145
Diastolic Blood Pressure mmHg	80	80
Total Cholesterol mmol/l	5.2	5.2
HDL Cholesterol mmol/l	1.3	1.3
LDL Cholesterol mmol/l	3.0	3.0
BMI	28	28
Albumin: creatinine ratio	14.2	14.2
PVD	N	N
Micro or macro albuminuria (albuminuria ≥50)	N	N
Atrial fibrillation	N	N
eGFR (ml/min/1.73 m^2)	70	70
WBC (x10^9/l)	7	7
Heart rate (bpm)	79	79
Haemoglobin (g/dl)	14	14
Prior history of macrovascular disease	N	N
Prior history of microvascular disease	N	N

Source: ADVANCE—Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline; see Appendix 1 for summary table

It is important in each simulation all other factors are kept constant between simulations and limit variation to the utility weights as per instructions in the steps below. This includes assumptions around biomarker evolution; i.e. HbA1c and systolic blood pressure to be kept constant over time and not allow for evolution.

The main outputs required will be incremental **undiscounted** QALYs. As such, please set the discount rate to 0% for QALYs prior to running the simulations.

Challenge Simulations:

Step 1: Run a simulation using the baseline characteristics in Table 1 held constant over a 40-year period, separately for males and for females

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: Simulate four common interventions (plus all combined), separately for males and females

Re-run the simulation with four individual interventions (one-at-a-time and then all combined) 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 interventions combined

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 "Proposed Utility Value" from Figure 1 run the baseline simulation and estimate expected QALY, 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").

Step 4: Estimate incremental QALYs under different assumption regarding utility, separately for males and females

Repeat the simulation in Step 3 using different utility weights:

4.1 Low estimates of QALY: Use the lower limits of the 95% CIs for **All** utility values listed in Figure 1.

4.2 *High estimates of QALY*: Use the upper limits of the 95% CIs for **All** utility values listed in Figure 1

Step 5: Identify how much each utility value contributes to incremental QALYs

The final set of estimates will involve **only the first intervention (0.5%-point reduction in HbA1c).** It will involve varying each of the health state utility values in your model one at and time using the

lower and upper limits of the 95% CIs to determine the sensitivity of incremental QALYs to changes in the utility value associated with each health state.

Step 6: (Optional)

Re-run Steps 1 and 2, but instead of using 0.785 for people without complications, use 0.681 (the lower limit of the 95% CI). Repeat this simulation for an intervention involving **0.5%-point reduction in HbA1c.** Record incremental QALYs for each change in utility compared to baseline (control).

Repeat the above in a second simulation using 0.889 (the upper limit of the 95% CI) and record incremental QALYs as per above.

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 3, which intervention evoked the greatest change in incremental QALY?
B) Based on your results in Step 5, list three health states which evoked the greatest change in incremental QALY and the health state inducing the least change.
C) Provide an overview of what you learnt from this challenge.

Submission:

Prior to the meeting, please submit the Excel spreadsheet ("MH CHALLENGE 9 – QOL Challenge_GROUP") to Mount Hood at: mthood2016@gmail.com by **September 21, 2018**. 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.