Te Whatu Ora
Health New Zealand

Cost-Utility Analysis of Diabetes Remission in People Recently Diagnosed with Type 2 Diabetes

Counties Manukau
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Executive Summary

People with type 2 diabetes mellitus can achieve remission (<48 mmol/mol) and improve their glycemic control through weight loss using a low calorie diet. In other settings (United Kingdom), the cost-effectiveness of diabetes reversal has been established. The purpose of the current model is to adapt the United Kingdom Prospective Diagnostic Study (UKPDS) Outcomes Model (OM) 2 and assess the cost-effectiveness of diabetes reversal in the Counties Manukau (CM) District[1] setting.

Three scenarios were tested using a life-time horizon:

Scenario 1. The cost-effectiveness of diabetes remission (to 42 mmol/mol) was assessed in individuals with poorly controlled diabetes at 75 mmol/mol

Scenario 2. As 1, but further adjusting complication risks to assess the equitable impact of diabetes reversal on Maaori and Pacific

Scenario 3. Assesses the impact of good glycemic control (48 mmol/mol) and weight loss maintained for five years in people with HbA1c of 64 mmol/mol, i.e. delayed progression of HbA1c and BMI.

The estimates reported are life-expectancy, quality-adjusted life-years (QALYs) and costs, used to calculate the incremental net-monetary benefit (NMB) to assess cost-effectiveness. Wider personal and social benefits are not included.

Scenario 1 found for a 50-year-old European/Other male, the intervention is estimated to gain 0.73 year of life-expectancy and after adjusting for quality of life, 0.33 years of full health with lower life-time health costs ($3,848). The incremental NMB suggests the District could invest up to $13,854 to achieve this benefit (Table 1) and still consider itself in the good value-for-money zone. Ethnic-specific analysis for Maaori (Table 11) and Pacific (Table 12) estimated higher benefits and incremental NMB than European/Other - $15-20,000, so an even better value-for-money range. Lastly, the impact of well controlled diabetes is reported in Scenario 3 (Table 1), suggesting similar cost-effectiveness.

Taking a (conservative) willingness to pay $30,000 per QALY, this study suggests that the District should be willing to invest up to $14,000 per European/Other person and higher for Maaori/Pacific to reverse diabetes purely on the direct health outcomes achieved, and the avoidance of healthcare costs through the reduction of complications of diabetes. The higher complication rate currently seen for Maaori and Pacific people with diabetes, particularly renal complications, drive a higher life

[1] Prior to July 2022 known as Counties Manukau District Health Board; now termed *Te What Ora Counties Manukau*, a District of Te Whatu Ora Health New Zealand.

expectancy and QALY gain on reversal. This demonstrates Te Tiriti and an equity driven approach would see the District wanting to prioritise diabetes reversal for Maaori and Pacific; this study suggests there is also a financial incentive to do so.

This study did not assess the wider benefits of HbA1c reduction and weight loss beyond diabetes and its complications (e.g. impact on cancers), nor did it look beyond the health system. It thus significantly under-estimates the overall benefit.

Table 1 Incremental NMB for diabetes and weight related interventions at $30,000 Willingness to Pay (WTP) threshold in the CM District setting

	Maaori	Pacific	European/ Other	Asian-Indian
Scenario 1 Diabetes Reversal				
Incremental Life expectancy	0.98	1	0.73	0.88
Incremental QALYs	0.44	0.42	0.33	0.35
Incremental Costs	$ (771)	$ (1,517)	$ (3,848)	$ (1,452)
Incremental NMB	$ 13,934	$ 14,189	$ 13,854	$ 11,919
Scenario 2 Diabetes Reversal in Maaori and Pacific populations				
Incremental Life expectancy	1.19	1.08		
Incremental QALYs	0.60	0.56		
Incremental Costs	$ (2,664)	$ 882		
Diabetes Reversal equitable impact	$ 20,558	$ 15,885		
Scenario 3 Good HbA1c control				
Incremental Life expectancy	1.11	0.89	0.81	0.56
Incremental QALYs	0.51	0.40	0.34	0.28
Incremental Costs	$ (3,176)	$ (2,189)	$ (2,469)	$ (6,256)
Incremental NMB	$ 18,572	$ 14,139	$ 12,524	$ 14,507

Introduction

Type 2 diabetes mellitus is a significant population health issue as 5% of the New Zealand population is suffering from type 2 diabetes currently; and this number is projected to increase by 70-90% within the next 20 years.[2] Maaori, Pacific and Indian populations are disproportionately represented in the diabetes population.[3] Specifically, CM District (formerly Counties Manukau DHB) has more people with high BMI and diabetes than any other Te Whatu Ora District with a net increase of 2,000 people with diabetes each year. It can lead to loss of healthy life years, reduce life expectancy and increase burden on the patient as well as the health system.[4]

A computer-simulation model can be used to evaluate the clinical benefits and economic costs of health interventions. By assessing the impact of interventions on risk factor levels and the progression of type 2 diabetes, it allows estimation of long-term outcomes including the occurrence of diabetes complications (Table 2) and death. This also allows estimation of life expectancy, quality-adjusted life-years (QALYs) and costs associated with diabetes complications. A cost-effectiveness analysis using this information can support decision-making in the health-care settings.[5] This is particularly relevant for chronic and progressive conditions where the time horizon of interest exceeds the length of clinical trials. Health economic models fill this gap by estimating the costs and benefits of new interventions and comparators across the appropriate time horizon to inform resource allocation.[6]

Table 2 List of diabetes-related complications included in the model

Ischemic Heart Disease (IHD)	Myocardial Infarction (MI)	Stroke	Congestive Heart Failure (CHF)	Diabetic Ulcer	Amputation	Blindness[7]	Renal Failure

[2] PwC (2021). *The Economic and Social Cost of Type 2 Diabetes*.

[3] Singh, H, Papaconstantinou D, Chan WC. (2022) Cardiovascular Disease in the Northern Region, in publication.

[4] Zhang, P., & Gregg, E. (2017). Global economic burden of diabetes and its implications. *The Lancet. Diabetes & Endocrinology*, *5*(6), 404-405

[5] Hayes, A. J., Leal, J., Gray, A. M., Holman, R. R., & Clarke, P. M. (2013). 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*, 56(9), 1925-1933.

[6] Palmer, A. J., Si, L., Tew, M., Hua, X., Willis, M. S., Asseburg, C., ... & Clarke, P. M. (2018). Computer modeling of diabetes and its transparency: a report on the eighth mount hood challenge. *Value in Health*, *21*(6), 724-731.

[7] Blindness in one eye only persisting for three months in the original UKPDS OM 2 but expanded with an ongoing utility detriment beyond the first year.

Note: Second events for myocardial infarction, stroke and amputation are also included.

To do this, a previously-published model was adapted for use in CM District. The United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (OM) 2 is based on patient-level data from 5,102 participants with newly diagnosed type 2 diabetes mellitus and followed over a 20-year trial period. Additionally, 4,031 participants were followed over a 10-year post-trial monitoring period. The new version (updating the 2004 UKPDS – OM 1) was developed using additional data and outcomes.

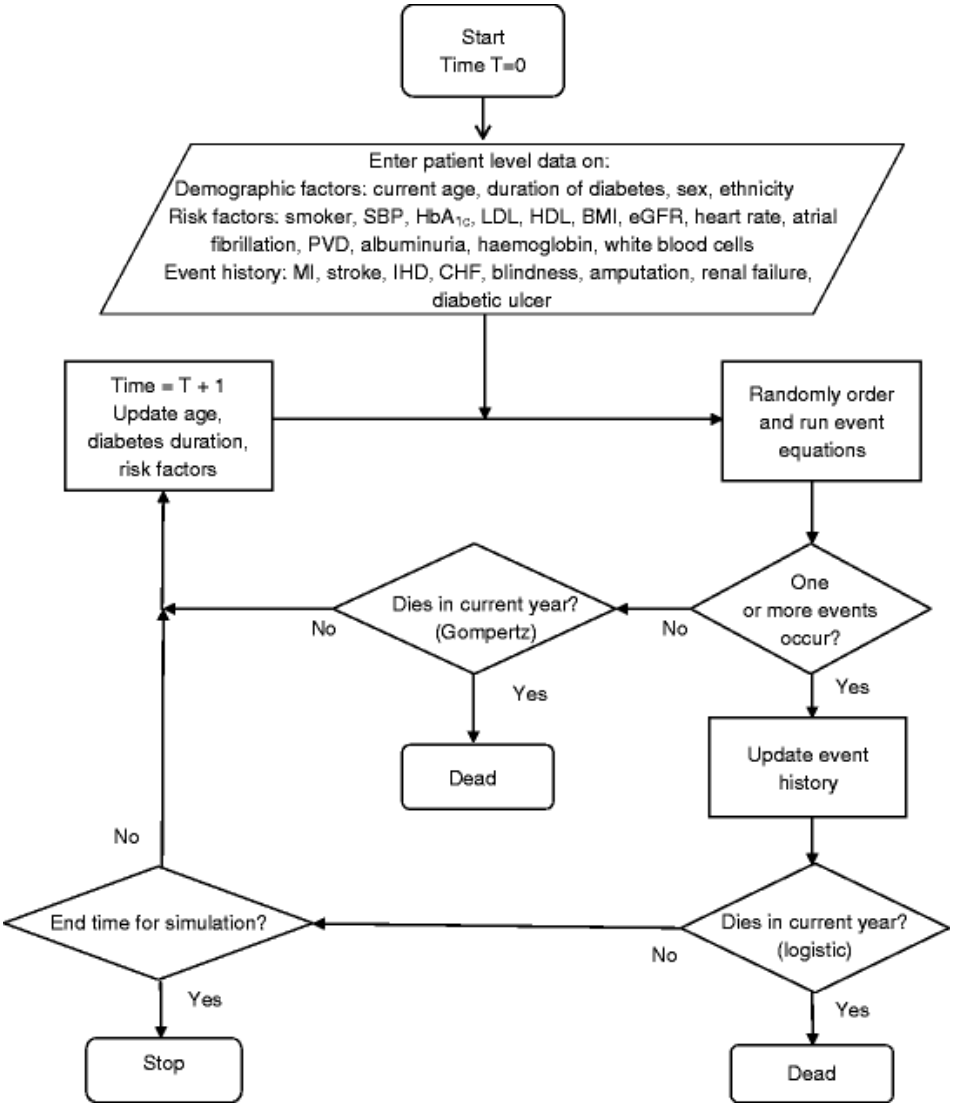
The main objectives of this modelling exercise are to replicate the UKPDS OM 2 in the CM District setting, including adjustments to transition probabilities to ensure generalisability to local population. The model also assesses the impact of diabetes reversal in the CM District setting by ethnicity. The base-case scenario assumes European/Other is the same as Caucasian population in UKPDS study and adjustments for Maaori and Pacific ethnic groups are included as relative risks within the various Scenarios.

Modelling Methods

Model Structure

Following the UKPDS OM model, a patient-level simulation model was created in Microsoft Excel to estimate major diabetes-related complications for adults with type 2 diabetes aged 30 years and above. The model considered outcomes over a lifetime horizon (to 100 years) using annual cycles.

Figure 1 Flowchart showing structure of the UKPDS OM 2 model



Source: Hayes et al.[5]

Mortality and Risk Equations

To predict how patients move through this algorithm, the model uses a series of parametric risk equations for eight diabetes-related complications, three second event equations and four mortality equations. Figure 1 shows the structure of the simulation model. Table 3 shows the inputs at patient level data on demographic factors clinical risk factors and event history.[5] Hence, the patient is included with predefined health risk factors and can experience one or more nonfatal diabetes-related complications and/or die in any cycle.

Table 3 Model Inputs for UKPDS OM 2

Demographic Factors	Clinical Risk Factors	Event History	
Current age	Systolic blood pressure (SBP)	MI	
Duration of diabetes	HbA1c	Stroke	
Gender	Low-density lipoprotein (LDL)	IHD	
Ethnicity	High-density lipoprotein (HDL)	CHF	Appendix A lists the functional form and parameters for both complication and mortality risk equations used in this model. After each period in which the patient survives,
Smoking status	Body mass index (BMI)	Blindness	
	Estimated glomerular filtration rate (eGFR)	Amputation	
	Heart rate	Renal failure	
	Atrial fibrillation	Diabetic ulcer	
	Peripheral vascular disease (PVD)		
	Albuminuria		
	Haemoglobin		
	White blood cells		

patient history (i.e. age, diabetes duration, clinical risk factor values and event histories) is updated and this then informs the risk equations in the future cycles. If the patient experiences a complication, a permanent utility decrement is applied for the event and for complication history until death. When the model predicts the patient dies, the cycle number at death is used to calculate life expectancy and the sum of utility detriments is subtracted from the total QALYs. Similarly, the costs associated with complication event and history are accumulated each year until the end of simulation (death).[5]

Within the UKPDS OM 2, the mortality risk is estimated using four risk equations for all-cause mortality accounting for patient's history and complication status covering the cases where (1) patients have no current/prior complications, (2) patients have experienced any MI, stroke, IHD, CHF, amputation or renal failure in this year but had no prior history of any events, (3) patients have prior history of any MI, stroke, IHD, CHF, amputation or renal failure in this year but have no new complications and (4) patients have prior history of a complication and are also experiencing a new or recurrent event. Not all complications will affect the estimated death rates as Hayes et al[5] found that blindness and ulcer events were not associated with mortality in the first year of event.

Impact of Diabetes Risk Factors

UKPDS OM 2 includes risk factors for SBP, HbA1c, LDL, HDL, BMI, eGFR, heart rate, atrial fibrillation, PVD, albuminuria, haemoglobin and white blood cells. These risk factors are assumed to increase over-time, and the model presented here uses risk factor progression equations published in a paper by Leal et al,[8] estimated using patient-level data from UKPDS trial and 10-years post-trial monitoring period. Appendix B lists the parameters used for the progression of risk factors.

UKPDS vs CM District UKPDS version

There are key differences between the UKPDS OM 2 and the model used to predict outcomes for CM District. Firstly, the UKPDS OM 2 considers events sequentially where each event is considered separately so that a new event/complication may affect the probability for all other subsequent events/complications in this period. This is done in a random order to allow the probabilities of each complication to affect subsequent complications in turn. For example, if stroke occurs first, its probability (and uncertainty) is resolved and might affect amputation without a prior ulcer. This is computationally challenging and the model presented here instead considers event probabilities based on previous period's history only, rather than any 'new' history in this period. This means, if there is a stroke this period, it does not affect the probability of anything else, underestimating the chances of complications happening. This may have a marginal impact on estimated life expectancy.

Health utilities

Utilities are preference values that individuals attach to their health state from 0 (representing the worst health state) to 1 (perfect/full health). These utility values are used to calculate QALYs by multiplying the life-years by the health-related quality of life (weighted according to the associated utility score).[9] The UKPDS OM 2 starting utility of 0.807 is sourced from the United Kingdom population of people with diabetes. Table 4 shows the utility detriments applied in UKPDS OM 2 in the event year and subsequent years. The detriments for MI, IHD, stroke, amputation, CHF were

[8] Leal, J., Alva, M., Gregory, V., Hayes, A., Mihaylova, B., Gray, A. M., ... & Clarke, P. (2021). Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). *Diabetic Medicine*, *38*(10), e14656.
[9] Virgili, G., Koleva, D., Garattini, L., Banzi, R., & Gensini, G.F. (2010). Utilities and QALYs in health economic evaluations: glossary and introduction. *Internal and emergency medicine, 5*(4), 349-352.

derived from UKPDS patients[10] and values for renal failure and ulcer are from a meta-analysis on quality of life studies.[11]

Table 4 Utility detriments for diabetes-related complications from UKPDS

	UKPDS OM 2		NZ Equivalent		Current Study	
	Event	Subsequent Years	Event	Subsequent Years	Event	Subsequent Years
IHD	0	0			-0.08	-0.08[12]
MI	-0.065	0			-0.074[12]	0
Heart failure	-0.101	-0.101	-0.192	-0.192	-0.192	-0.192
Stroke	-0.165	-0.165			-0.165	-0.165
Amputation	-0.172	-0.172			-0.172	-0.172
Blindness	0	0	-0.060	-0.060	-0.060	-0.060
Renal failure	-0.33	-0.33			-0.33	-0.33
Ulcer	-0.21	-0.21			-0.21	-0.21

The initial comparison (validation) testing model outputs assumed utility detriments as per the UKPDS OM 2. The middle section in Table 4 provides NZ equivalents of the detriments reported by Alva et al[10] and Lung et al.[11] The third section in Table 4 details the utilities used in the current analysis (Scenarios and sensitivity analysis). For complications where NZ equivalent weights were not available, UKDPS OM 2 are assumed. Note that whilst the UKPDS OM2 model does not include a utility detriment (or disutility) for IHD and blindness, disutility values exist for these issues in NZ and

[10] Alva, M., Gray, A., Mihaylova, B., & Clarke, P. (2014). The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. *Health economics*, *23*(4), 487-500.

[11] Lung, T. W., Hayes, A. J., Hayen, A., Farmer, A., & Clarke, P. M. (2011). A meta-analysis of health state valuations for people with diabetes: explaining the variation across methods and implications for economic evaluation. *Quality of Life Research*, *20*(10), 1669-1678.

[12] Global Burden of Disease Collaborative Network. *Global Burden of Disease 2019 (GBD 2019) Disability Weights*. Seattle, United States of America. Institute for Health Metrics and Evaluation (IHME), 2020.

are used in this model.[13] The same utility detriments are assumed for males and females and for all ages.

Cost of diabetes-related complications

All costs in the model are presented as 2021 NZ Dollars as a base year. The cost of diabetes each year is estimated at $4,519 in 2019 based on local data.[14] This was inflated by $428 to $4,947 for the 2021 base year using Reserve Bank of New Zealand inflation calculator.[15] The cost estimates for health care utilisation for each diabetes-related complication were extracted from all-NZ public hospitalisation data from the National Minimum Datasets (NMDS) with the base year 2021. It is assumed first and second events for MI and stroke carry the same costs. To calculate health care costs in the years following an event(s), UKPDS OM 2 default costs from the model were used a guide. The subsequent year(s) cost for each complication were divided by the cost of the event. The calculated proportions were multiplied to the complication costs estimated from the hospitalisation data. For example, UKPDS OM 2 estimates the cost of a MI in the event year is Great Britain Pound (GBP) 6,775 and in following years GBP 1,397, meaning the cost associated with MI in the following year(s) is 0.21 (1,397/6775) of the event cost. The calculated proportions were used to estimate costs in subsequent years for each complication in NZ.

Costs for diabetes complications vary significantly by ethnicity, therefore, costs by ethnicity were used as formulas in the model. The estimated costs for each one of the complications are provided in Appendix C.

Net Monetary Benefit (NMB)

Most cost-effectiveness analyses report the incremental cost-effectiveness ratio (ICER), however, the costs for diabetes reversal and other hypothetical treatments (Scenarios) are not included in the analysis. In such cases, NMB provides an indication of the benefit of treatment, and so the maximum additional costs that it would be cost-effective to pay to gain those benefits (with equity concerns potentially increasing this amount). For example, if the net benefit is $2,000, a hypothetical treatment costing $2,000 or less per person to get that impact will be cost-effective.

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[13] Blakely T, Foster R, Wilson N, and BODE3 Team. (2012). *Burden of Disease Epidemiology, Equity and Cost-Effectiveness (BODE3) Study Protocol. Version 2.0*. Wellington: Department of Public Health, University of Otago.

[14] Jackson, G., Chan, WC., & Papaconstantinou P. (2019) *Cost-effectiveness of diabetes reversal*. Counties Manukau Health internal document.

[15] Reserve Bank of New Zealand (2022). *Inflation Calculator.* https://www.rbnz.govt.nz/monetary-policy/about-monetary-policy/inflation-calculator

Therefore, to assess the cost-effectiveness of interventions, NMB is reported for the intervention arm as well as the comparator. NMB is calculated by multiplying the QALYs by the value of the cost effectiveness threshold (λ) (maximum amount a decision-maker is willing to pay for 1 unit of health outcome [QALY]) and then subtracting the cost from the result. Incremental NMB is calculated by multiplying the incremental QALYs by the value of the cost-effectiveness threshold minus the incremental costs. It is the monetary value of the additional benefit of the new technology after the incremental costs have been netted out.**Error! Bookmark not defined.**

No official 'willingness to pay' (WTP) threshold exists for New Zealand. Analysts often 'back-calculate' from Pharmac data on the incremental spend each year to derive an estimate for the health system at large.[16] Of course Pharmac has many other considerations apart from cost-per-QALY in its funding decisions[17], but even Treasury's CBAx Tool[18] uses this method, suggesting $32,258 as the average amount invested by Pharmac to achieve a gain of one QALY in 2020, adjusted for inflation to 2021-dollar terms. World Health Organisation suggests using GDP per person as a threshold for each country, which would be more than $63,000 for New Zealand. For the purposes of this study we use $30,000 as a conservative round number.

Demography

Statistics NZ defines ethnicity as 'the ethnic group or groups that people identify with or feel they belong to' and 'a measure of cultural affiliation, as opposed to race, ancestry, nationality or citizenship'. Ethnicity in this analysis is defined at the first level for European, Maaori and Pacific. While Asian is also included in Level 1 ethnicity classification, Asian-Indian is used as UKPDS OM 2 and includes this population group in the parametric equations. This was considered necessary given the disproportionate burden of diabetes experienced by NZ Indians in the Asian ethnic group, and the size of the Indian population in Counties Manukau. The scenario analysis used PREDICT-1 baseline characteristics for the diabetes sub cohort as a source for age, type 2 diabetes duration, SBP and eGFR.[19] The UKPDS model does not account for socioeconomic deprivation for calculating risk of complications. Therefore, deprivation is not included in this analysis.

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[16] For example Barton B, Love T. *Economic impact of excess weight in Aotearoa*. Sapere Sept 2021 hapai.co.nz/sites/default/files/Economic-Impact-of-Excess-Weight-in-NZ-15-Nov-2021.pdf

[17] Metcalfe, S, Rodgers A, Werner R, Schousboe C. 2012 PHARMAC has no cost-effectiveness threshold. *NZ Med J* 2012 (24 Feb); 125: 99-101

[18] The Treasury (2021). *CBAx Tool User Guidance*. www.treasury.govt.nz/publications/guide/cbax-tool-user-guidance Sept 2021

[19] Pylypchuk, R., Wells, S., Kerr, A., Poppe, K., Harwood, M., Mehta, S., ... & Jackson, R. (2021). Cardiovascular risk prediction in type 2 diabetes before and after widespread screening: a derivation and validation study. *The Lancet*, *397*(10291), 2264-2274.

Scenarios considered

The results begin with a comparison between this model and the UKPDS OM 2, followed by a one-way sensitivity analysis of the risk-factors driving outcomes (life expectancy). Scenario 1 assesses the value of diabetes reversal in people with poorly controlled diabetes, followed by an equitable ethnicity-specific analysis for Maaori and Pacific people in Scenario 2. Scenario 3 focuses on well controlled HbA1c levels for people recently diagnosed with diabetes, using initial HbA1c levels from PREDICT study. The outcomes reported in scenario analyses include life expectancy, QALYs, NMB and incremental NMB at $30,000 WTP threshold.

Results

1. Testing model outputs compared with UKPDS OM2

Appendix D lists the patient risk-factor profile and life-expectancy and QALY estimates with different HbA1c values used for model validation. Table 5 shows the estimates for the well-controlled person with 58 mmol/mol HbA1c vs a person with the same characteristics but with 97 mmol/mol HbA1c for a Caucasian male. Appendix D includes figures showing the convergence of mean for life expectancy for 8,000 loops. Compared to UKPDS OM 2 example, the difference in life expectancy of 1.5 years and 1.21 QALYs is comparable as the suggested difference in life expectancy is 1.3 years. While the difference between patients with a lower and higher HbA1c is comparable, the actual values for life expectancy and QALYs are lower, this may be attributable to differences in methods described above. Additionally, estimates may differ slightly because of the set of random numbers used but the differences are in the right direction and supported by the probabilities for diabetes related complications being higher for a patient with higher HbA1c. We emphasize the analysis are read in light of this and more weight should be given to incremental differences.

Table 5 Estimates for model validation between the current and original UKPDS OM 2

HbA1c	QALYs – Current model	Life expectancy Current model	QALYs – Original UKPDS OM 2	Life expectancy original UKPDS OM 2
97	15.16	19.5	16.2	22.7
58	16.37	21	17.9	24.0
Difference	1.2	1.5	1.7	1.3

2. Scenario 1

Aim:

Assess the potential cost-effectiveness of diabetes reversal (HbA1c of 42 mmol/mol), targeting individuals with poorly controlled diabetes (75 mmol/mol) and recently diagnosed (one year or less since diagnosis) with diabetes. By extension, assessing the value of reduced risk for renal failure following diabetes reversal. The model assumes a successful intervention lasting at least 2 years, with individuals following the standard model path from there.

Population:

To populate the model, data on baseline factors such as the age of a recently diagnosed individual (50 years) with type 2 diabetes, years since diagnosis (1 year), and BMI (31.4) for males from NZ's PREDICT study were used. Baseline data for risk factors on males from the PREDICT study was used to input risk factors,[19] if a risk factor value for NZ diabetes population was not available, UKPDS OM 2 example values were assumed. No pre-existing conditions and non-smoker status was assumed. Appendix F (Table 25) details the risk-factor profile for Scenario 1 and subsequent Scenarios.

Methods:

As discussed in diabetes risk factors, time-path equations by Leal et al[8] for risk-factors progression were included to populate the model. The diabetes reversal to 42 mmol/mol HbA1c (including a decrease in average BMI to 27) at T=0 and risk-factor progression meant the individual is in remission (HbA1c <48 mmol/mol) for 2 approximately years. The starting utility was kept the same as UKPDS but the values for utility detriments outlined in Table 3 were applied as they occurred. Additionally, costs and benefits were discounted at 3.5%.

For ethnicity specific analysis involving Maaori and Pacific, solely the probability of renal failure was inflated by 3.6 and 3.3 times the European/Other probabilities, respectively, to reflect the increased risk experienced by these populations. In Scenario 1 for example, the risk of renal failure for European/Other in the first cycle of the simulation is 0.004 but for Maaori it is 0.014 and 0.013 for Pacific, increasing over time. As mentioned in Appendix D, the UKPDS equation for renal failure does not include a coefficient for HbA1c and there is lack of data on risk reduction with improved glycemic control given the short length of clinical trials. Clinical experts in CM District estimate the risk of renal failure is reduced by 10% or 20% (moderately) upon diabetes reversal across the lifetime. The results are reported here with conservative reduction of 10% across all ethnicities. However, there may be a larger effect than 10% and Appendix G includes estimates for analyses with 20% reductions. Secondly, the negative coefficient for BMI in renal failure equation was contrary to reductions in BMI, meaning lower BMI values increased the probability of renal failure.

As a result, a BMI adjustment ensured the BMI values were consistent across the two simulations (i.e. 75 mmol/mol and 42 mmol/mol) and the higher BMI value was selected for renal failure equation. Risk equations for other complications with BMI coefficient were not manipulated. Therefore, two these two adjustment were included across all ethnicities. While this Scenario inflated the risk of renal failure for Maaori and Pacific, see Scenario 2 for further risk adjustments.

Results:

The current model estimates a 50 year old European/Other male would gain 0.73 life-years (0.33 QALYs) by diabetes reversal with lower costs ($3,848 per person with diabetes) attributable to fewer morbidities. As shown in Table 6, assuming the WTP is $30,000 for one QALY, the healthcare system will be able to spend up to $13,854 to achieve this benefit. However, if the risk of renal failure is assumed to reduce by 20%, the individual gains 0.19 life years, 0.10 QALYs further, costs $552 less and the health system is able to spend up to $17,199 per person (Appendix G). The impact of diabetes reversal is similar in Asian-Indian with higher incremental costs, meaning the incremental NMB is higher for European/Other.

Table 6 Estimates for European/Other for diabetes reversal from 75 to 42 mmol/mol with 10% reduction in risk of renal failure.

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	22.98	11.55	$ 118,239	$ 228,187
42	23.71	11.88	$ 114,391	$ 242,042
Incremental	0.73	0.33	$ (3,848)	
INMB				$ 13,854

Note: The NMB for 42 mmol/mol subtracted from NMB for 75 mmol/mol simulation equal the incremental NMB. NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Tables 7 to 8 show the impact of diabetes reversal with the probability of renal failure probabilities inflated for Maaori and Pacific, estimating lower life expectancy and QALYs compared to European/Other overall. Importantly, the incremental gains are higher for Maaori and Pacific, but reduction in costs per person for Maaori and Pacific are smaller than European/Other. However, it is estimated the health system is able to invest (spend) more per Maaori and Pacific compared to European/Other. Appendix G shows greater reductions in costs for Maaori and Pacific with a 20% reduction in risk of renal failure and significantly higher incremental NMBs than European/Other as well as other benefits. Lastly, the Asian-Indian analysis showed similar benefits in life-years and QALYs as European/Other but higher incremental costs per person, and as a result there is a lower incremental NMB that could be invested in these gains.

Table 7 Estimates for Maaori for diabetes reversal from 75 to 42 mmol/mol with the probability of renal failure inflated by 3.6 times compared to European/Other with 10% risk reduction for renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	20.55	10.31	$ 180,554	$ 128,746
42	21.52	10.75	$ 179,783	$ 142,717
Incremental	0.98	0.44	$ (771)	
INMB				$ 13,934

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 8 Estimates for Pacific for diabetes reversal from 75 to 42 mmol/mol with the probability of renal failure inflated by 3.3 times compared to European/Other with 10% risk reduction for renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	20.74	10.42	$ 178,259	$ 134,456
42	21.73	10.85	$ 176,742	$ 148,645
Incremental	1.00	0.42	$ (1,517)	
INMB				$ 14,189

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 9 Estimates for Asian-Indian for diabetes reversal from 75 to 42 mmol/mol with 10% risk reduction for renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	23.11	11.64	$ 119,814	$ 229,247
42	23.99	11.98	$ 118,362	$ 241,166
Incremental	0.88	0.35	$ (1,452)	
INMB				$ 11,919

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Comment:

Whilst the UKPDS OM 2 model included Caucasian and Asian-Indian ethnicities, specific adjustments for Maaori and Pacific were included given the high rates of renal failure observed in these populations with diabetes. Glycemic control plays an important in role reducing the risk of renal failure. The probability of renal failure was not influenced by HbA1c directly and to capture the impact of diabetes reversal and a modest reductions in risk was incorporated. Without this reduction, the model estimated higher costs per person after diabetes reversal and lower benefits for Maaori and Pacific than European/Other despite the probabilities being inflated by 3.6 and 3.3 times European/Other probabilities. Secondly, without the BMI adjustment, the model estimated negative incremental life expectancy, QALYs and significantly higher incremental costs along with negative incremental NMBs for Maaori and Pacific. These two adjustments were included to ensure the model produced estimates consistent with clinic expertise.

The estimates showed the gap in life expectancy for Maaori/Pacific and European/Other influenced by high renal failure rates, illustrating the burden of renal failure on health outcomes, specifically in Maaori and Pacific communities. Importantly, the difference of 0.3 (Maaori 3.6 and Pacific 3.3) in

risk inflation is highlighted by lower estimates of life expectancy, QALYs and higher costs for Maaori compared to Pacific. The cost of diabetes reversal is anticipated to be low and the relatively higher incremental NMBs suggest these are likely to remain cost-effective when intervention costs are included. Although this Scenario only inflated probabilities for renal failure, the following Scenario includes further risk inflation for other diabetes-related complications. The NMB values reported in this report for European/Other and Asian-Indian are higher than Maaori and Pacific, given the longer life expectancy, higher QALYs and low costs.

3. Scenario 2:

Aim:

Assess the equitable impact of diabetes reversal by increasing the risk for all diabetes-related complications in ethnic groups such as Maaori and Pacific compared to European/Other and attempt to overcome the lack of data on Maaori and Pacific risk-factor profiles. Scenario 1 is repeated with more assumptions on relative risk of complications for Maaori and Pacific compared to European/Other.

Population:

As for Scenario 1.

Methods:

As per Scenario 1 but incorporating further known additional risks by ethnicity using relative differences in rates of hospitalisations as relative risk across all of the complications listed in Appendix H, showing the relative differences in rates assumed as relative risk to inflate probabilities. This partially addresses the data limitations around risk factors by ethnicity. The risk of all-cause mortality was assumed as per UKPDS OM 2.

Results:

The estimates for European/Other from Scenario 1 are used here for comparison with Maaori and Pacific. Although, the life expectancy estimates in this Scenario are lower for Maaori and Pacific compared to Scenario 1, the incremental life expectancy for Maaori and Pacific are higher than European/Other and their respective estimates in Scenario 1. Secondly, the incremental gains in QALYs are higher for Maaori and Pacific compared to their respective QALY estimates in Scenario 1. Whilst the same pattern holds for incremental costs for Maaori, the cost per Pacific person is higher in this Scenario. Compared to European/Other, the incremental NMB remains higher for Pacific but lower than Maaori and Pacific estimates in Scenario 1. This may be due to higher incremental costs for Maaori compared to European/Other and Pacific and Maaori in Scenario 1. Appendix G shows similar trends as Scenario 1 with higher benefits for Maaori and Pacific than European/Other compared to European/Other with a 20% reduction in risk of renal failure. However, the incremental NMB is highest for Maaori, followed by Pacific.

Table 10 Estimates for European/Other for diabetes reversal from 75 to 42 mmol/mol as per Table 6 in Scenario 1

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	22.98	11.55	$ 118,239	$ 228,187
42	23.71	11.88	$ 114,391	$ 242,042
Incremental	0.73	0.33	$ (3,848)	
INMB				$ 13,854

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 11 Estimates Maaori for diabetes reversal from 75 to 42 mmol/mol with further risk adjustments with 10% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	17.58	9.01	$ 164,678	$ 105,694
42	18.77	9.61	$ 162,014	$ 126,253
Incremental	1.19	0.60	$ (2,664)	
INMB				$ 20,558

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 12 Estimates Pacific for diabetes reversal from 75 to 42 mmol/mol with further risk adjustments with 10% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
75	17.19	8.86	$ 147,658	$ 118,220
42	18.28	9.42	$ 148,539	$ 134,105
Incremental	1.08	0.56	$ 882	

INMB				$ 15,885

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Comment:

It was hypothesised, the increased risk for diabetes-related complications will result in lower estimates of life expectancy and QALYs compared to scenarios 1. The incremental NMBs reported in Tables 10 to 12 show the value of diabetes reversal in Maaori is higher than Pacific and European/Other as indicated by larger dollar figures. However, the model estimated lower incremental NMBs for Pacific in this Scenario compared to the previous Scenario. Compared to Scenario 1, the lower costs for Maaori and Pacific maybe attributable to lower life-expectancies.

4. Scenario 3

Aim:

Assess the impact of well controlled (i.e. delayed progression) diabetes in a recently diagnosed individual by maintaining the HbA1c and BMI values constant for the first five years of the simulation. This likely represents of a mixture of interventions.

Population:

Using the same demographic and risk-factor profile as Scenario 1 but using HbA1c value from PREDICT[19] assuming recently diagnosed with diabetes have a HbA1c of 64 mmol/mol and BMI 31.4 progressing naturally over life-time (100 years max age) compared to an individual with a HbA1c of 48 mmol/mol and BMI 27 for the first five years.

Methods:

As per Scenario 1 with the exception of successful diabetes reversal, may represent participants who are able to reduce their weight and HbA1c to some extent using the diabetes reversal intervention and maintain the change over five years. Additionally, the results are only reported with 10% decrease in risk of renal failure across the simulation as it is assumed the individuals are not fully successful in reversing diabetes, hence, a conservative approach is modelled.

Results:

Similar to Scenario 1, the impact of renal failure is evident in reduced life expectancy for Maaori and Pacific despite delaying the progression of diabetes. This is reflected by the life expectancy for Maaori and Pacific at HbA1c of 48mmol/mol and 27 BMI being lower than life expectancy for European/Other at 64 mmol/mol HbA1c and 31.4 BMI. However, a similar trend to diabetes reversal is evident with greater benefits and life expectancy gains for Maaori and Pacific compared to European/Other and Asian-Indian.

The incremental QALYs are the lowest in Asian-Indian, followed by European/Other, Pacific and highest in Maaori. The same is true for gains in life expectancy. Using a $30,000 WTP threshold, the health system is able to invest more in Maaori, Pacific and Asian-Indian to achieve the benefits reported in Tables 13 to 16.

Table 13 Estimates for European/Other for delayed progression from 64 to 48 mmol/mol with 10% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
64	23.03	11.60	$ 117,073	$ 230,816
48	23.84	11.93	$ 114,604	$ 243,340
Incremental	0.81	0.34	$ (2,469)	
INMB				$ 12,524

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 14 Estimates for Maaori for delayed progression from 64 to 48 mmol/mol with BMI adjustment and 10% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	IMB
64	20.69	10.35	$ 184,779	$ 125,819
48	21.81	10.87	$ 181,603	$ 144,392
Incremental	1.11	0.51	$ (3,176)	
INMB				$ 18,572

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 15 Estimates for Pacific for delayed progression from 64 to 48 mmol/mol with BMI adjustment and 10% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
64	20.90	10.49	$ 177,105	$ 137,644
48	21.80	10.89	$ 174,916	$ 151,784
Incremental	0.89	0.40	$ (2,189)	
INMB				$ 14,139

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Table 16 Estimates for Asian-Indian for delayed progression from 64 to 48 mmol/mol with BMI adjustment and 10% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	NMB
64	23.26	11.68	$ 122,925	$ 227,327
48	23.82	11.95	$ 116,669	$ 241,834
Incremental	0.56	0.28	$ (6,256)	
INMB				$ 14,507

Note: NMB and INMB are computed assuming that health is valued at $30,000 per QALY.

Comment:

It is unlikely all individuals who take up the diabetes reversal intervention will achieve diabetes remission but it may still be beneficial and allow them to control their diabetes more effectively. Compared to Scenario 1, the value of diabetes reversal when comparing a patient with a HbA1c of 42 and 48mmol/mol shows greater incremental NMB in diabetes reversal for European/Other but the incremental NMBs are marginally higher for Pacific, Asian-Indian and Maaori for delayed diabetes progression compared to Scenario 1.

Summary of results

Table 17 Incremental NMB for diabetes and weight related interventions at $30,000 WTP threshold in the CM District setting with 10% reduction in risk of renal failure

Intervention	Maaori	Pacific	European/Other	Asian-Indian
Scenario 1 Diabetes Reversal				
Incremental Life expectancy	0.98	1	0.73	0.88
Incremental QALYs	0.44	0.42	0.33	0.35
Incremental Costs	$ (771)	$ (1,517)	$ (3,848)	$ (1,452)
Incremental NMB	$ 13,934	$ 14,189	$ 13,854	$ 11,919
Scenario 2 Diabetes Reversal in Maaori and Pacific populations				
Incremental Life expectancy	1.19	1.08		
Incremental QALYs	0.60	0.56		
Incremental Costs	$ (2,664)	$ 882		
Diabetes Reversal equitable impact	$ 20,558	$ 15,885		
Scenario 3 Good HbA1c control				
Incremental Life expectancy	1.11	0.89	0.81	0.56
Incremental QALYs	0.51	0.40	0.34	0.28
Incremental Costs	$ (3,176)	$ (2,189)	$ (2,469)	$ (6,256)
Incremental NMB	$ 18,572	$ 14,139	$ 12,524	$ 14,507

Note: Incremental NMB figures are computed assuming that health is valued at $30,000 per QALY.

Discussion

An existing patient-level simulation model was adapted to assess the potential long-term cost-effectiveness of diabetes and weight-management interventions related to diabetes complications and mortality. The model integrated risk-factor time-path equations for more realistic simulations, highlighting one of strengths of the current model. Across the life-time horizon, the impact of interventions on natural progression of diabetes-related risk factors such as lowering HbA1c was cost-effective (using a WTP threshold of $30,000 as shown in the Table 17). The current model found higher benefits for diabetes reversal across all ethnicities compared to the benefits reported by Xin et al in a long term cost-effectiveness analysis.[20] This includes higher benefits for Maaori and Pacific as well as higher incremental NMBs when compared to European/Other and Asian-Indian. Given the cost of diabetes reversal intervention is anticipated to be low as evidenced by Xin et al it is likely the intervention would remain cost-effective when these costs are included in the analysis. The transparent approach used in this analysis allows the results to be compared with other interventions targeting type 2 diabetes. Note that the wider benefits of HbA1c control and weight loss beyond cardiovascular disease (impact on cancers, lungs and joints etc) are not captured, under-estimating the overall benefit. Also, wider societal and personal benefits are not included.

The deterministic sensitivity analysis identified risk factors with the greatest impact on life expectancy. However, multiple factors are influenced by clinical and non-clinical interventions. While the integrated time-path equations accurately reflect deterioration of metabolic control, the influence of weight reduction and HbA1c on the progression of other risk-factors such as SBP is not included.

There are a number of limitations in this analysis. Firstly, as described in the methods, the current model calculates probabilities based on the previous cycle rather than populating spreadsheets randomly for each complication to allow the occurrence of an event to affect subsequent complications in the same cycle. This may underestimate the probabilities and occurrence of events and increase life expectancy. Secondly, all-cause mortality equations are used for Maaori and Pacific analysis. The differences in life expectancy between European/Other and Maaori and Pacific are well documented and it is unknown whether all causes of mortality have been included.[21] Whilst the current model used UK mortality equations, they may not include other factors relevant to people in NZ, hence, there may be implications concerning the drop in life expectancy due to diabetes. The excess risk of mortality experienced by Maaori and Pacific by other co-morbidities and causes of

[20] Xin, Y., Davies, A., Briggs, A., McCombie, L., Messow, C. M., Grieve, E., ... & Lean, M. E. (2020). Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the Diabetes Remission Clinical Trial (DiRECT)/Counterweight-Plus weight management programme. *Diabetologia*, *63*(10), 2112-2122.
[21] Singh, H, Papaconstantinou D, Jackson G (2021) Life Expectancy and Mortality in Counties Manukau (2020 Update).

death may be underestimated in this analysis given Maaori and Pacific people are diagnosed with diabetes earlier and may lose more years.

Another limitation is that the demographic variable values including age, HbA1c and BMI are assumed to be the same across all the ethnic groups. If Maaori and Pacific did not experience disadvantages, the duration of diabetes may well be 1 year as assumed in the Scenarios, however, given the systemic inequities and health system disadvantage, the duration of diabetes may well be 5-6 years due to delayed diagnosis and treatment. Secondly, assuming the same intervention effects across all groups is unlikely as Maaori and Pacific may be younger, whose BMI is unlikely to be the same as European/Other given the rates of obesity are estimated to be higher in Pacific communities, making it difficult to assess the cost-effectiveness. Additionally, Maaori and Pacific face difficulties accessing equitable health care, which is one of the key drivers for high rates of diabetes-related complications, addressing some of these obstacles to improve access/quality of care may have a positive and broader impact than estimated by the model.

Hayes et al[5] acknowledge the need to demonstrate external validity in the applicability of the model to other populations which are known to have different patient risk-factor and complication profiles. This was noted in the current model when the risk of renal failure was inflated three times or higher as European for Maaori and Pacific. The diabetes reversal with the renal failure probability inflation produced lower estimates for 42mmol/mol individuals than the same individual with 75mmol/mol and higher BMI. This was partly due to the renal failure equation including a negative association for BMI and the overall inflation to the renal failure probability. This was addressed by adopting a pragmatic approach by maintaining the BMI time-path consistent across the two simulations (75 and 42 mmol/mol for example) but enabling the manipulating of BMI for all other equations. This highlighted one of the difficulties in inflating probabilities for one of the complications. As the model is complex, it may be the impact of weight loss is assessed better using a change in other risk-factors such as cholesterol or other risk-factors. This is highlighted by Scenario 2, estimating higher benefits for Maaori and Pacific when the probability of all complications is inflated. Given the data limitations, further assumptions were required but patient level data from CM District diabetes services including successful diabetes reversal in Maaori and Pacific should be used to extrapolate the long-term impact of diabetes and weight management services for evaluation of effectiveness and cost-effectiveness in the future.

The relative differences used to inflate probabilities may account for factors other than diabetes and may reflect issues beyond the scope of this analysis. For example, inequitable/delayed access to diagnosis and treatment may also account for higher rates of renal failure in Maaori and Pacific people with diabetes. It may be if Maaori and Pacific were not disadvantaged by the healthcare system, the relative difference may be lower. Furthermore, the relative difference in rates of renal failure between Maaori and Pacific and European/Other is not solely due to high HbA1c and overweight/obesity, other risk factors such as SBP and eGFR may have a stronger impact, which has

not been tested in the current model. These issues may shadow the true value of diabetes reversal in Maaori and Pacific, which may be higher than the current estimates.

The model assumed the same detriments as first events for secondary MI, stroke and amputation. An updated version of the UKPDS model should include QALY weights derived specifically for second events. Secondly, the assumed hospitalisation costs (as primary diagnosis) reflect event costs and subsequent costs were derived as proportion of event costs based on UKPDS OM 2 costs given the similarities in the UK and NZ health systems. Event specific and subsequent costs should be derived separately in future enhancements.

Lastly, the cost data was obtained from National Minimum Dataset based on hospitalisation events where each one of the diabetes-related complications was the primary diagnosis. However, an event may include unrelated costs to complication, for example, cost of co-morbidities leading to longer stays, which the model does not account for.

Conclusion

The results of this health economic analysis suggest that diabetes reversal in people recently diagnosed with type 2 diabetes is likely to be cost-effective given the risk-factor profiles, but should be interpreted with caution given the lack of ethnic specific data. It is recommended the cost-effectiveness is re-assessed using patient level data in the CM District setting and remission period is measured to build better understanding of assessing the value of diabetes remission via weight loss.

Appendix A: Equations used for transition probabilities

Table 18 Functional form, parameters and coefficients used for equations for diabetes-related complications and mortality

Risk equation for developing complications	Mean	Functional Form
1st CHF		
lambda	-12.332	Weibull
p	1.514	
Age Diagnosed	0.068	
At Fib	1.562	
BMI	0.072	
eGFR <60	-0.22	
LDL	0.012	
MMALB	0.771	
PVD	0.479	
Amp History	0.658	
Ulcer History	0.654	
1st IHD		
lambda	-6.709	Weibull
p	1.276	
Age Diagnosed	0.016	
Female	-0.532	
eGFR	-0.053	
HDL	-0.065	
LDL	0.023	
PVD	0.486	

SBP	0.058	
Amp History	0.526	
CHF History	0.824	
1st MI Male		
lambda	-8.791	Exponential
Age Diagnosed	0.045	
HbA1C	0.108	
HDL	-0.049	
LDL	0.023	
MMALB	0.203	
PVD	0.34	
SBP	0.046	
Smoker	0.277	
WBC	0.026	
Amp History	0.743	
CHF History	0.814	
IHD History	0.846	
Stroke History	0.448	
1st MI Female		
lambda	-8.708	Weibull
p	1.376	
Age Diagnosed	0.041	
eGFR <60	-0.28	

HbA1C	0.078	
LDL>35	0.035	
MMALB	0.277	
PVD	0.469	
SBP	0.056	
Smoker	0.344	
WBC	0.07	
CHF History	0.853	
IHD History	0.876	
2nd MI		
lambda	-4.179	
LDL	0.021	Exponential
MMALB	0.344	
1st Stroke		
lambda	-13.053	
p	1.466	
Age Diagnosed	0.066	
Female	-0.42	
At Fib	1.476	Weibull
eGFR <60	-0.19	
HbA1C	0.092	
LDL	0.016	
MMALB	0.42	

SBP	0.17	
Smoker	0.331	
WBC	0.04	
Amp History	1.09	
IHD History	0.481	
2nd Stroke		
lambda	-9.341	
p	1.956	
Age Diagnosed	0.046	Weibull
MMALB	0.537	
Smoker	0.656	
Blindness in one eye		
lambda	-11.607	
Age Diagnosed	0.047	
HbA1C	0.171	
Heart rate	0.08	Weibull
SBP	0.068	
WBC	0.052	
CHF History	0.841	
IHD History	0.61	
Ulcer History		

lambda	-11.295	Logistic
Age Diagnosed	0.043	
Female	-0.962	
BMI	0.053	
HbA1C	0.16	
PVD	0.968	
1st amputation no prior ulcer		
lambda	-14.844	Weibull
p	2.067	
Age Diagnosed	0.023	
Female	-0.445	
At Fib	1.088	
HbA1C	0.248	
HDL	-0.059	
Heart rate	0.098	
MMALB	0.602	
PVD	1.01	
SBP	0.086	
Smoker	0.04	
Stroke History	1.299	
1st amputation prior ulcer		
lambda	-0.881	Exponential
Age Diagnosed	-0.065	

PVD	1.769	
2nd amputation		
lambda	-3.455	Exponential
HbA1C	0.127	
Renal Failure		
lambda	3.549	Exponential
Age Diagnosed	-0.029	
Female	-0.869	
BMI	-0.054	
eGFR <60	-1.031	
eGFR>60	-0.487	
HAEM	-0.268	
HDL	0.027	
MMALB	1.373	
SBP	0.085	
WBC	0.029	
Amp History	1.108	
Blind History	0.732	
Death in years with no history or events		
lambda	-10.908	Gompertz
ϕ	0.098	

Female	-0.229	
Smoker	0.379	
Death in first year of event(s)		
lambda	-6.916	
Diabetes duration	0.042	
Current age	0.058	
Heart rate	0.124	
PVD	0.367	
Smoker	0.444	Logistic
Amp Event	-0.734	
IHD Event	0.423	
MI Event	1.309	
Renal Event	0.584	
Stroke Event	0.547	
Death in years with history but not event(s)		
lambda	-9.207	
ϕ	0.073	
BMI CAT1	1.083	
BMI CAT3	-0.293	
MMALB	0.348	Gompertz
Smoker	0.374	
WBC	0.048	
CHF History	0.632	
Renal History	1.15	

Ulcer History	0.473	
Death in subsequent year(s) of events		
lambda	-4.868	Logistic
At Fib	1.081	
Current age	0.05	
HDL	0.068	
PVD	0.352	
WBC	0.089	
Amp Event	-1.267	
Amp History	0.753	
Blind History	-1.727	
IHD Event	0.583	
IHD History	-0.507	
MI Event	0.982	
MI History	0.44	
Renal History	0.961	
Stroke Event	-0.619	

Source: Hayes et al.[5]

Appendix B: Risk-factor time-path equations

Equations estimating annual risk factor values of continuous variables[8]

Risk factor (Y)	**HbA1c**	**SBP**	**LDL**	**HDL**	**BMI**	**HEART R**	**WBC**	**HAEM**
Measurement frequency	Annual	Annual	Annual	Annual	Annual	Every 3 years	Every 3 years	Every 3 years
Units	%	mmHg	mmol/l	mmol/l	kg/m^2	bpm	$1x10^6$ ml	g/dL
Parameters	Estimate of coefficient (SE)							
Constant	1.419	29.007	0.763	0.170	0.830	31.231	1.446	5.040
Female	0.054	0.684	0.065	0.043	0.045	1.006	0.087	-0.349
Asian-Indian	0.046	-1.393	-0.074		-0.087			
Value of Y in previous year*	0.724	0.669	0.578	0.603	0.952	0.327	0.460	
ln (year since diagnosis)	0.141	0.570	-0.042		-0.165	0.918	0.167	-0.326
First recorded value of Y	0.081	0.118	0.210	0.220	0.034	0.272	0.292	0.692

Table 19 Parameters and beta coefficients (SE) for eight equations estimating annual risk factor values of continuous variables from first recorded value

Equations for estimating annual risk factor values of binary variables[8]

Table 20 Functional form, parameters and beta coefficients (SE) for seven equations estimating annual risk factor values of binary variables from first recorded value

Risk factor/event	**MIC ALB**	**PVD**	**AT FIB**	**SMOKER**	**EGFR<60[a] (binary)**	**EGFR<60[b] (continuous)**	**EGFR≥60[c] (continuous)**
Measurement frequency	Annual	Every 3 years	Every 3 years	Every 3 years	Annual	Annual	Annual
Functional form	Weibull	Weibull	Exponential	Logistic	Weibull	Tobit	Tobit
Parameters							
Constant	-9.047	-12.271	-13.313	0.016	-11.784	26.102	23.970
Γ/σ	1.138	1.515			1.871	9.452	12.575
Female	-0.463			-0.297	0.745	-2.409	-2.985
Asian-Indian					-0.302	1.229	2.404
Age at diagnosis	0.012	0.057	0.089	-0.050	0.080		
Smoker in previous year	0.329	0.865		2.018			
Smoker at first recorded value				5.535			
SBP in previous year (/10)	0.186	0.098			0.075		
HbA1c in previous year	0.165	0.095					
BMI in previous year	0.028	0.023	0.065		0.014		
HDL in previous year (x10)	-0.030				-0.028		
LDL in previous year (x10)		0.025			0.008		

Risk factor/event	**MIC ALB**	**PVD**	**AT FIB**	**SMOKER**	**EGFR<60[a] (binary)**	**EGFR<60[b] (continuous)**	**EGFR≥60[c] (continuous)**
Measurement frequency	Annual	Every 3 years	Every 3 years	Every 3 years	Annual	Annual	Annual
Functional form	Weibull	Weibull	Exponential	Logistic	Weibull	Tobit	Tobit
Parameters							
eGFR in previous year						0.567	0.406
First recorded value of eGFR						0.138	0.297
ln (year since diagnosis)				-1.574		-3.280	-3.013

Appendix C: Costs for diabetes-related complications

Table 21 Ethnic-specific costs for non-fatal events

	Maaori	Pacific	Asian	European/Other
CHF	$7,581	$6,717	$6,962	$9,639
IHD	$8,878	$8,703	$6,996	$10,916
MI	$9,885	$3,916	$4,369	$1,346
MI_2	$9,563	$7,225	$6,868	$3,443
Stroke	$5,642	$2,645	$4,152	$1,301
Stroke_2	$8,015	$4,715	$8,286	$1,910
Blindness	$2,665	$2,665	$2,665	$2,665
Amputation	$23,432	$16,388	$23,210	$11,009
Amputation_2	$23,432	$16,388	$23,210	$11,009
Ulcer	$5,441	$3,342	$5,034	$1,959
Renal Failure	$11,917	$11,917	$11,917	$11,917

Note: Secondary event costs are based on New Zealand totals due to small numbers in CM Health.

Table 22 Subsequent year(s) costs for diabetes-related complications

	Maaori	Pacific	Asian	European/Other
CHF	$7,581	$6,717	$6,962	$9,639
IHD	$8,878	$8,703	$6,996	$10,916
MI	$9,885	$3,916	$4,369	$1,346
MI_2	$9,563	$7,225	$6,868	$3,443
Stroke	$5,642	$2,645	$4,152	$1,301
Stroke_2	$8,015	$4,715	$8,286	$1,910
Blindness	$2,665	$2,665	$2,665	$2,665

Amputation	$23,432	$16,388	$23,210	$11,009
Amputation_2	$23,432	$16,388	$23,210	$11,009
Ulcer	$5,441	$3,342	$5,034	$1,959
Renal Failure	$55,000	$57,500	$50,000	$50,000

Note: The subsequent event costs are based on estimates from UKPDS base-analysis costs. It assumed Blindness in one eye is associated with an event cost only

Appendix D: Model Comparison and Initial Analysis of Scenarios

Model Comparison

The first example in the UKPDS OM 2 Manual assesses the impact of fixed differences in HbA1c values over time, 97 vs 57 mmol/mol on life expectancy and QALYs. That is someone with very out of control diabetes compared with someone well-controlled. For simplicity, all risk factors were kept constant through the entire simulation. and discount rate was set to 0. To reduce Monte Carlo error, 8,000 loops were simulated.

Table 23 Risk-factor profile for model validation as per UKPDS OM 2 Manual Example 1

Demographic characteristics Value	
Ethnicity	Caucasian/European/Other
Gender	Male
Current Age	55 years
Duration of T2DM	5 years
BMI	30
Risk factor values	
Atrial fibrillation (AF)	No
Peripheral vascular disease (PVD)	No
Current smoker	No
Micro/macro-albuminuria (albuminuria)	No
HDL cholesterol	1.22 (mmol/l)
LDL cholesterol	2.59 (mmol/l)
Systolic blood pressure	133.6 (mmHg)
HbA1c for subject one	97 mmol/mol
HbA1c for subject two	58 mmol/mol
Heart rate	81 (bpm)
White blood cell count (WBC)	6.85 (x 10^6 ml)

Haemoglobin	14.10 (g/dl)
Glomerular filtration rate (eGFR)	80 (ml/min/1.73m2
Pre-existing events	
History of ischemic heart disease	No
History of congestive heart failure	No
History of amputation	No
History of blindness in one eye	No
History of stroke N	No
History of myocardial infarction	No
History of Ulcer	No
Discounting start year	0

The estimates for the patient with 57 mmol/mol HbA1c had a life expectancy of 21 years (Figure 2) and 16.37 QALYs compared to the patient with 97 mmol/mol HbA1c with 19.5 years (Figure 3) of life expectancy and 15.16 QALYs. Figures 2 and 3 show the convergence of mean for life expectancy for 8,000 loops. Compared to UKPDS OM 2 example, the difference in life expectancy of 1.5 years and 1.21 QALYs is comparable as the suggested difference in life expectancy is 1.3 years.

Table 24 Estimates from the current model for HbA1c values - 58 and 97 mmol/mol

HbA1c Value (mmol/mol)	Life Expectancy (years)	QALYs
97	19.5	15.16
58	21	16.37
Difference	1.5	1.2

Figure 2 Convergence of life expectancy mean at 57 mmol/mol HbA1c kept constant

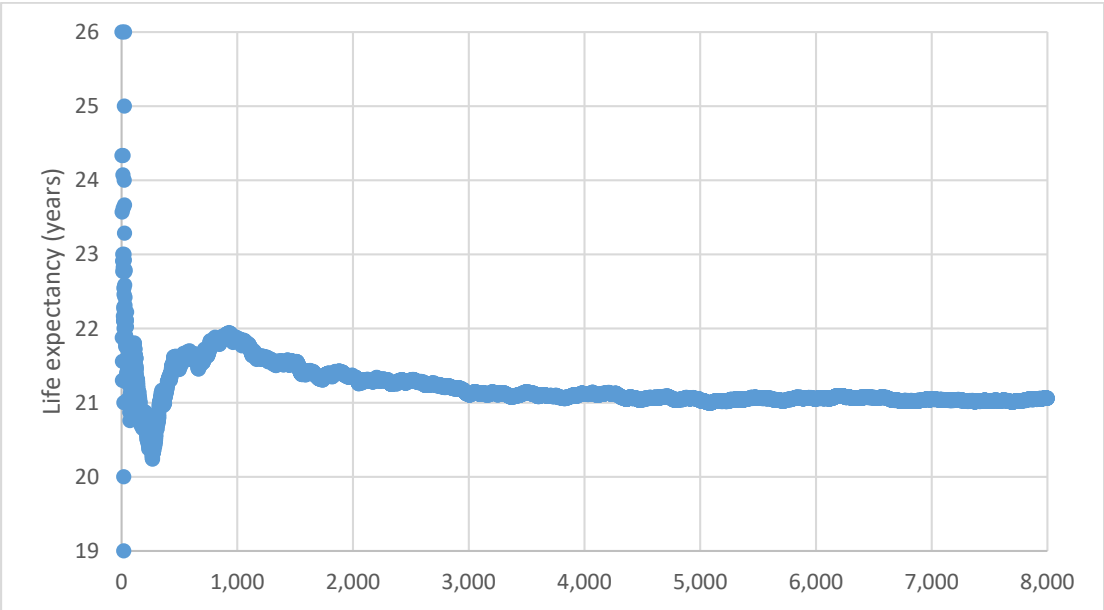
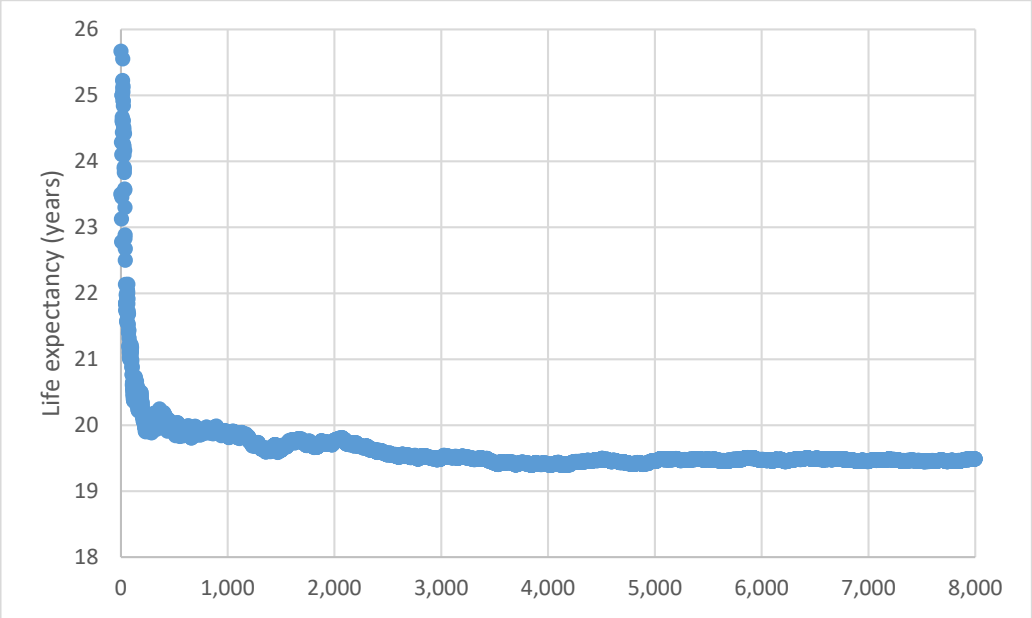


Figure 3 Convergence of life expectancy mean at 97 mmol/mol HbA1c kept constant



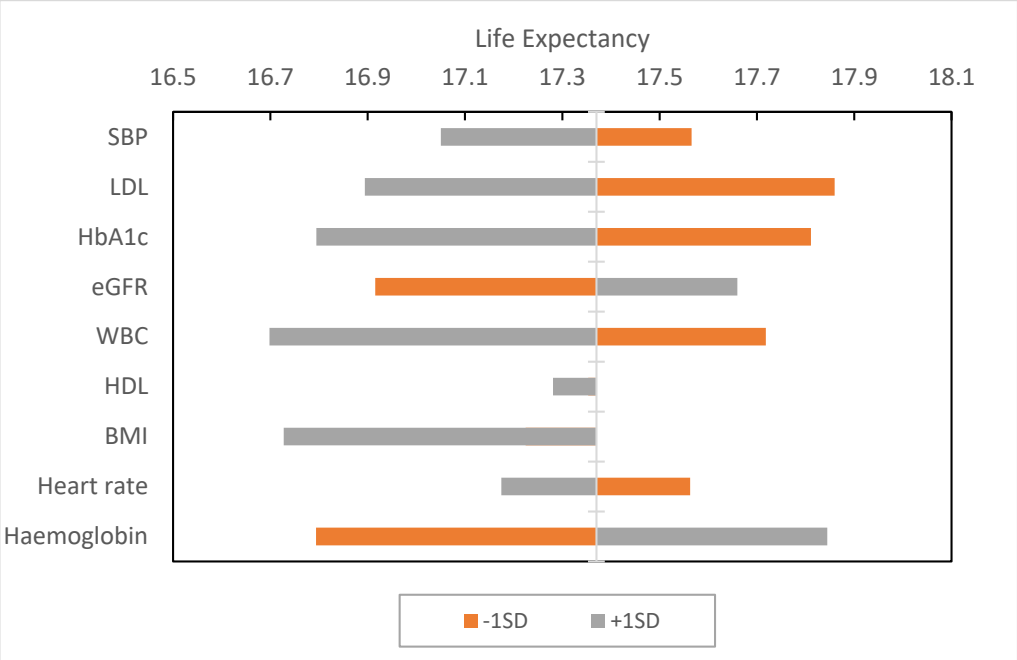
Initial analysis of Scenarios

Initial analyses of Scenarios involving diabetes reversal found HbA1c did not impact the renal failure probability, simulations with identical risk-factor profiles with 75 mmol/mol and 42 mmol/mol HbA1c values produced similar risk probabilities. Therefore, a modest reduction (10% and 20% [intervention simulation for lower HbA1c value]) in risk of renal failure was informed by expert judgement from a CM District Senior Medical Officer. Secondly, the analysis found BMI is negatively associated with higher renal failure probability. As a result, the diabetes reversal in Maaori and Pacific produced estimates with minimal change in QALYs and/or in the opposite direction. This was addressed by adopting a pragmatic approach maintaining the BMI consistent across the two simulations (higher and lower HbA1c values) for renal failure but allow BMI manipulation for all other complications. For example, the progression of 31.4 BMI for renal failure is the same for an individual with poorly controlled diabetes (75 mmol/mol) and in remission (42 mmol/mol).

Appendix E: One-way sensitivity analysis of Scenarios

One-way sensitivity analyses were conducted to assess parameter uncertainty and identify risk factors driving outcomes. The importance of continuous risk factors in estimating life expectancy depends on the risk equations in which they are significant and their associated hazard ratios. Using time-path equations, the patient profile and tornado plot (Figure 4) centred at 17.37 years of life expectancy found WBC, BMI and HbA1c are three most important risk-factors, ordered from the risk factor with the highest influence on life expectancy. Whereas, HDL has the smallest impact, -0.02 year reduction in life expectancy with 1 negative standard deviation (SD) change from the mean 1.19 mmol/l. Lastly, BMI had the second smallest reduction in life expectancy of 0.15 years with 1 negative SD from the mean 31.4 m/kg^2.

Figure 4 Tornado plot showing one-way sensitivity analysis of change in life expectancy arising from +1 SD (grey) and -1 SD (orange)



SBP 132 +/- 15 mmHg

LDL 3 +/- 0.6 mmol/l

HbA1c 7.9 +/- 4.1%

eGFR 89 +/- 16.8 ml min^{-1} (1.73m)$^{-2}$

HDL 1.19 +/- 0.3 mmol/l

BMI 31.4 +/- 6.8 m/kg^2

Heart Rate 72 +/- 12 bpm

Haemoglobin (HAEM) 145 +/- 13 g/l

White Blood Cells (WBC) 6.8 +/- 1.8 * 10^6 /ml

Note: HDL and BMI negative SD values are overlapped by positive SD values and reported in the paragraph above. To convert values for HbA1c % into mmol/mol, subtract 2.15 and multiply by 10.929. Current age 50 years (male) and age at diagnosis 49 years.

Demographic characteristics Value	
Ethnicity	European/Other
Gender	Male
Current Age	50 years
Duration of T2DM	1 year
BMI in Simulation 1	31.4
BMI in Simulation 2	27
Risk factor values	
Atrial fibrillation (AF)	No
Peripheral vascular disease (PVD)	No
Current smoker	No
Micro/microalbuminuria (albuminuria)	No
HDL cholesterol	1.19 (mmol/l)
LDL cholesterol	2.59 (mmol/l)
Systolic blood pressure	132 (mmHg)
HbA1c in Simulation 1	75 mmol/mol
HbA1c in Simulation	42 mmol/mol
Heart rate	81 (bpm)
White blood cell count (WBC)	6.85 (x 10^6 ml)
Haemoglobin	14.10 (g/dl)
Glomerular filtration rate (eGFR)	89 (ml/min/1.73m2
Pre-existing events	
History of ischemic heart disease	No
History of congestive heart failure	No
History of amputation	No

History of blindness in one eye	No
History of stroke N	No
History of myocardial infarction	No
History of Ulcer	No
Discounting start year	0
Discount rate	3.5%

Appendix F: Risk-factor values used in Scenarios.

Table 25 Risk-factor profile for Scenarios

Appendix G: Cost-effectiveness estimates for Scenarios with 20% reductions in risk of renal failure

Scenario 1

Table 26 Estimates for European/Other for diabetes reversal from 75 to 42 mmol/mol with 20% reduction in risk of renal failure.

HbA1c (mmol/mol)	LE	QALYs	Costs	30000 WTP - NMB
75	22.98	11.55	$ 118,239	$ 228,187
42	23.90	11.97	$ 113,839	$ 245,386
	0.92	0.43	$ (4,400)	
INMB				$ 17,199

Table 27 Estimates for Maaori for diabetes reversal from 75 to 42 mmol/mol with the probability of renal failure inflated by 3.6 times compared to European/Other with 20% risk reduction for renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	30000 WTP - NMB
75	20.55	10.31	$ 180,554	$128,746
42	21.62	10.81	$ 170,728	$153,572
	1.07	0.50	$ (9,826)	
INMB				$ 24,794

Table 28 Estimates for Pacific for diabetes reversal from 75 to 42 mmol/mol with the probability of renal failure inflated by 3.3 times compared to European/Other with 20% risk reduction for renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	30000 WTP - NMB
75	20.74	10.42	$ 178,259	$ 134,456
42	22.03	11.03	$ 168,036	$ 162,735
	1.29	0.60	$ (10,224)	
INMB				$ 28,278

Table 29 Estimates for Asian-Indian for diabetes reversal from 75 to 42 mmol/mol with 20% risk reduction for renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	30000 WTP - NMB

75	23.11	11.64	$ 119,814	$ 229,247
42	24.05	11.99	$ 117,474	$ 242,083
	0.94	0.35	$ (2,340)	
INMB				$ 12,836

Scenario 2

Table 30 Estimates Maaori for diabetes reversal from 75 to 42 mmol/mol with further risk adjustments with 20% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	$30000 WTP
75	17.58	9.01	$ 164,678	$ 105,694
42	18.98	9.72	$ 154,087	$ 137,394
	1.40	0.70	$ (10,591)	
INMB				$ 31,700

Table 31 Estimates Pacific for diabetes reversal from 75 to 42 mmol/mol with further risk adjustments with 20% reduction in risk of renal failure

HbA1c (mmol/mol)	LE	QALYs	Costs	$30000 WTP
75	17.19	8.86	$ 147,658	$ 118,220
42	18.64	9.58	$ 144,596	$ 142,775
	1.45	0.72	$ (3,061)	
INMB				$ 24,555

Appendix H: Ethnic-specific adjustments to inflate risk of complications

The data on relative rates of hospitalisation to European/Other is drawn from the National Minimum Dataset (NMDS), Ministry of Health from 2010-2020. Data was stratified by Districts with a focus on CM District, prioritised ethnicity (Maaori, Pacific, Asian and European/Other) among adults aged 15 years and above. The age-standardised rates were calculated, indicating the rate per 100,000 people, standardised to the age structure of the 2021 estimated resident population in NZ sourced from Stats NZ by direct method. Due to the small numbers for second events for MI and stroke, same relative difference as the first event were assumed using domiciled population for CM District. Specifically, the rates of renal failure were calculated using people with diabetes in CM District as the denominator. The calculations for other complications used the relevant District population as denominator excluding amputations as noted below.

To show equitable impact of diabetes reversal in Maaori and Pacific, the risk probabilities for diabetes-related complications were inflated by the ratios reported in Table 32 using European/Other as control. For example, the probability of renal failure for European/Other in Scenario 1 at T=1 is 0.004 and for Maaori it is 0.014 (0.004 * 3.6) and 0.013 for Pacific, increasing over time. As a result, the higher rate of complication(s) for Maaori and Pacific decreased life-expectancy (increased probability of death) but the mortality equations were not adjusted separately. Additionally, relative differences for Asian are not reported here as the UKPDS OM 2 included Asian-Indian.

Table 32 Relative difference in rates of hospitalisation used to inflate diabetes-related complications (compared to European/Other as control) in CM District

Relative Difference in Rates			
Complication	European/Other	Maaori	Pacific
CHF	1	3.96	3.61
IHD	1	1.18	1.64
MI_1	1	1.34	1.79
MI_2	1	1.34	1.79
Stroke_1	1	1.4	1.72
Stroke_2	1	1.4	1.72
Blind	1	1	1
Ulcer	1	2.92	3.86
Amp W/O Ulcer	1	1.01	0.42

Amp W Ulcer	1	1.01	0.42
Amp_2	1	1.01	0.42
Renal Failure	1	3.6	3.33

Source: CM District analysis of NMDS data, 2010-2020, Ministry of Health.[3]

Notes:

1. The UKPDS OM 2 includes equations for amputation without a prior ulcer (Amp W/O Ulcer), amputation with a prior ulcer (Amp W Ulcer) and second amputation (Amp_2). The same relative difference is assumed across all the complications involving amputation.
2. Due to low numbers in toe amputation, other lower limb amputations in CM District, therefore the total for NZ is assumed