National Institute for Health and Care Excellence

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Type 2 diabetes in adults: management (update)

Health economic model report

NICE Guideline

Methods, evidence and recommendations

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Final report

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Contents

1 Introduction

In 2015, NICE published a guideline on 'Type 2 diabetes in adults: management' (NG28) which covered several aspects of diabetes management including pharmacological treatments for the management of blood glucose levels. The evidence used to inform this guideline typically focused on the effect of diabetes treatments on glycaemic control measures such as HbA1c.

Since the publication of this guideline. NICE has become aware that the evidence base for pharmacological treatments used in Type 2 diabetes has expanded. Several drugs included in NG28 have now been explored in cardiovascular outcome trials (CVOTs); trials which look at the effect of anti-diabetic treatments on cardiovascular outcomes rather than glycaemic control.

The CVOT trials differ from the 'standard' non-CVOT trials used to inform NG28 in several ways:

- Population: CVOT trials were typically conducted in people with Type 2 diabetes who are at high risk of cardiovascular events
- Outcomes: CVOT trials look at the effect of treatments on diabetic/cardiovascular events ('hard outcomes') rather than on blood glucose levels ('surrogate outcomes')
- Comparators: CVOT trials typically follow a treat-to-target design in which the treatments given in accompaniment to the intervention and placebo are allowed to vary, meaning that the background treatments received in the comparator arm can differ to those in the intervention arm.

This guideline update will focus on incorporating evidence from these CVOTs into recommendations about the management of Type 2 diabetes. To support the guideline, a de novo economic analysis has been developed to explore the cost-effectiveness of treatments studied in CVOTs compared to current standard care (and where appropriate, compared to each other) in adults with Type 2 diabetes. This analysis expands on the economic analysis used to inform NG28. Because this is a rapid update, the clinical review was restricted to look at evidence from the CVOT trials and did not look at evidence on blood glucose outcomes; the economic model was aligned to the clinical review.

The economic model outlined in this report uses a patient-level simulation to generate a cohort of patients receiving standard care, and feeds this into a multi-state cohort model in which treatment effects from the CVOTs are applied.

Evidence on the effectiveness of treatments studied in CVOTs has been taken from the clinical review, with evidence on the non-CVOT studies included in the standard care arm taken from the clinical review and economic analysis from NG28.

The economic model described below including the model structure, input and associated R codes were reviewed by the Warwick evidence review group. Comments given by the evidence review group were addressed and incorporated where appropriate.

2 Methods

2.1 Model overview

2.1.1 Populations

The population covered by the model is adults with Type 2 diabetes.

Subgroup analyses were also used to explore:

- People with a BMI of greater than or equal to 30kg/m^2
- People at high risk of a cardiovascular event who have not had a prior event
- People who have had a prior cardiovascular event
- People who have had a prior cardiovascular event and people at high risk of a cardiovascular event who have not had a prior event.

Further information about subgroup analyses is outlined in section 3.1.

Analyses were stratified by level of treatment intensification to provide results for populations at initial therapy, first intensification and second intensification. Further details about the modelled populations are outlined in section 2.3.1.

2.1.2 Interventions

The interventions explored in the model are anti-diabetic treatments studied in cardiovascular outcome trials (CVOTs):

- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, dulaglutide, oral semaglutide, injectable semaglutide)
- SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)
- Pioglitazone

The committee chose to explore interventions as individual drugs rather than assuming class-level effects. This was an a priori decision made on the basis that even if class effects for cardiovascular outcomes were observed, there may be within-class differences in factors such as mode of administration and drug cost that could still lead to differences in the cost effectiveness of drugs within the same class.

The model structure (outlined further in section 2.2.) required a comparator treatment regimen representing standard care without treatments studied in the CVOT trials, against which the interventions could be compared. Standard care treatments were modelled via the UKPDS[1] which required data on blood glucose outcomes. As these outcomes were not extracted in the clinical review, the non-CVOT standard care treatments were aligned to those used in NG28. Standard care was defined by level of treatment intensification as:

- Initial therapy – metformin
- First intensification – metformin and sulfonylurea
- Second intensification – metformin, sulfonylurea and NPH insulin.

The committee agreed that these treatments were representative of standard care in the absence of any of the drugs studied in the CVOT trials. During development, the clinical review identified one CVOT trial comparing linagliptin to glimepiride (a sulfonylurea) which would have allowed sulfonylurea to be modelled as a CVOT intervention rather than as a component of standard care. However, the committee considered that glimepiride was not

widely used in clinical practice and so was not representative of sulfonylureas as a class. Because of this, the committee preferred to continue modelling sulfonylurea using blood glucose outcomes extracted in NG28 as they considered this data was more representative of the form of sulfonylurea used in current clinical practice.

Interventions are explored both as additions to the standard care comparator treatments and as replacements of components of standard care.

2.1.3 Time horizon and model perspective

The model developed to support this guideline is a cost-utility analysis run over a lifetime horizon (40 years). A discount rate of 3.5% is applied to both costs and quality-adjusted life years (QALYs). The model uses and NHS and PSS perspective for costs and aims to capture all direct health effects in line with the NICE reference case.

2.2 Model structure

2.2.1 Choice of model

A literature review of the economic evidence found no directly applicable cost-utility analyses (CUAs) that covered all the interventions for this review question and was based on evidence from the CVOT trials (see Section 1.1.7 of the Evidence Review). On this basis, an original health economic analysis has been developed to support the guideline.

Several of the CUAs considered in the literature review were informed by existing diabetes simulation models. Although none of the CUAs were directly applicable (the majority were excluded on the basis that they only looked at pairwise comparisons), the diabetes simulation models used in the CUAs were considered to have potential relevance to the guideline. The Mount Hood Diabetes Challenge Network is a network of researchers dedicated to collaborating and improving health economic diabetes simulation models[2]. The committee were presented with the diabetes models from the 2018 Mount Hood Challenge Conference to consider whether any of the existing diabetes simulation models would be suitable for use in the health economic analysis. The committee took into account the setting and populations used to develop the models, whether the models were readily available to NICE and whether the models allowed sufficient flexibility to run its preferred treatment comparisons. The committee noted that several of the models were industry funded. Whilst recognising that models funded by industry could still be robust for decision making, the committee felt it was most appropriate to use a non-industry funded model in the first instance. A summary of the committee's considerations is presented in Table HE001:

Table HE001:Diabetes simulation models considered by committee

Model	Reference	Committee consideration
BRAVO	Shao et al. 2018[3]	Exclude – non-UK population
Cardiff	McEwan et al. 2015[4]	Exclude – industry funded
CDC/RTI	Hoeger et al. 2009[5]	Exclude – non-UK population
ECHO – T2DM	Willis et al. 2013[6]	Exclude – industry funded
IQVIA CORE	Palmer et al. 2004 article[7]	Include for further consideration
Michigan Model MMD	Zhou et al. 2005[8]	Exclude – non-UK population
PROSIT Model	Schramm et al. 2016[9]	Exclude – industry funded
SPHR Diabetes Model	Thomas et al. 2014[10]	Exclude – fixed treatment pathway, societal perspective
Treatment Transitions Model	Smolen et al. 2014[11]	Exclude – non-UK population
UKPDS OM2	Hayes et al. 2013[1]	Include for further consideration

Of the 10 diabetes models presented, the committee considered that the IQVIA CORE[7] and UKPDS[1] models were most suitable for use in the health economic analysis.

A full description of the UKPDS OM2 along with a diagrammatic representation of the model can be found in the Hayes et al. 2013 article[1], with further details outlined in Section 2.2.2. In brief, the UKPDS OM2 works by extrapolating risk factors (such as HbA1c) over time for a cohort of patients with Type 2 diabetes. Treatment effects are applied to risk factors at a set point in the model and affect the trajectory of the relevant risk factors over time. In each cycle of the model, event equations are applied to the updated risk factor values to estimate whether patients experience a diabetic event (such as MI or mortality). In this way, the UKPDS uses the evidence of treatment effects in 'surrogate' risk factors (such as HbA1c) to estimate 'hard' diabetic outcomes (such as MI or mortality) outcomes rather than modelling the treatment effects on hard outcomes explicitly.

A full description of the IQVIA CORE model can be found in the Palmer et al. 2004 article[7]. Diabetes progression is simulated using a series of inter-dependent sub-models which simulate diabetic and cardiovascular events. Interactions between these sub models are modelled using Monte Carlo simulations with tracker variables. As with UKPDS, treatment effects on long-term diabetic and cardiovascular outcomes are modelled via surrogate risk factors.

The committee noted that the mechanisms of the CORE model were less transparent than those of the UKPDS, and that on initial exploration the UKPDS offered more flexibility for the incorporation of evidence from the CVOT trials. On this basis, the committee preferred to use the UKPDS OM2 in the health economic analysis.

The clinical review and economic analysis in NG28 were primarily focused on evidence of treatment effects on surrogate outcomes. The purpose of this guidance update is to review the evidence from the new CVOT-style trials, and incorporate this alongside the existing evidence base from NG28. The CVOT trials provide evidence about treatment effects on hard diabetic outcomes rather than the surrogate outcomes modelled in the UKPDS. Because the CVOT studies explored in the clinical review for this update do not collect data on surrogate risk factors it is not possible to model them directly through the UKPDS. However, the UKPDS can be used to model a non-CVOT standard care arm against which the CVOT drugs are compared. The standard care arms in the CVOT trials have limited applicability to the population being considered in this guideline update (all people with Type 2 diabetes) as they are restricted to people with high cardiovascular risk. Further, the treat-to-target design of the CVOTs meant that the treatments given in the standard care arm were not comparable to the treatments given in the standard of care + CVOT drug arm. Due to these reasons, the committee considered that modelling standard care via the UKPDS was preferred to using the standard care arms from the CVOT trials. A comparison of the standard care arm generated by the UKPDS with the standard care arm of an example CVOT trial is outlined in Appendix B.

Due to the difference in the evidence base for CVOT and non-CVOT drugs, the health economic analysis supporting this guidance needs to include and reconcile evidence of treatment effects on both surrogate and hard outcomes. For this reason, the model structure in our analysis extends the UKPDS OM2 by feeding the outputs from the patient-level simulation of a cohort on standard care into a multi-state model in which treatment effects observed in the CVOTs can be applied. Further details of the model structure are given in Sections 2.2.2 to 2.2.4.

2.2.2 Implementation of UKPDS

Full details of the UKPDS OM2 are documented in the Hayes et al. 2013 paper[1]. Due to the requirement to extend the UKPDS to feed into a multi-state model, the implementation of UKPDS OM2 was done in R. Details outlining the equivalence of the standard Excel

implementation of UKPDS and the R implementation used in this guideline are available in Appendix A: R implementation of UKPDS.

In the implementation, baseline data for a Type 2 diabetes cohort were simulated based on summary statistics and a correlations matrix of variables collected by The Health Improvement Network (THIN)[12]; further details are outlined in Section 2.3.1. Time-path equations developed by the UKPDS[13] were used to extrapolate variables over 40 years for each individual in the cohort. The equations were derived from a 20-year trial with 10 years additional post-trial follow-up and were derived for 13 variables: HbA1c, systolic blood pressure (SBP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), BMI, microalbuminuria, creatinine, heart rate, white blood cell count, haemoglobin, atrial fibrillation and peripheral vascular disease.

Risk factor equations from UKPDS OM2 are applied to the extrapolated variables to calculate whether individuals have a diabetic event in a given year. If an individual does experience an event the event history will be recorded for all subsequent years. Details of the risk factor equations are summarised in ESM 4 and 5 of the Hayes et al. 2013 paper[1] . Applying the time-path extrapolations and risk factor equations to the baseline cohort gives a patient-level simulation of a cohort of patients with Type 2 diabetes over 40 years which captures the nature and timing of diabetic events.

Treatment effects can be incorporated by applying changes to variables at a given time point; these treatment effects alter the value of the variable and shift its trajectory leading to a change in diabetic events predicted by the risk factor equations. Over time the variable will converge back to the trajectory it would have had in the absence of treatment, with the implication that treatment effects are not indefinite.

NG28 used the UKPDS to model all comparators (see NG28 Appendix F Section 3.4) as its clinical review considered evidence of treatment effects on surrogate outcomes. However, the UKPDS component of this economic analysis is only being used to generate a standard care arm and is not being used to model the CVOT drugs (which are the focus of this guideline). For this reason, the treatments being modelled via the UKPDS do not have to represent an optimal treatment sequence and instead only have to serve as a representative standard care arm against which the CVOT drugs can be compared. The committee were asked to choose a representative standard care treatment sequence for initial therapy, first intensification and second intensification. Details of this treatment sequence are outlined in Section 2.1.2 and 2.3.2 (Table HE007). The committee were also asked to choose an average HbA1c level at which patients' treatment would be intensified in the model. The committee decided to use a HbA1c level of 7.5%.as the intensification threshold in line with recommendation 1.6.8 in NG28, but were aware that this was an average value that might not be representative of all patients.

Evidence on the treatments outlined in Table HE007 was taken from the clinical review in NG28. As with NG28, treatment effect on HbA1c was applied at the end of year 1 (see NG28 Appendix F section 3.2.4 for details about the approach and rationale).

In the analysis, a cohort of 20,000 patients were run through the model 100 times to reduce Monte-Carlo error. Risk-factor event equations were derived from 50 bootstraps to characterise any uncertainty associated with the derivation of the event equations from the original trial data.

The output of the UKPDS module is a patient-level simulation of a cohort of patients receiving standard care treatment over 40 years which captures the nature and timing of diabetic events.

2.2.3 Multi-state model

A multi-state model was set-up with states for all possible events, event histories and combination of events/histories modelled in the UKPDS. For example, there would be separate states for:

- MI in current year, no history of prior MI
- MI in current year, history of MI
- MI and stroke in current year, history of MI
- MI and fatal stroke in current year, history of MI.

Events possible in the model are fatal and non-fatal MI, fatal and non-fatal stroke (with separate events for first and subsequent stroke and MIs), fatal and non-fatal ischemic heart disease, fatal and non-fatal heart failure, blindness, renal failure, ulcer, and amputation. This leads to a model with over 700 potential states.

For each year in the model, the patients simulated in the UKPDS are ascribed to the states reflecting their modelled events and event histories. This is used to calculate state membership for the cohort of patients on standard care over time, and the probability that a patient will move from one state to another in a given cycle. These time-varying transition probabilities are then converted into per year event rates.

Hazard ratios for the CVOT drugs compared to placebo were taken from the clinical review for all available diabetic and cardiovascular events that were captured in the UKPDS. Where events were not captured in the CVOT, a hazard ratio of 1 was assumed.

For each CVOT drug, the hazard ratios were applied to the standard care transition rates derived from the UKPDS component of the model for each relevant event to create a new set of transition rates; these transition rates were then converted back to transition probabilities. This was done for all events and combinations of events in the multi-state model. This process generated state transition probabilities for the standard care arm and all CVOT drugs. A cohort of patients reflective of the cohort run through the UKPDS was run through the multi-state model to estimate state membership for all CVOT drugs. This process gives state membership over time for cohorts of people on standard of care and on each CVOT intervention. If applying the CVOT treatment effect means fewer patients experience an event, these patients are assumed to remain in the states they were in during the previous cycle. Competing risks are not accounted for in the multi-state model and therefore as a simplifying assumption, in cases where a patient would die in the standard care arm and not in the CVOT arm, they are assumed not to die of something else in that cycle.

Due to the number of events and event histories there are a high number of possible states. To reduce computation time, the model only includes states that arise in the patient-level UKPDS simulation rather than including all possible states. This means that in rare occurrences (<0.01%), applying a treatment effect to the state membership generated from the UKPDS may lead to patients with histories that do not have corresponding states (described as ‘homeless’ in the model). In this instance, it is assumed that the patients remain in the UKPDS state. Whilst a limitation, this happens only in very rare occasions (<0.01%) and does not affect any states with meaningfully high occupancy and hence is unlikely to have any substantial impact on the final results.

2.2.4 Attributing costs and QALYs

Treatment-specific utility values and costs were applied to each health state in the model to generate costs and QALYs for each cohort. For more information on costs and utility values see Section 2.3.

A proportion of patients on each treatment are assumed to experience hypoglycaemic events which would be associated with increased resource use and a utility decrement. To reflect

this, costs and utility values are adjusted to reflect the proportion of patients who experience hypoglycaemic events on each treatment. This proportion experiencing events is modelled as treatment-specific whilst the utility decrement and costs associated with a hypoglycaemic event are assumed to be the same across all treatments. Further details on the rates, costs and utility values associated with hypoglycaemic events are outlined in Section 2.3.2.5, 2.3.3.4 and 2.3.5.3.

A proportion of patients on each treatment are assumed to experience weight gain which would be associated with a utility decrement. To reflect this, utility values are adjusted as a weighted average based on the proportion of patients who do and do not experience weight gain. This proportion experiencing weight gain is modelled as treatment-specific whilst the utility decrement is assumed to be the same across all treatments. The adjusted utility values are applied for the duration of treatment. As a simplifying assumption, weight gain is assumed to have no impact on resource use; this is in line with assumptions made in NG28.

In practice, CVOT drugs may confer a blood glucose benefit which may mean that the time at which an individual would intensify treatment differs depending on whether they have or haven't had a CVOT drug. The CVOT trials included in the clinical review do not report treatment effect on blood glucose and so this has not been incorporated into the model. The model hence does not capture this potential change in the point of intensification, and instead makes the simplifying assumption that there are the same proportion of people at each intensification level for all treatment arms at any given point.

Note that in instances where a patient has multiple events, patients will experience the costs and disutility associated with both events. Hence each event is treated independently when attributing costs and QALYs.

The average costs and QALYs of each cohort can then be used to calculate ICERs for each relevant treatment comparison.

2.3 Model inputs

2.3.1 Baseline characteristics

UKPDS OM2 requires a baseline dataset containing demographics, clinical risk factors and pre-existing complications, detailed in Hayes et al.[1].

2.3.1.1 Baseline data source

The previous guideline considered 3 main data sources Health Survey for England (HSE), National Diabetes Audit (NDA) and The Health Improvement Network (THIN) (See NG28 Economic Appendix section 3.3.1 for full details[14]). These options were presented to the committee who were satisfied that the advantages of THIN, such as good coverage of risk factors, large sample size and the ability to extract correlations between risk factors, outweighed its two potential issues; an inability to select data by therapy level and lack of ethnicity data. To address the two main issues with the THIN dataset other sources were considered.

The previous version of this guideline extracted the median duration of diabetes in the included RCTs and used the values of 1.5 years, 4.5 years and 8.5 years as proxies for initial therapy, first intensification and second intensification respectively. These values were presented to the committee who agreed that they remained clinically plausible.

As ethnicity was not available in THIN we presented two potential sources of ethnicity data to the committee. The first was HSE data used in NG28. Whilst this data had the advantage of including a limited set of correlation data with THIN risk factors the committee strongly felt that the proportion of non-white patients (5%) was much lower than they saw in practice. For

this reason, the second option – data from the National Diabetes Audit[15] - was preferred. The values are outlined in Table HE002: Baseline ethnic characteristics.

Table HE002:Baseline ethnic characteristics

Ethnicity	Proportion
White (including others)	82.41%
Asian	13.12%
Black	4.47%
Source: National Diabetes Audit 2018/2019	

2.3.1.2 THIN data validation and missing variables

The committee were presented with summary statistics from the THIN dataset and considered all values to be clinically plausible with the exception of HbA1c. The mean HbA1c values were around 15 despite applying a transformation to values above 30 to convert any potential mmol/mol values to %. The committee confirmed that a mean HbA1c of 15 was not plausible and agreed to the proposal to substitute in HbA1c values from the NG28 THIN extract. As the mean HbA1c values were not thought to be plausible and in NG28 HbA1c only showed strong correlation with HbA1c at diagnosis all HbA1c correlations were set to 0, with the exception of HbA1c at diagnosis where the NG28 values were used. Table HE003: Baseline HbA1c correlations shows the correlation at each intensification level.

Table HE003: Baseline HbA1c correlations

Intensification Level	HbA1c and HbA1c at diagnosis correlation
Initial Therapy	0.89
First Intensification	0.33
Second Intensification	0.24
Source: NG28 THIN Extract	

As in NG28, the patient sampling distribution was restricted to be above 6% as the committee felt they would not expect to see or treat a person with type 2 diabetes with a HbA1c value below this level.

THIN reported means and standard deviations of risk factors for untransformed and logged variables. Inspection of the interquartile ranges confirmed that continuous risk factors were positively skewed with the exception of height and eGFR. Therefore all continuous risk factors except height and eGFR were modelled as lognormal variables.

The THIN dataset provided two sets of correlations, one which included patients with missing data, and one which only included correlations for patients where all risk factors were recorded. Correlation data based of the subset of patients with complete risk factors have the advantage that the correlation matrix is ensured to remain positive-definite which is crucial to generate a sample population. The disadvantage of this method is that it may introduce bias, as the subset of patients with complete risk factors (<10% of the total population at all intensification levels) may not be representative of the population as a whole. To avoid this potential bias we elected to use correlation data based on all patients. While this gives a true reflection of all correlations in the dataset, the correlation matrices were not positive definite. Therefore before generating the population we utilised the make.positive.definite function in R to generate the nearest positive definite matrix. The nearest positive-definite matrix correlation values were within 1% of the original correlation matrix giving confidence in the relevance of the generated population.

UKPDS OM2 required three additional risk factors that were not available in the THIN extract.

The first missing value was albuminuria. Adler et al.[16]reported the progression of microalbuminuria and macroalbuminuria from the UKPDS trial reporting prevalence at 5 year intervals. The committee confirmed that they did not believe that more robust data were available and were content to use the results. As this paper reported albuminuria prevalence at 0, 5 and 10 years, values were linearly interpolated to match our populations' diabetes durations of 1.5, 4.5 and 8.5 years. The values are shown in Table HE004: Albuminuria prevalence

Table HE004: Albuminuria prevalence

Years from diabetes diagnosis	Albuminuria prevalence
1.5	10.3%
4.5	16.3%
8.5	22.6%
Source: Adler et al[16]	

The final two missing risk factors were haemoglobin (g/dL) and heart rate. These values are not widely reported and the committee were comfortable using the IQVIA CORE diabetes model[7] default values of 14.5 for haemoglobin and 72 for heart rate for all patients. Due to lack of data, correlations were not included for these variables.

2.3.1.3 Baseline data values

Baseline characteristics and risk factors are shown in Table HE005 and Table HE006. For clarity, the untransformed means are presented, whereas for the THIN correlation matrices logged variables' means and standard deviations are displayed.

Table HE005: Baseline characteristics

	Initial therapy		First intensification		Second intensification	
Variable	**Mean**	**Source**	**Mean**	**Source**	**Mean**	**Source**
Female	43%	THIN	46%	THIN	43%	THIN
Age	58.79	THIN	61.07	THIN	63.95	THIN
Smoker	17%	THIN	17%	THIN	17%	THIN
HbA1c (%)	8.16%	NG28	7.3	NG28	7.5	NG28
HbA1c (mmol/mol)	66	NG28	56	NG28	58	NG28
SBP (mmHG)	134.6	THIN	133.11	THIN	134.44	THIN
LDL (mmol/mol)	2.55	THIN	2.32	THIN	2.29	THIN
HDL (mmol/mol)	1.22	THIN	1.25	THIN	1.23	THIN
eGFR (ml/min/1.73m^2)	73.7	THIN	73.48	THIN	71.37	THIN 2021
White Blood Cell Count	7.58	THIN	7.61	THIN	7.51	THIN
Albuminuria	10.30%	Adler et al[16]	16.30%	Adler et al[16]	22.6%	Adler et al[16]
Haemoglobin (g/dL)	14.5	CORE default	14.5	CORE default	14.5	CORE default
Heart Rate	72	CORE default	72	CORE default	72	CORE default

Table HE006: Baseline risk factor prevalence

	Initial therapy		First intensification		Second intensification	
Previous event*	**Proportion**	**Source**	**Proportion**	**Source**	**Proportion**	**Source**
IHD	1.4%	THIN	3.4%	THIN	6.0%	THIN
Stroke	0.3%	THIN	0.7%	THIN	1.3%	THIN

Previous event*	Initial therapy		First intensification		Second intensification	
	Proportion	Source	Proportion	Source	Proportion	Source
Blindness	0.4%	THIN	0.8%	THIN	1.3%	THIN
CHD	0.5%	THIN	1.1%	THIN	1.9%	THIN
MI	0.5%	THIN	1.2%	THIN	2.0%	THIN
Amputation	0.1%	THIN	0.1%	THIN	0.2%	THIN
Renal Failure	0.1%	THIN	0.2%	THIN	0.4%	THIN
Ulcer	0.2%	THIN	0.4%	THIN	0.8%	THIN
**Events were only captured in the THIN database if they happened after a diagnosis of diabetes*						

2.3.2 Treatment effects

There are two types of treatment effects applied in the model; effects on surrogate measures (HbA1c) or effects on hard outcomes such as MI and Stroke. As CVOT treatments are a focus for this guideline wherever possible treatment effects on hard outcomes have been used. For standard care drugs such as metformin and NPH insulin CVOT data was unavailable and therefore in order to model the treatment effect the changes to HbA1c and BMI were run through UKPDS (an individual patient simulation model) in order to quantify the effect on hard outcomes. A CVOT trial was identified comparing linagliptin and a sulfonylurea (glimepriride)[17]. The committee were presented with the option of modelling sulfonylureas using this CVOT trial but opted to model them using the UKPDS as they did not consider glimepiride to be used widely in clinical practice.

Hypoglycaemic event rates were extracted from NG28 for surrogate treatments and directly from the CVOTs where applicable.

In NG28 dropouts according to intolerance were also modelled. As outlined in Tables 88, 123 and 138 of NG28 Appendix F, the mean lifetime discounted QALYs associated with dropouts in the NG28 model were less than 0.003 for all treatments explored (this included non-CVOT and CVOT drugs). As the model run time was already extended and the variance in dropout rates was likely to have a minimal impact on overall results, the committee agreed not to include treatment dropouts and discontinuations in the model.

Treatment waning (and the assumptions which would have to be made with this such as point and rate of waning) was not explored. As patients were assumed to continue on treatments throughout the model, and in the absence of evidence of treatment effect waning, the costs and benefits of treatment were assumed to last throughout the model time horizon.

2.3.2.1 Treatment effects in UKPDS component of model

No new data was extracted for this section of the guideline and all treatment effects were sourced from NG28 (see section 2.1.2 for further details). While NG28 modelled a wide range of treatments (including some that are modelled using the CVOT results directly in this guideline) the surrogate treatments were only used to provide a reference treatment to apply the CVOT hazard ratios to. This can be thought of as the standard care or placebo arm of a CVOT trial.

The committee were asked whether CVOTs were likely to be added to non-CVOT standard care or whether they would replace components of non-CVOT standard care. The committee considered that this might vary, and that they would like to see analyses exploring both scenarios. To do this, two different intensification paths were modelled. The first included the treatments given as non-CVOT standard care (described in section 2.1.2), which enabled exploration of strategies where CVOTs were added to standard care. The second included the treatments given as non-CVOT standard care but with a component removed (to be replaced with a CVOT drug). The committee agreed that if CVOTs were used to replace components of standard care, the treatments they would replace would be metformin at initial therapy, sulfonylurea at first intensification and sulfonylurea at second intensification. Details of the treatment comparisons in each strategy are outlined in Table HE007: Intensification path.

Table HE007: Intensification path

Treatment stage	Addition strategy		Replacement strategy	
	Intervention	Comparator	Intervention	Comparator
Initial Therapy	CVOT + metformin	Metformin	CVOT	Metformin
First Intensification	CVOT + metformin + sulfonylurea	Metformin + sulfonylurea	CVOT + metformin	Metformin + sulfonylurea
Second Intensification	CVOT + metformin + sulfonylurea + NPH insulin	Metformin + sulfonylurea + NPH insulin	CVOT + metformin + NPH insulin	Metformin + sulfonylurea + NPH insulin

To model these treatments, treatment effects were extracted from NG28 at the relevant intensification stage. The derivation and full explanation of the treatment effects is available in the NG28 economic appendix, section 3.5. Treatment effects on hypoglycaemic events are detailed in Section 2.3.2.5.

Table HE008: Treatment effects

Treatment Stage	Treatment	Addition or Replace	HbA1c (%) change at 1 year	Beta*	Weight (kg) change at 1 year
Initial Therapy	Placebo	Replace	0.05	-0.499	0.391
Initial Therapy	Metformin	Addition	-0.789	-0.499	-2.101
First Intensification	Metformin	Replace	-0.789	-0.499	-2.101
First Intensification	Metformin - sulfonylurea	Addition	-0.665	-0.469	1.354
Second Intensification	NPH insulin - metformin - sulfonylurea	Replace	0.904	-0.95	3.816
Second Intensification	NPH insulin - metformin	Addition	-0.54	-0.95	1.703

The effect on HbA1c and weight was inputted into UKPDS in the first year, and again for further intensifications when a patient reached the HbA1c intensification threshold. As this section of the model was used primarily to provide a baseline event rate to which the CVOT hazard ratios are applied, only mean values were used for these treatment effects.

2.3.2.2 Diabetic events

The outputs of UKPDS were converted into a multi-state model to apply the CVOT treatment effects (hazard ratios) at a population rather than individual patient level. As the CVOT trials' hazard ratios are generated in this manner this approach was considered to be highly generalisable and applicable to the decision problem.

As the guideline covers the whole Type 2 diabetes population and the CVOT populations were confined to those at high – or very high – risk of cardiovascular events, to implement a consistent patient-wide model an assumption about the efficacy of CVOT drugs in other populations was required.

The committee noted that there was increased uncertainty about the efficacy of these drugs in lower risk populations as the CVOT trials were conducted in people at high risk of cardiovascular events. Committee members discussed an alternative approach would have been to model the CVOT treatments in the lower risk population using the effect on surrogate measures (HbA1c, BMI etc.) only. The committee felt that as the surrogate models' ability to

predict outcomes in the newer drug classes had been shown to be limited[18] that it would be preferable to assume that the CVOT hazard ratios could be applied to patients at lower intensification levels. In making this assumption the committee were aware that the uncertainty in the results would increase as the modelled population moves further from the CVOT trial population.

The clinical review extracted the following cardiovascular outcomes:

- 3-point MACE (major adverse cardiovascular event composite measure)
- MI
- Stroke
- Hospitalisation for heart failure
- Hospitalisation for angina
- Cardiovascular mortality.

Cardiovascular outcomes in the UKPDS events were first MI, second MI, first stroke, second stroke, congestive heart failure and ischaemic heart disease. Several assumptions were required to equate the data extracted from the clinical review with the UKPDS model outcomes.

The review protocol specified that data on MI and stroke should be extracted. Reporting on these outcomes differed across trials, with some trials stratifying events based on whether they were fatal or non-fatal and some trials reporting as a combined outcome (some trials did not report clear definitions). The clinical review focused on extracting non-fatal outcomes as these were most consistently reported across trials and avoided the risk of double-counting with measures of cardiovascular mortality (see Section 1.1.11.1 of the evidence review). These values were used in the economic model. Where non-fatal outcomes were not reported in trials, combined measures of non-fatal and fatal events were used for MI and stroke. It is worth noting that in trials reporting both non-fatal and all event outcomes, the hazard ratios did not significantly differ, showing that the effect on non-fatal outcomes and all outcomes from treatments were similar. Trials typically did not disaggregate MI and stroke into first and second events and so the same treatment effect was assumed for both.

The committee were satisfied that hospitalisation for heart failure was sufficiently similar to congestive heart failure, and accepted hospitalisation for angina as a proxy for ischaemic heart failure.

Data on 3-point MACE outcomes were not included in the model as MI, stroke and mortality were modelled separately. The approach to modelling of cardiovascular mortality is outlined in Section 2.3.2.3.

The table below shows the point estimates for outcomes from the clinical review used in the model. Full details of the uncertainty associated with these outcomes can be found in Section 1.1.6 of the Evidence Review.

Table HE009: Point estimates of outcomes

Trial	Treatment	Heart failure	Stroke	IHD	MI
CANVAS	Canagliflozin	0.67	0.9	NR	0.85
CARMELINA	Linagliptin	0.90	0.88	0.87	1.15
DECLARE	Dapagliflozin	0.73	1.01	NR	0.89
ELIXA	Lixisenatide	0.96	1.12	1.11	1.03
EMPA-REG	Empagliflozin	0.65	1.24	0.99	0.87
EXAMINE	Alogliptin	1.07	0.91	0.91	1.08
EXSCEL	Exenatide	0.94	0.86	NR	0.95
LEADER	Liraglutide	0.87	0.89	0.98	0.88

Trial	Treatment	Heart failure	Stroke	IHD	MI
PIONEER	Semaglutide (oral)	0.86	0.74	1.56	1.18
PROactive	Pioglitazone	NR	0.81	NR	0.83
REWIND	Dulaglutide	0.93	0.76	1.14	0.96
SAVOR-TIMI	Saxagliptin	1.27	1.11	1.19	0.95
SUSTAIN	Semaglutide (injection)	1.11	0.61	0.82	0.74
TECOS	Sitagliptin	1.00	0.97	0.9	0.95
VERTIS-CV	Ertugliflozin	0.70	1	NR	1.04
Outcomes are hazard ratios unless otherwise stated					

2.3.2.3 Cardiovascular mortality

The clinical review extracted data on all-cause mortality and cardiovascular mortality. It was not appropriate to include both measures of mortality in the model as cardiovascular mortality contributes to all-cause mortality; including both could lead to the double counting of cardiovascular deaths. The committee considered that the effect of CVOTs on mortality was likely to be via their cardiovascular benefits, and so preferred to focus on cardiovascular mortality.

In the model, treatment effects on cardiovascular events translate to a benefit in cardiovascular mortality. For example, if a CVOT treatment reduces risk of MI then in the multi-state model a proportion of patients who would have had an MI in the non-CVOT arm do not experience the MI. States without MIs have a lower risk of mortality than equivalent states with MIs, meaning that the reduced risk of MI then leads to a reduced risk of cardiovascular mortality. The implicit assumption behind this approach is that any treatment benefit on cardiovascular mortality comes entirely from reduced risk of MI, stroke, heart failure and/or IHD captured in the model.

An additional option was to make a further adjustment to the modelling of mortality and calibrate the estimates to align with the evidence on cardiovascular mortality extracted from the clinical review. The assumption behind this approach is that there are treatment benefits on cardiovascular mortality that are separate from, and not captured by, the reduced risk of MI, stroke, heart failure and/or IHD.

There are advantages and disadvantages to calibrating the model to the cardiovascular mortality data. The primary advantage of calibration is the ability to incorporate more trial evidence into the analysis. However, the cardiovascular mortality outcomes extracted from the clinical review had wide confidence intervals (see Evidence Review Appendix G) which presents some challenges to the approach. The wide confidence intervals indicate high uncertainty in the point estimates for cardiovascular mortality; calibrating the model to match these point estimates hence risks 'over-adjusting' the model to align to an estimate observed by chance. This risks double counting of cardiovascular benefits in some treatments and artificially reducing the benefits in others, which reduces comparability of results across treatment arms.

To test the ability of the model to predict cardiovascular mortality hazard ratios without additional adjustment, the modelled hazard ratios were compared with the trial hazard ratios (Table HE011). The model showed good predictive ability with 13 out of 15 simulated hazard ratios sitting within the trial confidence intervals and 9 treatments with an error rate under 5%. The model showed no clear trend towards over or underprediction for treatments where it fell within the trial confidence interval.

Table HE010: Comparison of modelled and trial hazard ratios

Trial	Treatment	UKPDS indirectly modelled HR	Trial HR	UKPDS unadjusted value in confidence interval	% error vs trial
CANVAS	Canagliflozin	0.86	0.87	Yes	-1%
CARMELINA	Linagliptin	0.98	0.96	Yes	2%
DECLARE-TIMI	Dapagliflozin	0.95	0.98	Yes	-3%
ELIXA	Lixisenatide	1.01	0.98	Yes	3%
EMPA-REG	Empagliflozin	0.94	0.62	No	51%
EXAMINE	Alogliptin	1.01	0.79	Yes	27%
EXSCEL	Exenatide	0.94	0.88	Yes	7%
LEADER	Liraglutide	0.90	0.78	Yes	16%
PIONEER	Semaglutide (oral)	1.08	0.49	No	121%
PROactive	Pioglitazone	0.94	0.94	Yes	0%
REWIND	Dulaglutide	0.95	0.91	Yes	4%
SAVOR-TIMI	Saxagliptin	1.09	1.03	Yes	5%
SUSTAIN	Semaglutide (injection)	0.81	0.98	Yes	-17%
TECOS	Sitagliptin	0.98	1.03	Yes	-5%
VERTIS-CV	Ertugliflozin	0.96	0.92	Yes	4%

For two treatments the modelled cardiovascular mortality hazard ratio did not fall within the trial hazard ratio; empagliflozin and oral semaglutide. The PIONEER trial found that oral semaglutide is associated with increased MI (the most common cardiovascular event) and unstable angina. The increased rates of these events drives higher mortality rates in the modelled population despite a trial cardiovascular mortality hazard ratio of 0.49. This trial observed 15 cardiovascular deaths in the treatment arm against 30 in the control arm, total numbers which are far lower than other CVOT trials. EMPA-REG found that empagliflozin is associated with a cardiovascular mortality HR of 0.62 (compared with a modelled 0.94), this figure was based on 137 and 172 deaths in the treatment and control arm respectively.

The committee recognised that there were limitations to each approach to modelling cardiovascular mortality. On balance it decided not to calibrate the results in the base-case, on the premise that cardiovascular mortality was likely to be mediated by events already captured in the model. The alternative calibration approach was explored as a sensitivity analysis.

2.3.2.4 Weight

The treatment effect on weight was not always included as an outcome in the CVOT trials, and where data was available it was not always in an easily extractable form requiring digitisation of charts in some cases. As the quality of this outcome varied substantially between studies and confidence intervals were not always available, the model was based on the point estimate weight change for all trials.

This weight change was applied to a person with the mean height (1.68m) and weight (88kg) from the THIN dataset and converted it to a BMI change to which the QALY impact was calculated.

The values used in the economic model are tabulated below:

Table HE011: Weight and BMI changes

Intervention	Modelled weight change (kg)	Modelled BMI Change (Based on Average THIN patient)
Canagliflozin	-1.60	-0.57
Linagliptin	0.25	0.09
Empagliflozin	-2.33	-0.83
Dapagliflozin	-1.80	-0.64
Lixisenatide	-0.78	-0.28
Alogliptin	0.06	0.02
Exenatide	-1.27	-0.45
Liraglutide	-2.30	-0.81
Oral semaglutide	-4.20	-1.49
Pioglitazone	2.69	0.95
Dulaglutide	-1.15	-0.41
Saxagliptin*	0.00	0.00
Inj. Semaglutide	-3.60	-1.28
Sitagliptin*	0.00	0.00
Ertugliflozin	-2.40	-0.85
**Trials did not report weight change so a value of 0 was assumed in the model*		

2.3.2.5 Hypoglycaemia

2.3.2.5.1 Reference treatment hypoglycaemic event rates

Initially, the committee were presented with the hypoglycaemia event rates for metformin, sulfonylurea and insulin that were reported by Dunkley et al. 2019[19]:

Table HE012:

Incidence of hypoglycaemia (per person-year by treatment group)			
	Metformin	**(Metformin +) sulfonylurea**	**(Metformin +) Insulin**
Non-severe	0.64	1.94	3.84
Severe	0.07	0.09	0.32
Nocturnal total	0.18	0.49	1.37

However, committee questioned the face validity of these results and commented that the metformin rates seemed high relative to the sulfonylurea rates. A further search of the literature did not identify any other sources of evidence we could use for the event rate in metformin. One paper reported hypoglycaemia rates for metformin (Wang et al. 2017[20]), but the definition of a severe hypoglycaemic episode was based on hospital admission which was inconsistent with the definitions used for all other treatments.

To address the committee's concerns, the baseline hypoglycaemic event rate for metformin was calculated by applying a hazard ratio taken from Bodmer et al.[21] to the sulfonylurea event rate presented in the Dunkley paper, to give the estimates outlined in Table HE014.

Table HE013: Incidence of hypoglycaemia (per person-year by treatment group)

Incidence of hypoglycaemia (per person-year by treatment group)			
	Metformin	**(Metformin +) sulfonylurea**	**(Metformin +) Insulin**
Non-severe	0.51	1.94	3.84
Severe	0.024	0.09	0.32
Nocturnal total	0.13	0.49	1.37

This approach leads to a larger difference in hypoglycaemia rates between metformin and sulfonylurea.

As Dunkley et al[19]. did not report all hypoglycaemic event rates for all surrogate treatment options in the model it was necessary to source relative hazard ratios for hypoglycaemia rates from the NG28 clinical review (Tables 48 and 56). The hypoglycaemia hazard ratio for placebo vs metformin at initial therapy was 0.67 and for metformin-NPH insulin-sulfonylurea vs metformin-NPH insulin at second intensification was 1.62. This hazard ratio was applied to the severe hypoglycaemia event rates from Dunkley et al[19]. and non-severe events were assumed to be increased or decreased by the same proportion.

Table HE014: Baseline hypoglycaemia rates

Treatment Stage	Treatment	Addition or Replacement	Hypoglycaemic event hazard ratio
Initial Therapy	Placebo	Replacement	0.67
Initial Therapy	Metformin	Addition	Reference Treatment – Dunkley 2019
First Intensification	Metformin	Replacement	Initial therapy rate modelled - Dunkley 2019
First Intensification	Metformin - sulfonylurea	Addition	Reference Treatment – Dunkley 2019
Second Intensification	NPH insulin -metformin - sulfonylurea	Replacement	1.62
Second Intensification	NPH insulin -metformin	Addition	Reference Treatment – Dunkley 2019

2.3.2.5.2 Relative hypoglycaemic event rates

For CVOT treatments the severe hypoglycaemia incidence rate ratios from the clinical review were applied to the baseline (non-CVOT rate). Non-severe events were assumed to increase by the same proportion.

Table HE015: Severe hypoglycaemia rates from CVOT studies

Trial	Treatment	Severe Hypoglycaemia (Incidence rate ratio)
CANVAS	Canagliflozin	1.32
CARMELINA	Linagliptin	0.98
DECLARE	Dapagliflozin	0.70
ELIXA	Lixisenatide	0.58

Trial	Treatment	Severe Hypoglycaemia (Incidence rate ratio)
EMPA-REG	Empagliflozin	0.87
EXAMINE	Alogliptin	1.12
EXSCEL	Exenatide	1.13
LEADER	Liraglutide	0.75
PIONEER	Semaglutide (oral)	1.77
PROactive	Pioglitazone	1.68
REWIND	Dulaglutide	0.87
SAVOR-TIMI	Saxagliptin	1.25
SUSTAIN	Semaglutide (injection)	1.05
TECOS	Sitagliptin	1.15
VERTIS-CV	Ertugliflozin	0.88
Outcomes are hazard ratios unless otherwise stated		

2.3.3 Costs

2.3.3.1 Treatment costs

2.3.3.1.1 CVOT Treatments

Doses for the CVOT treatments were aligned to those used in the trials. Combination tablets were not considered. Drug costs were based on prices published in the May 2021 NHS Drug Tariff[22]. CVOT treatments were assumed to have the same dosage for all time

Note that the treatment costs below do not include the cost of consumables or staff time.

Table HE016: Unit costs of CVOT treatments

Drug	Pack size	Unit Price	Assumed weighting	Modelled Daily Dose	Annual Cost
Alogliptin	28 x 25mg	£26.60	100%	25mg	£347
Alogliptin	28 x 12.5mg	£26.60	0%		
Alogliptin	28 x 6.25mg	£26.60	0%		
Canagliflozin	30 x 300mg	£39.20	100%	300mg	£477
Canagliflozin	30 x 100mg	£39.20	0%		
Dapagliflozin	28 x 10mg	£36.59	100%	10mg	£477
Dapagliflozin	28x 5mg	£36.59	0%		
Dulaglutide	4 x 0.75mg	£73.25	0%	0.214mg (1.5mg weekly)	£955
Dulaglutide	4 x 1.5mg	£73.25	100%		
Empagliflozin	28 x 10mg	£36.59	0%	25mg	£477
Empagliflozin	28 x 25mg	£36.59	100%		
Ertugliflozin	28 x 15mg	£29.40	100%	15mg	£383
Ertugliflozin	29 x 5mg	£29.40	0%		
Exenatide	4 x 2mg	£73.36	100%	0.286mg (2mg weekly)	£956

Drug	Pack size	Unit Price	Assumed weighting	Modelled Daily Dose	Annual Cost
Liraglutide	2x 18mg	£78.78	100%	1.8mg	£1,438
Linagliptin	28 x 5mg	£33.26	100%	5mg	£434
Lixisenatide	30 x 2µg	£57.93	100%	2µg	£705
Lixisenatide	15 x 1µg	£31.67	0%		
Pioglitazone	28 x 15mg	£1.57	0%	45mg	£36
Pioglitazone	28 x 30mg	£1.78	0%		
Pioglitazone	28 x 45mg	£2.74	100%		
Saxagliptin	28 x 5mg	£31.60	100%	5mg	£412
Saxagliptin	28 x 2.5mg	£31.60	0%		
Semaglutide (injectable)	1 x 4mg	£73.25	100%	0.141mg (1mg weekly)	£942
Semaglutide (oral)	30 x 3mg	£78.48	0%	14mg	£955
Semaglutide (oral)	30 x 7mg	£78.48	0%		
Semaglutide (oral)	30 x 14mg	£78.48	100%		
Sitagliptin	28 x 100mg	£33.26	100%	100mg	£434
Sitagliptin	28 x 25mg	£33.26	0%		
Sitagliptin	28 x 50mg	£33.26	0%		

2.3.3.1.2 Non-CVOT treatments

The only modelled drugs without a CVOT were metformin, sulfonylurea and NPH insulin. Drug unit costs were based on prices published in the May 2021 NHS Drug Tariff[22]. For oral drugs, the cheapest pack sizes (based on total cost per mg) in the NHS Drug Tariff were used and it was assumed no combination tablets were used. NPH insulin costs were taken from the Type 1 insulin guideline update (update of NG17). The treatment dosages were taken directly from NG28 and vary by year and intensification level, and treatment combination. The committee advised that gliclazide was the most commonly used sulfonylurea in the UK and was used to provide the modelled sulfonylurea. The per mg (or per unit) costs are multiplied by the treatment dosages (Section 2.3.4)to calculate the annual cost.

Table HE017: Unit costs of non-CVOT treatments

Drug	Measurement	Price	Source
Metformin	mg	£0.0000574	May 2021 NHS Drug Tariff
Sulfonylurea	mg	£0.000540	May 2021 NHS Drug Tariff
NPH insulin	unit	£0.0143	NICE T1 Insulin guideline (2020)

2.3.3.2 Diabetic event costs

When considering costs of long-term complications, the committee was presented with 2 potential options: firstly, sourcing long-term complication costs from relevant NICE guidelines, and secondly sourcing costs from a study based on the post-trial monitoring data of the UKPDS. The committee was of the opinion that the cost of managing long-term complications in patients with type 2 diabetes are likely to differ when compared to the general population. Hence it agreed to use information from the Alva et al[23]where possible as it was a based on a type 2 diabetic population in the UK.

Note that the Alva et al. study did not report costs for the management of renal complications and active ulcers. On the assumption that renal failure incurs the costs of renal replacement therapy, costs for renal complications were sourced from the current NICE guideline update on Chronic Kidney Disease[24] with the UK Renal Registry[25] used to estimate the distribution of renal replacement therapy modalities as 70% haemodialysis, 20.1% peritoneal dialysis and 9.9% transplant (UK Renal Registry 22nd annual report, Table 1.7 – RRT modality for UK patients still on RRT at 90 days). In line with the assumptions used in the Chronic Kidney Disease guideline update, dialysis costs were excluded from the costs of renal failure (see section J.2.3.4 of Chronic Kidney Disease Evidence Review 2.1 for explanation of this approach), so the cost of renal failure reflected the cost of renal transplant and did not incorporate dialysis costs. Costs for renal transplant were aligned to costs used in the Chronic Kidney Disease guideline update (see Table 34 of Chronic Kidney Disease Evidence Review 2.1); cost of transplant was assumed to be an average of the costs of transplants from living and deceased donors and cost of immunosuppressive therapy are incurred for all years after transplant. This leads to the cost of the first year of renal failure to be £20,897 and the cost of subsequent years to be £8,332. The cost of active ulcers was sourced from Kerr et al. 2019[26] who used hospital episode statistics (HES) data combined with relevant reference costs from the UK. More detailed information about the sources used, along with the relevant mean costs per year are shown in Table HE026: Management and complication costs.

Table HE018: Management and complication costs

Input variables	Mean cost per year(£)*	Source/ Comments
Annual cost of CVD complications		
MI 1st year	8419	Alva et al. 2015[23] - Results from the T2 Diabetes patients in the post trial monitoring period of 1997 – 2007 in the UKPDS. Resource use was obtained by looking at inpatient use as obtained from HES database. Non-inpatient costs are obtained using questionnaires. Costs obtained from HRG data.
MI 2nd+ years	2093	
Fatal MI	1744	
IHD 1st year	12190	
IHD 2nd+ years	2143	
Fatal IHD	4318	
Heart failure 1st year	4782	
Heart failure 2nd+ years	2805	
Fatal Heart failure	2805	
Stroke 1st year	9054	
Stroke 2nd+ years	2157	
Fatal Stroke	4534	
Renal Complications		
1st year	20897	UK Renal Registry 22nd annual report, NICE guideline on Chronic Kidney Disease[24]
2nd + years	8,332	
Blindness		
1st year	3606	Alva et al. 2015[23]
2nd+ years	1366	

Input variables	Mean cost per year(£)*	Source/ Comments
Ulcer		
Active ulcer	3,520	Kerr et al (2019)[26]
Amputation		
1st year	14041	Alva et al. 2015[23]
2nd + years	3902	

**Older costs have been inflated to 2020 prices using the Unit Costs of Health and Social Care 2020 indices[27]*

2.3.3.3 Administration and monitoring costs

The committee noted that some treatments will require increased costs associated with drug consumables and initiation time.

The committee felt that both sulfonylurea and insulin were likely to be associated with self-monitoring of blood glucose (SMBG). It was noted that the number of tests was likely to vary depending on whether the patient was a driver or not, with increased tests being required if driving. Non-drivers were modelled to have the following SMBG rates, provided by the committee. The cost of each SMBG was assumed to be £0.26 as in the NICE diabetes in pregnancy guideline (NG3).

Table HE019: Modelled SMBG tests per week

Treatment	SMBG per week
Sulfonylurea	4
Insulin	10.5

Insulin and GLP-1s also require injections and the cost of needles was also accounted for in the model. NPH insulin was associated with 1 injection per day (NG28) and the GLP-1s were modelled as weekly or daily injections in accordance with the associated CVOT. The only GLP-1 which was not associated with additional consumable costs was oral semaglutide which is available in tablet form. The cost of each needle was assumed to be £0.05 in line with assumptions used in the NICE guideline on Type 1 diabetes (NG17). The committee believed this value to be reasonable and noted that needles with a cost around than £5 per 100 were widely available. Injectable semaglutide, dulaglutide and exenatide have needles included with them. Hence additional needle costs were not assumed for these three injectable treatments.

Table HE020: Modelled injections

Treatment	Daily Injections
NPH Insulin	1
Semaglutide (injectable)	0.14
Liraglutide	1
Dulaglutide	0.14
Exenatide	0.14
Lixisenatide	1

Initiation costs for insulin and GLP-1s were also applied. The method and setting of initiating these drugs is subject to variation however the committee agreed that initiation via a nurse would likely represent best practice and that the times on the following table should be

sufficient to initiate the drug. Nursing costs were taken from PSSRU Unit Costs of Health and Social Care at £49 and £59 per hour for a Band 6 and Band 7 nurse respectively.

Table HE021: Administration resource use for insulins and GLP-1s

Treatment	Initiation appointments	Total Time
GLP-1	2 x 20 minute	40 minutes
Insulin	1 x 40 minute + 5 x 20 minute	2 hours 20 minutes

The table below summarises the consumable and staff costs used in the model.

Table HE022: Administration costs included in the model

Treatment	Cost
Needle	£0.05
SMBG	£0.26
Band 7 nurse (hourly)	£59
Band 6 nurse (hourly)	£49
GLP-1 initiation	£35.64
Insulin	£125.82

2.3.3.4 Hypoglycaemia costs

In the NICE guideline looking at type 1 diabetes in adults[28], a detailed evaluation in the costs of managing hypoglycaemic events in type 1 diabetic patients was done, with information from Hammer et al. 2009[29] being used to obtain the cost of severe hypoglycaemic events in type 1 diabetes patients. Hammer et al also reported these costs for a type 2 population, and after consultation with the committee, these costs were used in the analysis as the committee was of the opinion that the costs reported by Hammer et al for severe hypoglycaemic events in type 2 diabetes patients were reflective of a UK population. Geelhoed et al. 2013[30] shows that the costs associated with a non-severe hypoglycaemic event (NSHE) is minimal, with only 2.3% of patients experiencing a NSHE contacting a healthcare professional, and a NSHE only resulting in roughly 0.72 additional SMGB tests per week. Hence upon presenting these results to the committee a cost of 0 was assumed for a NSHE as the resource use was expected to be minimal. Details of these studies along with the costs used are reported in Table HE024: Hypoglycaemic costs.

Table HE023: Hypoglycaemic costs

Input variables	Mean cost per year*	Source/ Comments
Non-severe hypoglycaemic events	0	Information from Geelhoed et al[30] shows that the costs associated with a non-severe hypoglycaemic event (NSHE) are minimal, with only 2.3% of patients experiencing a NSHE contacting a healthcare professional, and a NSHE only resulting in roughly 0.72 additional SMGB tests per week. Hence a cost of 0 was assumed.
Severe hypoglycaemic event	£373	Based on information from Hammer et al[29] who reported results from 120 T2D patients in the UK. Here direct resource use costs included both in-hospital and outside of hospital (ambulance services, drugs administered, admission and care treatment, follow-up care, attendance by healthcare professional) at the time of SHE and in follow-up

Input variables	Mean cost per year*	Source/ Comments
		(additional doctor visits, SMGB tests, further education in self-management). Unit costs were sourced from country specific and obtained from local health tariffs, formularies, and office for national statistics. The other potential source for hypoglycaemic was a study by Heller et al[31] which reported resource use of severe hypoglycaemic events in 15 phase 3a trials. Given that this study only reported resource used (and not costs) a separate micro costing was needed to identify potential UK specific costs for ambulance, emergency room, non-medical assistance costs, etc. Given a lack of clarity about reliable sources for these costs we decided to use the data from Hammer et al, especially as the committee saw no significant limitations in the study by Hammer el al.

2.3.4 Doses

The treatment doses were taken directly from NG28, which used average doses from the included RCTs (NG28 Economic Appendix, Section 3.9).

2.3.4.1 Initial therapy

At initial therapy two treatments were modelled. Metformin was modelled for the addition question, where a CVOT drug was modelled as being added to existing therapy. Placebo was modelled for the replacement question, where a CVOT drug would replace metformin.

The doses are combined with the costs listed above to give an annual drug cost. Note that this excludes the cost of consumables which are covered in section 2.3.3.3.

Table HE024: Dose and annual drug cost

	Daily dose (mg)		Annual treatment cost	
Treatment	**Year 1**	**Year 2 onwards**	**Year 1**	**Year 2 onwards**
Metformin	1663.6	1751.5	£34.83	£36.67
Placebo	0	0	£0.00	£0.00

2.3.4.2 First intensification

At first intensification the treatment for the addition question is metformin-sulfonylurea. As the replacement question requires the removal of one of these drugs the committee stated that the drug most likely to be replaced is sulfonylurea. NG28 did not report treatment doses for metformin monotherapy at this stage of intensification and so the committee agreed that using initial therapy values would be appropriate in the absence of more robust data.

The doses are combined with the costs listed above to give an annual drug cost. Note that this excludes the cost of consumables which are covered in Section 2.3.3.3

Table HE025: Dose and annual drug cost

	Daily dose (mg)		Annual treatment cost	
Treatment	**Year 1**	**Year 2 onwards**	**Year 1**	**Year 2 onwards**
Metformin	1771.6	1858.6	£52.56	£67.22
Sulfonylurea	78.5	143.6		

2.3.4.3 Second intensification

At second intensification the treatment for the addition question is metformin-NPH insulin-sulfonylurea and the treatment for the replacement question is metformin – NPH insulin as the committee believed that sulfonylurea would again be the treatment most likely to be replaced.

The doses are combined with the costs listed above to give an annual drug cost. Note that this excludes the cost of consumables which are covered in Section 2.3.3.3. For insulin-based treatments these costs are large (around £200 per year).

Table HE026: Dose and annual drug cost

	Daily dose (mg)		Annual treatment cost	
Treatment	**Year 1**	**Year 2 onwards**	**Year 1**	**Year 2 onwards**
Metformin-NPH insulin				
Metformin	2234.2	2252.0	£294.17	£345.70
NPH insulin	47.4 units	57.2 units		
Metformin-NPH insulin-sulfonylurea				
Metformin	2079.5	2079.5	£224.88	£231.14
NPH insulin	28.7 units	29.9 units		
Sulfonylurea	160.0	160.0		

2.3.5 Utility values

2.3.5.1 Diabetic events

Committee were presented with two potential sources of utility values for diabetic events: a study of quality of life in UKPDS patients (Alva et al. 2014[32]), and a systematic review of utility values used in modelling of Type 2 diabetes (Beaudet et al. 2014[33]). Committee opted to use the values from Beaudet et al. as these were aligned to the values used in the Type 1 diabetes insulin update[28]. Beaudet et al. reports utility values for moderate retinopathy, vision threatening retinopathy and severe vision loss; committee considered that severe vision loss best corresponded to the blindness event modelled in the UKPDS (blindness in one eye). The study also disaggregates utility values for renal failure into modes of renal replacement therapy (hemodialysis, peritoneal dialysis and renal transplant). To align this to the renal failure outcome modelled in the UKPDS, a weighted average was taken based on distributions of renal replacement therapy modalities taken from the UK Renal Registry 22nd Annual Report[25] (Table 1.7); hemodialysis contributed 70% of the weighted average, peritoneal dialysis contributed 20.1% and renal transplant contributed 9.9%. For the baseline utility information from Alva et al[32] was used as this was a more up to date population of the UKPDS and was thought to be more reflective of a contemporary setting. Alva et al did also report information on the impact on quality of life for other diabetic events. However, this information was not used as there were concerns with the results of the recommended fixed effects model in the paper with respect to their plausibility, as it reported a positive utility impact for blindness in one eye and for a population with a history of MI. Given that a more up to date population was less likely to affect the disutility from diabetic events (given that it was calculated with respect the baseline quality of life), the concerns mentioned above outweighed the advantages of a more up to date population. A sensitivity analysis was run using information from Alva et al for disutility from diabetic events to check for the robustness of our methods. The utility values used in the model are outlined in Table HE028: Quality of life parameters. Utility decrements were not accounted for by age as this was difficult to implement within the multi-state model cohort structure and would significantly increase model run time. However, given that the baseline population utility was sourced from a type 2

diabetes population, the changes in utility with age have been partially accounted for. Furthermore, accounting for changes in utility with increasing age is unlikely to have a significant impact on the treatment decision given that this would apply across all treatment arms and would only have an impact if there were substantial differences between treatments in the time spent living in the model, which is not the case for all analyses. Note that when accounting for in the impact on quality of life due to diabetic events, decrements in quality of life was only assumed for the year of the event and not adjusted for in subsequent years (hence assumed to be permanent).

Table HE027: Quality of life parameters

Diabetic event	Utility value	Reference
Baseline	0.815	Alva et al[32]
IHD	-0.09	Beaudet et al. (2014)[33]
MI	-0.055	
Heart failure	-0.108	
Stroke	-0.164	
Amputation	-0.28	
Ulcer	-0.17	
Severe vision loss	-0.074	
Hemodialysis	-0.164	Beaudet et al. (2014)[33]. Weighted average taken from UK Renal Registry Annual Report.
Renal transplant	0.762	

2.3.5.2 Mode of administration

A systematic search was undertaken to identify sources reporting the impact on quality of life from different injection regimens. 27 papers were scanned for title and abstract with four of these selected to be scanned by full text. Of these, Evans et al[34], Olofsson et al[35] and Ridderstale et al[36] reported information on the differences in quality of life between once daily and twice daily regimens. However only Olofsson et al. reported to sufficient information to calculate the impact of life when a patient moves from 0 injections to 1 injection, as it reported baseline utility values.

Olofsson et al. collected data via a web based platform time-trade-off (TTO) study where respondents are asked to “trade off” a portion of their remaining life span for an improved health state when compared to a hypothetical health state. The TTO survey presented six hypothetical scenarios (+2 fixed insulin doses, +1 fixed insulin dose, +1 flexible insulin dose, +1 fixed insulin dose + 1kg weight gain, + 1 fixed insulin dose + 3kg weight gain and baseline diabetes without insulin) where the respondent could choose between living for the rest of his/her life with diabetes and receiving treatment with a basal insulin with certain attributes or live for a shorter time with full health. 991 TTO responses from Sweden were included (526 diabetic, 495 general). A willingness-to-pay questionnaire was also given to the participants. Results were reported for the general population and diabetic population under basal only and basal-bolus regimens. To inform the model, the quality of life of patients in the diabetic population receiving no injections and one injection were considered, suggesting that a utility decrement of 0.029 was experienced by patient for the additional injection. This utility decrement was applied to all CVOT treatments where an injection is used in the treatment administration process, with the value divided by 7 for treatments that involve weekly administration. The utility decrement was not applied to insulin injections as a simplifying assumption as these would be broadly equal between all treatment arms given that there is never significant difference in the proportion of people taking insulin between the treatment arms.

2.3.5.3 Hypoglycaemia

Sources for impact on quality of life from severe and non-severe hypoglycaemic events were identified by looking at the sources identified in the current NICE guideline update for type 1 diabetes[28]. In this guideline the impact of hypoglycaemic events on quality of life was identified by looking at primary sources for quality of life parameters from the systematic review of economic evidence. The guideline used information from Evans et al[37] who reported results for a diabetic population (inclusive of both type 1 and type 2 diabetic patients). This study was deemed feasible to be use in our analysis by the committee.

Evans et al. performed a web-based TTO study where respondents are asked to "trade off" a portion of their remaining life span for an improved health state when compared to a hypothetical health state. 8,286 respondents were included from the UK, USA, Canada and Germany, which included 551 type 1 and 1,603 type 2 diabetes patients. Impact on quality of life was reported for severe day time, severe nocturnal, non-severe daytime and non-severe nocturnal hypoglycaemic events, with results reported by country. Hence Evans et al. reported information on all four categories of hypoglycaemic events required and was therefore used in our analysis. Evans et al reported decrements in quality of life of -0.062 for daytime severe hypoglycaemic events . When looking at the impact on quality of life from non-severe hypoglycaemic events, the model accounts for diminishing non-severe hypoglycaemic utility (i.e. that the quality of life loss associated with having 2 non-severe hypoglycaemic events is less than twice the loss associated with 1 non-severe event) using information from Lauridson et al[38] whose analysis was based on the same data set as Evans et al. Lauridson et al reported disutility equations of $0.0141x^{0.3393}$ for non-severe daytime hypoglycaemic events, with x being the rate of hypoglycaemic events.

2.3.5.4 Weight

A utility decrement of -0.0061 was assumed per 1 unit increase in BMI above 25kg/m^2. This value was taken from Bagust et al. (2005)[39] and is consistent with the approach taken for modelling weight in NG28.

3 Subgroup and sensitivity analyses

3.1 Subgroup analyses

The committee were asked whether there were any subgroups in which the cost-effectiveness of the CVOT drugs might differ from the results from the main cohort of patients with Type 2 diabetes.

The committee decided against extracting subgroup data in the clinical review as they believed that the relative treatment effectiveness observed in the CVOT trials would be applicable to all subgroups, as the mechanism of action of the drugs was expected to have the same effect in all groups. For this reason, the treatment effects, costs and utility values outlined in Section 2.3.2 are applied for all subgroups.

However, the committee did believe that differences in the baseline characteristics of some groups of patients could lead to a difference in absolute treatment effectiveness, and hence cost-effectiveness, compared to the main cohort of patients being explored in the model.

The committee chose to explore the following subgroups:

- People with a BMI of greater than or equal to 30kg/m^2
- People at high risk of a cardiovascular event who have not had a prior event
- People who have had a prior cardiovascular event
- People who have had a prior cardiovascular event and people at high risk of a cardiovascular event who have not had a prior event.

3.1.1 BMI subgroup

The committee considered that people with a BMI of greater than 30kg/m^2 have a higher baseline risk of long-term diabetic and cardiovascular events and so may benefit more from CVOT interventions that reduce the risk of cardiovascular events.

3.1.2 High cardiovascular risk (primary prevention)

The committee noted that 10 of the 16 CVOT trials identified in the clinical review had selection criteria that included patients who were at high risk of cardiovascular events but had not had a previous event. The committee considered that in practice, clinicians may use different treatment options for the primary prevention of cardiovascular events in high risk patients compared to treatments given for glycaemic control in the broader Type 2 diabetes population. Committee recognised that all patients with Type 2 diabetes were likely to be at a higher cardiovascular risk than the general population, and so chose criteria to reflect a subgroup of patients that were at substantially higher risk of cardiovascular event than the main cohort. The committee chose to model a subgroup analysis based on the following criteria:

- Male aged ≥ 55 or female aged ≥ 60

AND at least one of the following:

- Systolic blood pressure ≥ 160
- Smoker
- LDL ≥ 3.5
- eGFR <45
- Presence of microalbuminuria
- BMI ≥ 35 (or ≥32 for BAME patients). The committee considered that cardiovascular risks associated with high BMI may differ by ethnicity and so opted to include patients with a

lower BMI in the subgroup if they were from a BAME family background. The THIN dataset only reported data on black and Asian ethnic background and so this was used as a proxy for the broader BAME group.

Evidence on the baseline characteristics for this subgroup was taken from the THIN database extract outlined in Section 2.3.1. The gender-stratified age threshold aligned to the criteria most commonly used across the CVOT trials that included the primary prevention subgroup. Remaining criteria were chosen by committee with the aim of generating a subgroup with a substantially higher cardiovascular risk than the main cohort, and were informed by the selection criteria used in the CVOT trials.

3.1.3 High cardiovascular risk (secondary prevention)

6 of the 16 CVOT trials identified in the clinical review were conducted exclusively in patients who had a previous cardiovascular event. The committee chose to explore a subgroup analysis aligned to this trial population to explore whether the optimal treatment for secondary prevention of cardiovascular events would differ from optimal treatments used in primary prevention or in the broader Type 2 diabetes population. Evidence on the baseline characteristics for this subgroup was taken from the THIN database extract outlined in Section 2.3.1.

3.1.4 High cardiovascular risk (primary and secondary prevention)

The committee were also interested in seeing cost-effectiveness results for the subgroups outlined in Sections 3.1.2 and 3.1.3 when combined.

3.2 Sensitivity analyses

Due to discounting, a greater weight is placed on costs and QALYs from events that happen in the short term (such as hypoglycaemic episodes, treatment-related weight gain and injections) compared to events that happen in the long term (such as averting a heart attack 20 years into the model). As short-term events were identified as key drivers in the model, sensitivity analysis was used to assess the effect of uncertainty in the model inputs for these events.

A sensitivity analysis was also conducted to explore the effect of adjusting for cardiovascular mortality rates observed in the CVOT trials (see section 3.5.6).

Due to model run times it was not possible to conduct a probabilistic sensitivity analysis for all subgroups at all treatment stages. As the majority of patients in the model are on second intensification, a probabilistic sensitivity analysis was run to explore uncertainty in this group for the main cohort of people with Type 2 diabetes.

3.2.1 Utility decrement for injections

As outlined in Section 2.3.5.2, a utility decrement was applied to CVOT treatments which involve administration by injection. This utility decrement has a substantial effect on the cost-effectiveness estimates as:

- The utility decrement is applied to all patients receiving the intervention for the duration of their treatment (which is assumed to be lifetime after treatment has commenced).
- The disutility can be incurred from an early point in the model (whenever treatment commences) meaning that QALYs associated with the injection decrement are weighted more heavily than QALYs associated with diabetic events predicted to happen several years into the future.

A sensitivity analysis was therefore run to explore the impact on cost-effectiveness estimates when the utility decrement was removed from the analysis. As the committee considered that there was likely to be some disutility associated with injections in practice, this sensitivity analysis represented an 'extreme' lower-bound scenario that was unlikely to be clinically plausible.

3.2.2 Hypoglycaemic events

Hypoglycaemic event rates for the CVOT drugs were taken from the clinical review. Several of the estimates were non-significant with wide confidence intervals, indicating uncertainty. Further to this, there was also uncertainty in the baseline rates of events to which the treatment effects were applied due to lack of evidence (see section 2.3.2.5).

Hypoglycaemic events were another key driver of the model, largely because they could happen at an early point in the model where QALY losses are less heavily discounted.

Due to the uncertainty around this parameter and its importance to the results, a sensitivity analysis was run to explore the effect of removing the influence of hypoglycaemic events on QALYs in the model.

3.2.3 BMI

The base-case analysis included the effect of CVOT drugs on BMI. As outlined in section 2.3.2.4, there were challenges to the estimation of these treatment effects as weight and BMI outcomes were not consistently reported in the CVOTs. Baseline BMI was calculated from the mean height and weight values in the THIN dataset and were applied to all patients meaning that heterogeneity in BMI was not captured.

As with hypoglycaemic events and injections, changes in BMI could lead to QALY gains or losses at an early point in the model when they are subject to less heavy discounting meaning that treatment effect on BMI is a potential key driver of the model.

Due to the uncertainty around this parameter and its importance to the results, a sensitivity analysis was run to explore the effect of removing treatment effect on BMI from the model.

3.2.4 Adverse events

A scenario analysis incorporating the severe adverse events (SAEs) reported in trials was conducted to assess the impact of potential differences in adverse event rates. This scenario analysis was only carried out for the second intensification-replacement question.

While there was considerable overlap, precise definitions for severe adverse event rates varied by trial and hence this information is included in a scenario to give an indication of any potential impact.

Severe adverse event rates were taken from the CVOT trials and the total % difference in events between arms was combined with the median follow-up to give an estimate for the treatment-related annual severe adverse event rate change. Where a trial did not report this information the average value from treatments in the same class was used. To estimate the impact of these events the cost and QALY values for severe hypoglycaemia are used. Note that the calculations for this sensitivity analysis are performed using the results produced by the MSM, and not within the MSM model itself.

Table HE028: Rates of adverse events

Trial	Treatment	Placebo Severe Adverse Event Rate	Treatment Severe Adverse Event Rate	Median follow-up years	Annual Increased Severe Adverse Events
CANVAS	Canagliflozin	NR	NR	NR	-0.5%
CARMELINA	Linagliptin	38.5%	37.0%	2.2	-0.7%
DECLARE	Dapagliflozin	36.2%	34.1%	4.2	-0.5%
ELIXA	Lixisenatide	22.1%	20.6%	2.08	-0.7%
EMPA-REG	Empagliflozin	25.4%	23.5%	3.2	-0.6%
EXAMINE	Alogliptin	35.5%	33.6%	1.5	-1.3%
EXSCEL	Exenatide	16.8%	16.6%	3.2	-0.1%
LEADER	Liraglutide	50.4%	49.7%	3.8	-0.2%
PIONEER	Semaglutide (oral)	22.5%	18.9%	1.49	-2.4%
PROactive	Pioglitazone	46.2%	48.4%	2.88	0.8%
REWIND	Duluglutide	NR	NR	NR	-0.9%
SAVOR-TIMI	Saxagliptin	NR	NR	NR	-1.0%
SUSTAIN	Semaglutide (injectable)	38.0%	34.3%	2	-1.9%
TECOS	Sitagliptin	NR	NR	NR	-1.0%
VERTIS-CV	Ertugliflozin	36.1%	34.5%	3.5	-0.4%

3.2.5 Cardiovascular mortality

In the base-case analysis cardiovascular mortality is modelled indirectly as a result of increased or decreased cardiovascular event rates reported from the CVOT trials.

In this sensitivity analysis the model was calibrated to match the cardiovascular mortality hazard ratio reported in the trials. Calibration to trial cardiovascular mortality hazard ratios was achieved by extracting the likelihood of cardiovascular mortality in each year for the reference treatment. The trial cardiovascular mortality hazard ratio was applied to this to give the expected annual hazard ratio adjusted likelihood of cardiovascular mortality. The model is then run with event hazard ratios (e.g. stroke, MI) applied as in the base case to give the change in mortality associated with differential event rates alone. The number of fatal events are then proportionally adjusted to match the expected annual hazard ratio adjusted likelihood of CV mortality calculated above. A corresponding adjustment is made to non-fatal events to ensure that overall event hazard ratios remain unchanged.

For the majority of treatments this resulted small differences (see Section 2.3.2.3 for details). Due to the extended run time of the model, this analysis was only run for the Second Intensification- Replacement population.

3.2.6 Impact on quality of life from diabetic events

The impact on quality of life from MI, stroke, IHD, heart failure and severe vision loss was sourced as from Alva et al. The analysis from Alva et al was done on a more recent study of the UKPDS, and was conducted to test for the robustness of the inputs used in the original analysis, as explained in section 2.3.5.1. The sensitivity analysis was undertaken on the second intensification replacement pathway. Shown below are the values used from Alva et al.

Table HE029: Quality of life parameters

Diabetic event	Utility value
IHD	-0.028
MI	-0.065
Heart failure	-0.101
Stroke	-0.165
Severe vision loss	0.033

3.2.7 Probabilistic sensitivity analysis

In the deterministic analysis, results were estimated for three levels of treatment intensification for regimens where CVOTs replaced components of the non-CVOT standard care and regimens where CVOTs were added to the non-CVOT treatments; this was repeated for 5 populations. Both the UKPDS and multi-state components of the model were associated with long model run times which was prohibitive to running probabilistic sensitivity analyses for all populations covered by the deterministic analysis.

Instead, a probabilistic sensitivity analysis was run on the analysis deemed as having most relevance to the decision problem, and with the greatest potential impact on the NHS: the population of people with Type 2 diabetes at second intensification where CVOT drugs are used to replace components of standard care. This population was chosen as follows:

- The majority of life years experienced in the model fall under the second intensification stage
- The committee considered that in practice clinicians would be more likely to prescribe CVOTs to replace components of treatment regimens rather than prescribing them as additional treatments in the interests of medicines optimisation and reducing potential side-effects.
- The broader population of people with Type 2 diabetes was less well aligned to the study populations from the CVOT trials and is thus associated with more uncertainty.

The UKPDS component of the model already incorporated a stochastic element through the use of bootstraps to select risk-factor equations and was run with a large cohort of patients to reduce Monte-Carlo error. The probabilistic sensitivity analysis therefore focused on varying the outputs of the UKPDS (i.e. the proportions of standard care patients in each state in the multi-state model after exiting the UKPDS), alongside the model inputs used in the multi-state model.

The probabilistic sensitivity analysis was run for 100 loops.

3.2.7.1 Parameter Table for probabilistic sensitivity analysis

Table HE030: Parameters used in probabilistic sensitivity analysis

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters*
Discount rate			
Costs	3.50%		
Effects	3.50%		
Hypoglycaemia rates			
First Intensification (Metformin + Sulfonylurea)			
Baseline rate of severe hypoglycaemic episodes per year	0.09 (0.038 , 0.211)	Dunkey et al. (2019)[19]	Lognormal: μ=-2.408 σ=0.435

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters*
Baseline rate of non-severe hypoglycaemic episodes per year	1.91 (1.433 , 2.546)	Dunkey et al. (2019)	Lognormal: μ=1.131 σ=0.141
Initial therapy (Metformin)			
Adjusted odds ratio of hypoglycaemia on metformin-sulfonylurea vs metformin	4.040 (3.274, 4.986)	Bodmer et al. (2008)[21]	Lognormal: μ=1.396; σ=0.107
Baseline rate of severe hypoglycaemic episodes per year	0.024 (0.0097, 0.067)	Calculated field	
Baseline rate of non-severe hypoglycaemic episodes per year	0.517 (0.35, 0.714)	Calculated field	
Second Intensification (NPH insulin + Metformin)			
Adjusted odds ratio of hypoglycaemia on metformin-sulfonylurea	0.32 (0.192 , 0.534)	Dunkey et al. (2019)	Lognormal: μ=-1.139 σ=0.262
Adjusted odds ratio of hypoglycaemia on sulfonylurea	3.1 (2.35 , 4.09)	Dunkey et al. (2019)	Lognormal: μ=1.131 σ=0.141
Complication costs			
Non-fatal event – year of event *(total costs in £ inflated to 2020 prices)*			
MI	8419 (6769 , 10069)	Alva et al. (2015)[23]	Normal: μ=8419 σ=841.9
IHD	12190 (9801 , 14579)	Alva et al. (2015)	Normal: μ=12190 σ=1219
Heart Failure	4782 (3845 , 5719)	Alva et al. (2015)	Normal: μ=4782 σ=478.2
Stroke	9054 (7279 , 10829)	Alva et al. (2015)	Normal: μ=9054 σ=905.4
Blindness	3606 (2899 , 4313)	Alva et al. (2015)	Normal: μ=3606 σ=360.6
Amputation	14041 (11289 , 16793)	Alva et al. (2015)	Normal: μ=14041 σ=1404.1
Ulcer	3520 (2830 , 4210)	Kerr et al. (2015)	Normal: μ=3520 σ=352
Renal Failure	20897 (16801 , 24993)	NICE CKD Guideline[24]	Normal: μ=20897 σ=2089.7
Fatal event – year of event *(total costs in £ inflated to 2020 prices)*			
MI	8419 (6769 , 10069)	Alva et al. (2015)	Normal: μ=8419 σ=841.9
IHD	12190 (9801 , 14579)	Alva et al. (2015)	Normal: μ=12190 σ=1219
Heart Failure	4782 (3845 , 5719)	Alva et al. (2015)	Normal: μ=4782 σ=478.2
Stroke	9054 (7279 , 10829)	Alva et al. (2015)	Normal: μ=9054 σ=905.4
Blindness	3606 (2899 , 4313)	Alva et al. (2015)	Normal: μ=3606 σ=360.6
Amputation	14041 (11289 , 16793)	Alva et al. (2015)	Normal: μ=14041 σ=1404.1

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters*
Ulcer	3520 (2830 , 4210)	Kerr et al. (2015)	Normal: μ=3520 σ=352
Renal Failure	20897 (16801 , 24993)	NICE CKD Guideline	Normal: μ=20897 σ=2089.7
Nonfatal event - subsequent year costs *(total costs in £ inflated to 2020 prices)*			
MI	2093 (1683 , 2503)	Alva et al. (2015)	Normal: μ=2093 σ=209.3
IHD	2143 (1723 , 2563)	Alva et al. (2015)	Normal: μ=2143 σ=214.3
Heart Failure	2805 (2255 , 3355)	Alva et al. (2015)	Normal: μ=2805 σ=280.5
Stroke	2157 (1734 , 2580)	Alva et al. (2015)	Normal: μ=2157 σ=215.7
Blindness	1366 (1098 , 1634)	Alva et al. (2015)	Normal: μ=1366 σ=136.6
Amputation	3902 (3137 , 4667)	Alva et al. (2015)	Normal: μ=3902 σ=390.2
Ulcer	3520 (2830 , 4210)	Kerr et al. (2015)	Normal: μ=3520 σ=352
Renal Failure	8332 (6699 , 9965)	NICE CKD Guideline	Normal: μ=8332 σ=833.2
Adverse event costs *(total costs in £ inflated to 2020 prices)*			
Severe hypoglycaemic episode	373 (300 , 446)	Hammer et al. (2009)[29]	Normal: μ=373 σ=37.3
Complication QALYs			
Severe Hypoglycaemia	-0.062 (-0.07 , -0.054)	Evans et al. (2013)[37]	Normal: μ=-0.062 σ=0.004
Non-severe Hypoglycaemia Base Parameter	-0.014 (-0.017 , -0.011)	Lauridsen et al. (2017)[38]	Normal: μ=-0.014 σ=0.001
Non-severe Hypoglycaemia Exponent	0.339 (0.273 , 0.406)	Lauridsen et al. (2017)	Gamma: μ=0.339 σ=0.034
MI	0.055 (0.043 , 0.068)	Beaudet et al. (2014)[33]	Gamma: μ=74.373 σ=0.001
IHD	0.09 (0.058 , 0.129)	Beaudet et al. (2014)	Gamma: μ=24.01 σ=0.004
HF	0.108 (0.056 , 0.176)	Beaudet et al. (2014)	Gamma: μ=12.242 σ=0.009
Stroke	0.164 (0.111 , 0.227)	Beaudet et al. (2014)	Gamma: μ=30.192 σ=0.005
Blindness	0.04 (0.018 , 0.07)	Beaudet et al. (2014)	Gamma: μ=9.093 σ=0.004
Amputation	0.28 (0.181 , 0.4)	Beaudet et al. (2014)	Gamma: μ=25.119 σ=0.011
Ulcer	0.17 (0.135 , 0.209)	Beaudet et al. (2014)	Gamma: μ=81.097 σ=0.002

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters*
Renal	0.164 (0.073 , 0.291)	Beaudet et al. (2014)	Gamma: μ=8.539 σ=0.019
Injection disutility	0.029 (0.003 , 0.055)	Oloffson et al. (2016)[35]	Normal: μ=0.029 σ=0.013
Disutility per unit of BMI over 25	0.006 (0.004 , 0.008)	Bagust et al. (2005)[39]	Normal: μ=0.006 σ=0.001
Annual CVOT modelled drug costs (daily dose unless stated)			
Alogliptin (25mg)	£347	NHS Drug Tariff May 2021[22]	
Canagliflozin (300mg)	£477		
Dapagliflozin (10mg)	£477		
Dulaglutide (1.5mg weekly)	£955		
Empagliflozin (25mg)	£477		
Ertugliflozin (15mg)	£383		
Exenatide (2mg weekly)	£956		
Liraglutide (1.8mg)	£1,438		
Linagliptin (5mg)	£434		
Lixisenatide (2μg)	£705		
Pioglitazone (45mg)	£36		
Saxagliptin (5mg)	£412		
Semaglutide (injectable) (1mg weekly)	£952		
Semaglutide (oral) (14mg)	£955		
Sitagliptin (100mg)	£434		
Non-CVOT drug cost per mg (£)			
Metformin	0.0000574		
Sulfonylurea	0.0005402		
NPH insulin	0.0143		
Consumable and NHS staff costs			
Band 7 Nurse hourly cost (£)	49 (39 , 59)	PSSRU Unit Costs of Health and Social Care 2020[27]	Normal: μ=49 σ=4.9
Band 8 Nurse hourly cost (£)	59 (47 , 71)	PSSRU Unit Costs of Health and Social Care 2020[27]	Normal: μ=59 σ=5.9
Insulin Initiation hours required	2.333 (1.88 , 2.79)	Committee assumption	Normal: μ=2.333 σ=0.233
GLP-1 initiation hours required	0.66 (0.531 , 0.789)	Committee assumption	Normal: μ=0.66 σ=0.066
Self-monitoring of blood glucose (£)	0.26	NICE CGM in Pregnancy[40]	
Injection Cost	£0.05	Committee assumption	

**Distributions have been sourced from uncertainty reported in respective studies where available, except in the case of disutility associated with non-severe hypoglycaemia, injection disutility, and event costs (except for severe hypoglycaemic event costs) where a variance equivalent to that of 10% of the mean value was assumed.*

4 Results

Base case results are reported across three stages of intensification (initial therapy, first intensification, second intensification) with CVOTs either as additions or replacements to the non-CVOT standard of care arm. For each CVOT drug, in addition to the projected QALYs and costs, the incremental QALYs, costs and ICERs when compared to the standard of care arm are also reported. The interventions and the respective comparators for each of the intensification stages are as follows:

- Initial therapy (replace): CVOT vs metformin
- Initial therapy (addition): CVOT + metformin vs metformin
- First intensification (replace): CVOT + metformin vs metformin + sulfonylurea
- First intensification (addition): CVOT + metformin + sulfonylurea vs metformin + sulfonylurea
- Second intensification (replace): CVOT+ metformin + sulfonylurea + NPH insulin vs metformin + sulfonylurea + NPH insulin
- Second intensification (addition): CVOT + metformin + sulfonylurea + NPH insulin vs metformin + sulfonylurea + NPH insulin

Net monetary benefit rankings are also reported for each of the analyses at a £20,000 threshold. These provide an indication of the cost-effectiveness of CVOT drugs in relation to each other.

All tables reporting results are ordered by drug class and within class by alphabetical order.

In addition to the total Type 2 population a number of subgroups were also considered in our analysis:

- A high BMI (BMI > 30kg/m2) subgroup
- High cardiovascular risk (primary prevention) – patients considered at high cardiovascular risk based on a number of baseline characteristics as explained in Section 3.1.2)
- High cardiovascular risk (secondary prevention) – patients who have experienced a previous cardiovascular event)
- High cardiovascular risk (primary and secondary prevention) – a combination of the above 2 groups.

A number of sensitivity analyses were also performed across all three intensification stages and for the total population and the relevant subgroups when CVOTs were used as replacements. These included:

- Assuming that the disutility from injections is 0
- Assuming that the disutility from hypoglycaemic events is 0

- Assuming that the disutility from an increase in BMI is 0
- Incorporating severe adverse events reported in trials
- Modelling cardiovascular mortality using hazard ratios reported in trials.

The tables below can be used to interpret the results using the tables below. Listed below are a couple of examples on how best to interpret the results.

- Example 1: If interested in looking at the use of alogliptin instead of sulfonylurea at first intensification in the general population with T2 diabetes, we would look at Table HE033 and see that it is dominated.
- Example 2: If we were interested in looking at adding canagliflozin to metformin, sulfonylurea and NPH insulin at second intensification in people with high cardiovascular risk but no prior event, we would look at Table HE043 and see it has an ICER of £31,780.

4.1 Base-case

Base case results followed a similar pattern across all analysed populations. This indicated that despite differences in baseline characteristics, changes in weight at 1st year, and treatment costs of the standard of care arm, treatment decisions were primarily driven by differences in cardiovascular risks between treatments considered. It is worth noting that whilst there were differences in the baseline characteristics of the populations, these differences were not significantly large. Hence when these characteristics were transformed to underlying cardiovascular risks is the SoC arm using the OM2 equations, the differences in underlying cardiovascular risks between arms were not significant enough to amplify any applied treatment effects in particular populations. SGLT2's and injectable semaglutide were the only treatments to have ICERs in the range of £20,000 to £30,000 across all populations, and dapagliflozin was the only CVOT to have an ICER below £20,000. Both DPP-4's and GLP-1's other than injectable semaglutide were either dominated or had very large ICERs compared to the non-CVOT arm. DPP-4's had generally lower ICERs than GLP-1's across all populations in the base case analysis. The cost-effectiveness of SGLT2's mainly stemmed from treatment effects supporting SGLT2's when compared to the non-CVOT arm.

4.1.1 Initial therapy

Table HE031: CVOTs as replacements

Drug	Cost (£)	QALY	Incremental cost (£)	Incremental QALYs	ICER
Alogliptin	£22,841	9.505	£4,416	-0.052	Dominated
Linagliptin	£23,665	9.577	£5,240	0.020	£264,993
Saxagliptin	£24,502	9.305	£6,077	-0.252	Dominated
Sitagliptin	£24,153	9.608	£5,728	0.051	£113,200
Dulaglutide	£31,056	9.710	£12,631	0.153	£82,804
Exenatide	£31,203	9.639	£12,778	0.082	£156,114
Liraglutide	£37,441	9.536	£19,016	-0.021	Dominated

Drug	Cost (£)	QALY	Incremental cost (£)	Incremental QALYs	ICER
Lixisenatide	£27,585	9.224	£9,160	-0.333	Dominated
Semaglutide (injection)	£30,958	10.046	£12,533	0.489	£25,616
Semaglutide (oral)	£32,280	9.309	£13,855	-0.248	Dominated
Pioglitazone	£19,705	9.538	£1,280	-0.019	Dominated
Canagliflozin	£25,166	9.830	£6,741	0.273	£24,657
Dapagliflozin	£24,423	9.902	£5,998	0.345	£17,375
Empagliflozin	£24,710	9.796	£6,285	0.239	£26,265
Ertugliflozin	£23,232	9.749	£4,807	0.192	£25,090

Table HE032: **CVOTs as additions**

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Alogliptin	£22,061	9.408	£4,496	-0.062	Dominated
Linagliptin	£22,813	9.491	£5,248	0.021	£248,971
Saxagliptin	£23,806	9.200	£6,241	-0.270	Dominated
Sitagliptin	£23,387	9.503	£5,822	0.033	£177,546
Dulaglutide	£30,154	9.631	£12,589	0.161	£78,166
Exenatide	£30,446	9.534	£12,881	0.064	£202,472
Liraglutide	£36,478	9.466	£18,913	-0.004	Dominated
Lixisenatide	£26,543	9.179	£8,977	-0.291	Dominated
Semaglutide (injection)	£30,130	9.943	£12,565	0.473	£26,552
Semaglutide (oral)	£31,890	9.147	£14,325	-0.323	Dominated
Pioglitazone	£19,212	9.373	£1,647	-0.097	Dominated
Canagliflozin	£24,485	9.696	£6,920	0.226	£30,664
Dapagliflozin	£23,399	9.837	£5,834	0.367	£15,899
Empagliflozin	£23,785	9.714	£6,220	0.244	£25,526
Ertugliflozin	£22,316	9.668	£4,751	0.198	£24,004

4.1.2 First intensification

Table HE033: CVOTs as replacements

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Alogliptin	£22,657	8.950	£4,183	-0.045	Dominated
Linagliptin	£23,409	9.017	£4,934	0.022	£221,103
Saxagliptin	£24,261	8.752	£5,786	-0.243	Dominated
Sitagliptin	£23,933	9.044	£5,458	0.049	£112,315

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Dulaglutide	£30,450	9.144	£11,976	0.149	£80,490
Exenatide	£30,614	9.073	£12,140	0.078	£155,507
Liraglutide	£36,517	8.979	£18,043	-0.016	Dominated
Lixisenatide	£27,112	8.680	£8,637	-0.315	Dominated
Semaglutide (injection)	£30,470	9.477	£11,995	0.482	£24,908
Semaglutide (oral)	£31,586	8.743	£13,111	-0.252	Dominated
Pioglitazone	£19,780	8.973	£1,306	-0.022	Dominated
Canagliflozin	£24,916	9.244	£6,441	0.249	£25,882
Dapagliflozin	£24,158	9.320	£5,684	0.325	£17,497
Empagliflozin	£24,435	9.209	£5,961	0.213	£27,927
Ertugliflozin	£23,001	9.171	£4,527	0.176	£25,755

Table HE034: CVOTs as additions

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Alogliptin	£22,878	8.705	£4,266	-0.064	Dominated
Linagliptin	£23,516	8.795	£4,905	0.027	£179,895
Saxagliptin	£24,592	8.487	£5,980	-0.281	Dominated
Sitagliptin	£24,181	8.792	£5,569	0.024	£231,735
Dulaglutide	£30,453	8.937	£11,841	0.169	£70,257
Exenatide	£30,832	8.825	£12,220	0.057	£213,122
Liraglutide	£36,412	8.790	£17,800	0.022	£808,413
Lixisenatide	£26,908	8.518	£8,297	-0.250	Dominated
Semaglutide (injection)	£30,622	9.230	£12,010	0.462	£25,974
Semaglutide (oral)	£32,300	8.413	£13,688	-0.355	Dominated
Pioglitazone	£20,467	8.640	£1,855	-0.128	Dominated
Canagliflozin	£25,297	8.970	£6,685	0.202	£33,152
Dapagliflozin	£24,035	9.141	£5,423	0.373	£14,540
Empagliflozin	£24,454	9.006	£5,842	0.238	£24,584
Ertugliflozin	£23,026	8.967	£4,414	0.199	£22,153

4.1.3 Second intensification

Table HE035: CVOTs as replacements

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Alogliptin	£23,704	8.077	£3,876	-0.047	Dominated

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Linagliptin	£24,350	8.150	£4,522	0.026	£175,448
Saxagliptin	£25,203	7.878	£5,375	-0.247	Dominated
Sitagliptin	£24,936	8.163	£5,108	0.039	£130,822
Dulaglutide	£30,853	8.276	£11,025	0.152	£72,742
Exenatide	£31,095	8.194	£11,267	0.070	£161,775
Liraglutide	£36,453	8.133	£16,625	0.008	£1,984,769
Lixisenatide	£27,630	7.856	£7,802	-0.268	Dominated
Semaglutide (injection)	£31,067	8.584	£11,239	0.460	£24,453
Semaglutide (oral)	£32,049	7.846	£12,221	-0.278	Dominated
Pioglitazone	£21,314	8.073	£1,486	-0.051	Dominated
Canagliflozin	£25,950	8.344	£6,122	0.220	£27,851
Dapagliflozin	£25,030	8.448	£5,202	0.323	£16,088
Empagliflozin	£25,329	8.328	£5,501	0.204	£26,958
Ertugliflozin	£23,967	8.296	£4,140	0.172	£24,052

Table HE036: CVOTs as additions

Drug	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Alogliptin	£23,553	7.810	£3,949	-0.065	Dominated
Linagliptin	£24,080	7.903	£4,475	0.029	£156,837
Saxagliptin	£25,161	7.592	£5,557	-0.283	Dominated
Sitagliptin	£24,814	7.891	£5,210	0.016	£329,076
Dulaglutide	£30,453	8.048	£10,849	0.173	£62,654
Exenatide	£30,922	7.926	£11,318	0.051	£222,593
Liraglutide	£35,927	7.922	£16,323	0.048	£343,276
Lixisenatide	£27,020	7.668	£7,416	-0.207	Dominated
Semaglutide (injection)	£30,833	8.325	£11,229	0.450	£24,950
Semaglutide (oral)	£32,385	7.491	£12,781	-0.384	Dominated
Pioglitazone	£21,665	7.722	£2,061	-0.153	Dominated
Canagliflozin	£25,972	8.048	£6,368	0.173	£36,849
Dapagliflozin	£24,523	8.243	£4,918	0.368	£13,357
Empagliflozin	£24,973	8.098	£5,369	0.224	£24,011
Ertugliflozin	£23,616	8.066	£4,011	0.191	£20,983

4.1.4 Net monetary benefit rankings

Shown below is the ranking of CVOTs based on the net monetary benefit at a willingness to pay-per-QALY of £20,000 for each of the analyses.

Table HE037: NMB Rankings

	Initial therapy		First intensification		Second intensification	
Drug	**Replace**	**Addition**	**Replace**	**Addition**	**Replace**	**Addition**
Alogliptin	10	10	10	10	10	10
Linagliptin	9	8	9	7	8	7
Saxagliptin	12	13	13	13	13	13
Sitagliptin	8	9	8	9	9	8
Dulaglutide	11	11	11	11	11	11
Exenatide	13	12	12	12	12	12
Liraglutide	16	15	16	15	15	15
Lixisenatide	14	14	14	14	14	14
Semaglutide (injection)	7	6	7	6	6	5
Semaglutide (oral)	15	16	15	16	16	16
Pioglitazone	6	7	6	8	7	9
Canagliflozin	4	5	4	5	5	6
Dapagliflozin	1	1	1	1	1	1
Empagliflozin	5	4	5	4	4	4
Ertugliflozin	3	3	3	3	3	3

4.2 Subgroup analyses

The tables below outline ICERs and net monetary benefit rankings (at £20,000 per QALY) for the subgroup analyses at each stage of treatment. The definitions of the subgroups considered are explained in more detail in Section 3.1. Subgroup results are reported across the three stages of intensification for the add or replace populations. In general, SGLT2's and injectable semaglutide remained the treatments with ICERs in the range of £20,000 to £30,000 across all subgroups, with dapagliflozin continuing to have ICERs below £20,000. The only notable change in the results when compared to the base case is in the subgroup looking at patients with a prior cardiovascular event. Here, the ICER for pioglitazone drops below £30,000 when CVOTs are used as replacements in the initial therapy and fist intensification stages. This is largely due to the favourable treatment effects pioglitazone has for the outcome of stroke; patients in the subgroup have a higher risk of stroke and are therefore expected to have a greater benefit from pioglitazone. Across other subgroups, the change in the characteristics of the baseline population did not result in significant differences after the application of treatment effects on cardiovascular outcomes. Whilst it was expected that treatments reducing the risk of cardiovascular events would be more cost-effective in higher cardiovascular risk groups, there seems to be no particular trend of this. This shows that any amplified treatment benefits in these populations are offset by the lower life expectancy in these population, meaning that treatment benefits are experienced for a shorter time frame. Dapagliflozin continues to be the only CVOT to have an ICER below

£20,000 in all subgroups. The cost-effectiveness of injectable semaglutide also improved in the subgroup limited to a population with a prior cardiovascular event.

4.2.1 Initial therapy

Table HE038: CVOTs as replacements

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£183,668	9	Dominated	10	£253,608	9	£201,896	8
Saxagliptin	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£101,109	8	£81,304	8	£108,516	8	£120,975	9
Dulaglutide	£69,424	11	£63,370	11	£67,182	11	£85,297	11
Exenatide	£122,848	12	£108,617	13	£122,487	12	£161,964	12
Liraglutide	Dominated	16	£303,233	16	£40,782,855	16	Dominated	16
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£23,569	7	£21,304	6	£23,877	7	£27,345	7
Semaglutide (oral)	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Pioglitazone	£64,230	5	£19,029	2	£59,915	5	Dominated	6
Canagliflozin	£20,113	3	£20,906	4	£20,318	3	£23,468	5
Dapagliflozin	£16,151	1	£16,556	1	£16,259	1	£16,550	1
Empagliflozin	£24,863	6	£22,147	5	£24,963	6	£23,366	4
Ertugliflozin	£22,212	4	£33,181	7	£22,502	4	£22,460	3

Table HE039: CVOTs as additions

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£180,134	8	Dominated	10	£246,771	8	£197,198	8
Saxagliptin	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£142,839	9	£106,216	8	£156,778	9	£198,878	9
Dulaglutide	£67,281	11	£60,963	11	£65,234	11	£80,323	11
Exenatide	£148,989	12	£127,832	13	£148,364	12	£213,942	12
Liraglutide	£1,553,519	15	£243,109	15	£1,404,163	15	Dominated	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£24,383	6	£21,916	4	£24,671	6	£28,353	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Pioglitazone	Dominated	7	£56,283	6	Dominated	7	Dominated	7
Canagliflozin	£24,032	4	£24,057	5	£24,225	5	£29,178	5
Dapagliflozin	£15,124	1	£15,380	1	£15,207	1	£15,193	1
Empagliflozin	£24,581	5	£21,567	3	£24,633	4	£22,858	4
Ertugliflozin	£21,725	3	£31,165	7	£21,995	3	£21,675	3

4.2.2 First intensification

Table HE040: CVOTs as replacements

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£138,696	8	Dominated	10	£369,885	9	£183,720	8
Saxagliptin	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£105,129	9	£83,261	8	£110,870	8	£120,070	9
Dulaglutide	£68,843	11	£61,113	11	£66,033	11	£83,644	11
Exenatide	£126,756	12	£109,784	13	£125,883	12	£163,007	12
Liraglutide	£35,964,948	16	£325,168	16	£6,643,086	16	Dominated	16
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£23,454	7	£20,993	4	£23,331	7	£26,589	7
Semaglutide (oral)	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Pioglitazone	£1,025,547	5	£21,248	3	£91,791	5	Dominated	6
Canagliflozin	£21,472	3	£23,043	5	£22,184	3	£24,706	5
Dapagliflozin	£16,268	1	£17,506	1	£16,679	1	£16,696	1
Empagliflozin	£26,369	6	£25,700	6	£27,374	6	£24,642	4
Ertugliflozin	£22,430	4	£38,814	7	£24,246	4	£23,119	3

Table HE041: CVOTs as additions

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£120,902	8	Dominated	10	£266,890	8	£151,725	7
Saxagliptin	Dominated	13	Dominated	12	Dominated	13	Dominated	13

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Sitagliptin	£201,139	9	£131,110	8	£221,458	9	£266,194	9
Dulaglutide	£61,290	11	£55,751	11	£59,153	11	£72,499	11
Exenatide	£162,634	12	£137,387	13	£161,440	12	£226,351	12
Liraglutide	£460,831	15	£204,321	15	£443,008	15	£758,333	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£24,463	6	£21,802	4	£24,311	6	£27,784	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	£409,706	7	Dominated	7	Dominated	8
Canagliflozin	£26,382	5	£28,176	6	£27,395	5	£31,213	5
Dapagliflozin	£13,600	1	£15,123	1	£13,960	1	£13,916	1
Empagliflozin	£23,189	4	£23,620	3	£24,089	4	£21,881	4
Ertugliflozin	£19,488	2	£32,106	5	£20,926	3	£20,037	3

4.2.3 Second intensification

Table HE042: CVOTs as replacements

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£104,352	8	Dominated	10	£305,102	8	£149,539	8
Saxagliptin	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£129,695	9	£102,271	8	£134,630	9	£138,629	9
Dulaglutide	£64,090	11	£54,974	11	£60,943	11	£74,695	11
Exenatide	£137,975	12	£114,845	13	£134,624	12	£166,108	12
Liraglutide	£757,120	15	£232,157	15	£607,944	15	£1,547,900	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£23,480	6	£21,081	3	£23,101	6	£25,932	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	£38,455	4	Dominated	7	Dominated	7
Canagliflozin	£23,846	4	£25,011	6	£24,662	4	£25,991	5
Dapagliflozin	£14,908	1	£16,271	1	£15,356	1	£15,316	1
Empagliflozin	£25,448	5	£25,521	5	£26,482	5	£23,623	4
Ertugliflozin	£20,803	3	£34,530	7	£22,979	3	£21,503	3

Table HE043: CVOTs as additions

Drug	High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	10	Dominated	10
Linagliptin	£97,103	7	Dominated	9	£246,597	7	£134,885	7
Saxagliptin	Dominated	14	Dominated	12	Dominated	13	Dominated	14
Sitagliptin	£321,442	9	£182,968	8	£347,829	9	£385,056	8
Dulaglutide	£55,610	11	£49,436	11	£53,423	11	£64,164	11
Exenatide	£178,294	12	£143,429	13	£173,505	12	£231,266	12
Liraglutide	£260,762	15	£153,184	15	£244,485	15	£327,747	15
Lixisenatide	Dominated	13	Dominated	14	Dominated	14	Dominated	13
Semaglutide (injection)	£23,842	5	£21,516	4	£23,497	5	£26,531	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	8	Dominated	7	Dominated	8	Dominated	9
Canagliflozin	£30,359	6	£31,299	6	£31,576	6	£33,789	5
Dapagliflozin	£12,407	1	£13,944	1	£12,826	1	£12,783	1
Empagliflozin	£22,712	4	£23,422	3	£23,704	4	£21,245	4
Ertugliflozin	£18,320	2	£29,163	5	£20,072	3	£18,930	2

4.3 Sensitivity analyses

The tables below outline ICERs and net monetary benefit rankings (at £20,000 per QALY) for the sensitivity analyses exploring injection disutilities, hypoglycaemic events and BMI across subgroups at each stage of treatment. For brevity the analyses presented are restricted to the exploration of CVOTs as replacements.

Section 4.3.4 outlines results from adding serious adverse events to the analysis. Section 4.3.5 outlines results of the sensitivity analysis exploring the alternative approach to modelling cardiovascular mortality. Section 3.2.6 provides results using an alternative source for estimating quality of life impact for diabetic events.

4.3.1 Utility decrement for injections (set to 0)

When the disutility from injections was set to 0, there were no significant change in the results to that of the base case analysis.

4.3.1.1 Initial therapy

Table HE044: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£264,993	9	£183,668	9	Dominated	10	£253,608	9	£201,896	8
Saxagliptin	Dominated	14	Dominated	15	Dominated	13	Dominated	15	Dominated	14
Sitagliptin	£113,200	8	£101,109	8	£81,304	8	£108,516	8	£120,975	9
Dulaglutide	£60,912	12	£53,207	11	£49,951	11	£51,935	11	£62,249	12
Exenatide	£93,491	13	£80,233	13	£74,975	14	£80,162	13	£95,559	13
Liraglutide	£52,060	15	£49,035	14	£44,216	15	£49,060	14	£51,787	15
Lixisenatide	£216,659	11	£329,611	12	£302,496	12	£282,925	12	£177,445	11
Semaglutide (injection)	£22,971	6	£21,283	5	£19,681	2	£21,547	6	£24,356	7
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	£64,230	6	£19,029	3	£59,915	5	Dominated	6
Canagliflozin	£24,657	4	£20,113	3	£20,906	5	£20,318	3	£23,468	5
Dapagliflozin	£17,375	1	£16,151	1	£16,556	1	£16,259	1	£16,550	1
Empagliflozin	£26,265	5	£24,863	7	£22,147	6	£24,963	7	£23,366	4
Ertugliflozin	£25,090	3	£22,212	4	£33,181	7	£22,502	4	£22,460	3

4.3.1.2 First intensification

Table HE045: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£221,103	9	£138,696	8	Dominated	10	£369,885	9	£183,720	8
Saxagliptin	Dominated	14	Dominated	15	Dominated	13	Dominated	14	Dominated	14
Sitagliptin	£112,315	8	£105,129	9	£83,261	8	£110,870	8	£120,070	9
Dulaglutide	£59,651	12	£52,870	11	£48,549	11	£51,272	11	£61,370	12
Exenatide	£93,348	13	£81,929	13	£75,619	14	£81,721	13	£95,998	13

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Liraglutide	£51,466	15	£48,878	14	£44,799	15	£48,888	15	£51,313	15
Lixisenatide	£213,520	11	£279,469	12	£334,750	12	£257,116	12	£173,696	11
Semaglutide (injection)	£22,417	4	£21,194	5	£19,453	2	£21,141	4	£23,771	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	£1,025,547	6	£21,248	4	£91,791	6	Dominated	7
Canagliflozin	£25,882	5	£21,472	3	£23,043	5	£22,184	3	£24,706	5
Dapagliflozin	£17,497	1	£16,268	1	£17,506	1	£16,679	1	£16,696	1
Empagliflozin	£27,927	6	£26,369	7	£25,700	6	£27,374	7	£24,642	4
Ertugliflozin	£25,755	3	£22,430	4	£38,814	7	£24,246	5	£23,119	3

4.3.1.3 Second intensification

Table HE046: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£175,448	8	£104,352	8	Dominated	10	£305,102	8	£149,539	8
Saxagliptin	Dominated	15	Dominated	15	Dominated	13	Dominated	15	Dominated	15
Sitagliptin	£130,822	9	£129,695	9	£102,271	8	£134,630	9	£138,629	9
Dulaglutide	£55,266	12	£50,001	11	£44,590	11	£48,148	11	£56,390	12
Exenatide	£95,830	13	£86,679	13	£78,153	14	£85,596	13	£97,327	13
Liraglutide	£47,985	14	£45,825	14	£42,380	15	£45,566	14	£47,648	14
Lixisenatide	£131,083	11	£137,711	12	£141,782	12	£132,980	12	£116,668	11
Semaglutide (injection)	£22,079	4	£21,231	4	£19,541	2	£20,990	4	£23,279	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	Dominated	7	£38,455	4	Dominated	7	Dominated	7
Canagliflozin	£27,851	6	£23,846	5	£25,011	6	£24,662	5	£25,991	5
Dapagliflozin	£16,088	1	£14,908	1	£16,271	1	£15,356	1	£15,316	1
Empagliflozin	£26,958	5	£25,448	6	£25,521	5	£26,482	6	£23,623	4

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Ertugliflozin	£24,052	3	£20,803	3	£34,530	7	£22,979	3	£21,503	3

4.3.2 Hypoglycaemic events (disutility from hypoglycaemic events = 0)

When the disutility from hypoglycaemic events was set to 0, pioglitazone was the most cost-effective treatment option as the analysis did not incorporate the impact of quality of life experienced by patients having an increase in hypoglycaemic events due to pioglitazone as reported in the PROactive trial. Canagliflozin was the only other CVOT to have an ICER below £20,000 due to similar reasons.

4.3.2.1 Initial therapy

Table HE047: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	9	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£377,624	10	£223,764	9	Dominated	10	£345,880	9	£258,665	9
Saxagliptin	Dominated	11	Dominated	13	Dominated	11	Dominated	13	Dominated	11
Sitagliptin	£58,012	8	£56,059	8	£49,735	8	£58,355	8	£59,821	8
Dulaglutide	£106,341	13	£83,434	11	£74,060	12	£79,966	11	£111,057	13
Exenatide	£101,112	12	£86,896	12	£78,997	13	£86,680	12	£103,326	12
Liraglutide	Dominated	16	Dominated	16	£3,209,782	16	Dominated	16	Dominated	16
Lixisenatide	Dominated	15	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Semaglutide (injection)	£23,782	6	£21,995	6	£19,873	3	£22,274	6	£25,331	7
Semaglutide (oral)	Dominated	14	Dominated	14	Dominated	14	£3,455,714	14	Dominated	14
Pioglitazone	£7,023	1	£5,276	1	£7,187	1	£5,502	1	£7,639	1
Canagliflozin	£17,643	2	£15,220	2	£16,198	2	£15,377	2	£16,950	2
Dapagliflozin	£22,960	4	£20,431	4	£20,182	5	£20,552	4	£21,571	4
Empagliflozin	£30,246	7	£27,990	7	£23,952	6	£28,091	7	£26,366	6
Ertugliflozin	£30,246	5	£25,743	5	£42,319	7	£26,110	5	£26,427	5

4.3.2.2 First intensification

Table HE048: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	9	Dominated	10	Dominated	9	Dominated	9	Dominated	10
Linagliptin	£298,662	10	£161,018	9	Dominated	10	£694,625	10	£232,861	9
Saxagliptin	Dominated	11	Dominated	13	Dominated	11	Dominated	13	Dominated	11
Sitagliptin	£56,470	8	£55,502	8	£49,664	8	£57,306	8	£58,214	8
Dulaglutide	£104,249	12	£84,195	11	£71,586	12	£79,619	11	£110,184	13
Exenatide	£99,199	13	£87,153	12	£78,628	13	£86,764	12	£102,053	12
Liraglutide	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Lixisenatide	Dominated	15	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Semaglutide (injection)	£23,097	5	£21,832	5	£19,541	3	£21,713	5	£24,599	7
Semaglutide (oral)	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Pioglitazone	£7,308	1	£5,755	1	£7,719	1	£6,164	1	£7,937	1
Canagliflozin	£18,079	2	£15,778	2	£17,342	2	£16,249	2	£17,424	2
Dapagliflozin	£23,656	4	£21,168	4	£22,009	5	£21,781	4	£22,242	4
Empagliflozin	£32,935	7	£30,437	7	£28,613	6	£31,796	7	£28,338	6
Ertugliflozin	£31,754	6	£26,483	6	£54,639	7	£29,239	6	£27,754	5

4.3.2.3 Second intensification

Table HE049: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	9	Dominated	10	Dominated	9	Dominated	9	Dominated	10
Linagliptin	£233,903	10	£119,829	9	Dominated	10	£604,534	10	£188,549	9
Saxagliptin	Dominated	12	Dominated	13	Dominated	11	Dominated	13	Dominated	13
Sitagliptin	£55,113	8	£54,701	8	£50,735	8	£55,965	8	£56,501	8
Dulaglutide	£98,091	11	£82,878	11	£66,567	12	£77,130	11	£101,827	11
Exenatide	£94,886	13	£85,686	12	£76,304	13	£84,438	12	£96,417	12

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Liraglutide	Dominated	16	Dominated	16	£8,719,808	16	Dominated	16	Dominated	16
Lixisenatide	Dominated	15	Dominated	15	Dominated	15	Dominated	15	Dominated	15
Semaglutide (injection)	£22,516	5	£21,661	5	£19,484	3	£21,316	5	£23,827	7
Semaglutide (oral)	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Pioglitazone	£8,536	1	£7,293	1	£8,585	1	£7,652	1	£9,080	1
Canagliflozin	£18,085	2	£16,095	2	£17,556	2	£16,629	2	£17,235	2
Dapagliflozin	£22,969	4	£20,761	4	£21,726	5	£21,416	4	£21,370	4
Empagliflozin	£33,084	7	£30,806	7	£29,638	6	£32,233	7	£28,009	6
Ertugliflozin	£30,886	6	£25,615	6	£51,647	7	£29,242	6	£26,651	5

4.3.3 BMI (changes in QoL due to changes in BMI set to 0)

When the disutility from BMI was set to 0, SGLT2's and injectable semaglutide remained the treatments with the lowest ICERs in all type 2 diabetes patients across the three stages of intensifications considered where CVOT's were used as replacements. The cost-effectiveness of dapagliflozin did increase to marginally above £20,000 in some subgroups. In the three subgroups of patients with a higher cardiovascular risk, pioglitazone was the most cost-effective treatment option due to a combination of the reduced stroke risks stemming from pioglitazone and the fact that the impact on the quality of life of patients having an increased BMI due pioglitazone was not incorporated in the analysis.

4.3.3.1 Initial therapy

Table HE050: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£199,144	7	£149,228	8	Dominated	10	£192,277	8	£161,200	7
Saxagliptin	Dominated	12	Dominated	13	Dominated	11	Dominated	12	Dominated	12
Sitagliptin	£113,200	8	£101,109	9	£81,304	8	£108,516	9	£120,975	8
Dulaglutide	£104,577	11	£84,312	11	£75,050	12	£80,950	11	£108,587	11
Exenatide	£277,061	13	£187,888	12	£153,509	13	£186,748	13	£296,032	13

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Liraglutide	Dominated	15	Dominated	16	£29,745,358	15	Dominated	16	Dominated	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£32,592	9	£29,449	7	£25,162	6	£29,883	7	£35,426	9
Semaglutide (oral)	Dominated	16	Dominated	15	Dominated	16	Dominated	15	Dominated	16
Pioglitazone	£22,467	3	£11,724	1	£11,774	1	£12,104	1	£29,939	3
Canagliflozin	£29,612	4	£23,407	4	£23,690	4	£23,627	4	£27,922	5
Dapagliflozin	£20,359	2	£18,730	2	£18,810	2	£18,843	2	£19,245	1
Empagliflozin	£36,319	6	£33,659	6	£27,743	5	£33,753	6	£31,034	6
Ertugliflozin	£38,637	5	£32,407	5	£59,453	7	£32,906	5	£32,793	4

4.3.3.2 First intensification

Table HE051: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£173,038	8	£118,030	8	Dominated	10	£250,960	8	£149,207	7
Saxagliptin	Dominated	12	Dominated	13	Dominated	11	Dominated	12	Dominated	12
Sitagliptin	£112,315	9	£105,129	9	£83,261	8	£110,870	9	£120,070	8
Dulaglutide	£100,913	11	£83,449	11	£71,890	12	£79,250	11	£105,914	11
Exenatide	£274,737	13	£197,005	12	£155,603	13	£194,321	13	£299,051	13
Liraglutide	Dominated	15	Dominated	15	Dominated	16	Dominated	16	Dominated	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£31,392	7	£29,253	7	£24,617	5	£28,896	7	£34,103	9
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	15	Dominated	15	Dominated	16
Pioglitazone	£26,098	3	£15,243	1	£13,094	1	£14,883	1	£36,115	3
Canagliflozin	£31,339	5	£25,235	4	£26,445	4	£26,123	4	£29,640	5
Dapagliflozin	£20,526	2	£18,898	2	£20,050	3	£19,408	2	£19,440	1
Empagliflozin	£39,542	6	£36,495	6	£33,583	6	£38,328	6	£33,300	6
Ertugliflozin	£40,369	4	£32,930	5	£83,588	7	£37,099	5	£34,300	4

4.3.3.3 Second intensification

Table HE052: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£143,612	8	£92,177	8	Dominated	10	£218,840	8	£125,735	7
Saxagliptin	Dominated	12	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£130,822	9	£129,695	9	£102,271	8	£134,630	9	£138,629	8
Dulaglutide	£89,057	11	£76,592	11	£63,548	11	£72,033	11	£91,996	11
Exenatide	£293,331	13	£224,597	12	£165,478	13	£214,813	12	£307,934	12
Liraglutide	Dominated	15	Dominated	15	£953,913	15	Dominated	15	Dominated	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£30,561	7	£29,236	7	£24,698	6	£28,413	7	£32,903	9
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	£93,906	3	£58,820	3	£19,263	2	£36,820	3	£236,511	3
Canagliflozin	£34,043	5	£28,421	5	£28,958	4	£29,393	5	£31,315	6
Dapagliflozin	£18,634	1	£17,124	1	£18,474	1	£17,653	1	£17,610	1
Empagliflozin	£37,603	6	£34,817	6	£33,310	5	£36,540	6	£31,440	5
Ertugliflozin	£36,484	4	£29,636	4	£66,542	7	£34,339	4	£30,955	4

4.3.4 Adverse events (incorporating severe adverse events reported in trials)

When incorporating severe adverse events reported in trials into our analysis, no significant differences were seen in the cost-effectiveness results as shown by the table below.

Table HE053: Incorporating adverse events reported in trials for the second intensification replacement population

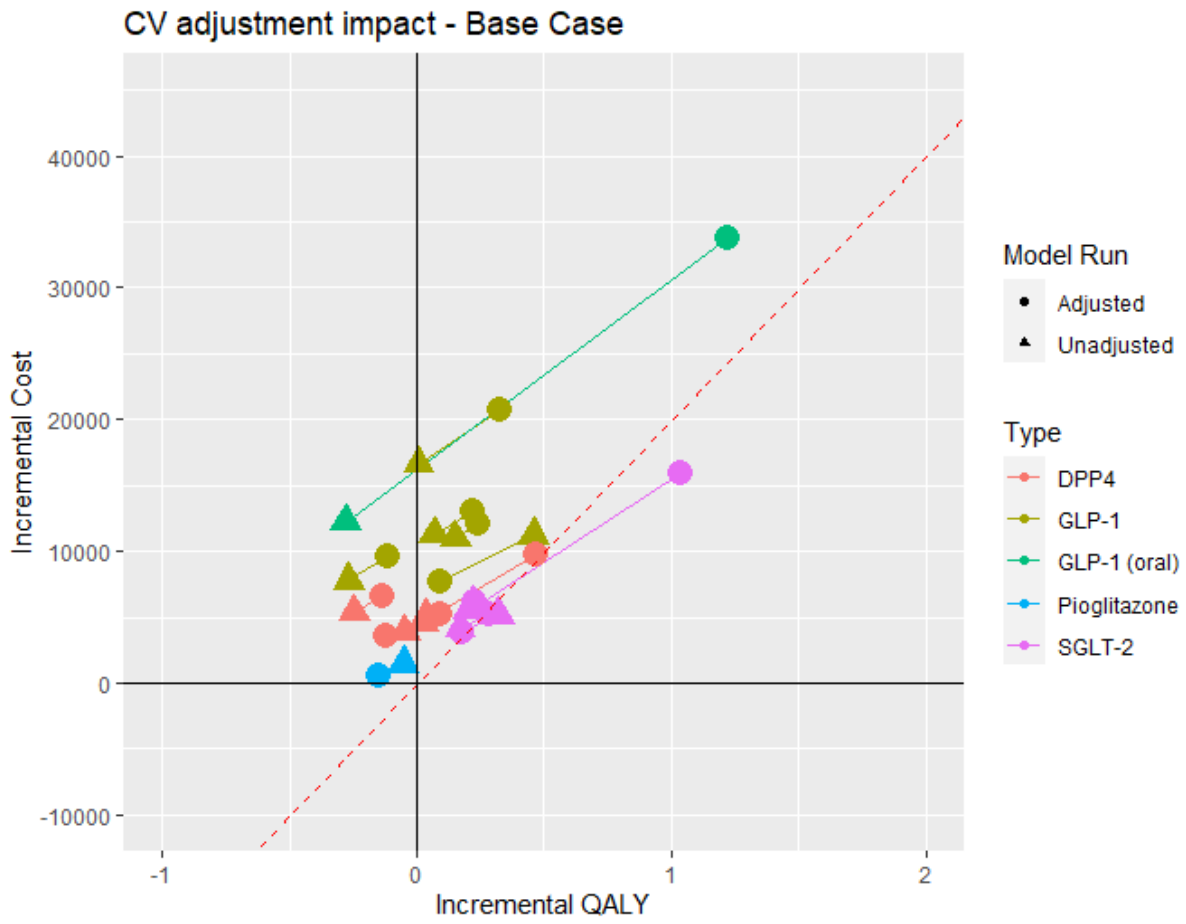
Treatment	ICER including SAE	Base-case ICER
Alogliptin	Dominated	Dominated
Linagliptin	£176,450	£175,448
Saxagliptin	Dominated	Dominated
Sitagliptin	£128,638	£130,822
Dulaglutide	£69,873	£72,742
Exenatide	£169,624	£161,775
Liraglutide	£2,746,039	£1,984,769
Lixisenatide	Dominated	Dominated
Semaglutide (injection)	£25,082	£24,453
Semaglutide (oral)	Dominated	Dominated
Pioglitazone	Dominated	Dominated

Treatment	ICER including SAE	Base-case ICER
Canagliflozin	£26,376	£27,851
Dapagliflozin	£15,845	£16,088
Empagliflozin	£27,025	£26,958
Ertugliflozin	£24,698	£24,052

4.3.5 Adjusting for cardiovascular mortality (model calibrated to match the cardiovascular mortality hazard ratio reported in trials)

The chart below displays the effect of this change on the cost-effectiveness plane in the second intensification replace population. For legibility treatments from the same class are grouped by colour although individual treatment results are given in the table below. The dashed red line corresponds to an ICER of £20,000 compared with the baseline, no-CVOT treatment.

Figure 1: Effect of adjustment for cardiovascular mortality



For most treatments, the rankings based on the NMBs at £20,000/ QALY in the sensitivity analysis results are very similar to the base case. This suggests a good model fit in the base case where cardiovascular mortality was calculated indirectly. Exceptions to this are explained in more detail below.

Table HE054

	Pre adjustment Base-Case ICER	Post-adjustment CV-adjusted ICER	Pre-adjustment Base-case Rank @20k	Post-adjustment CV-adjusted Rank @20k
Alogliptin	Dominated	£20,705	10	5
Linagliptin	£175,448	£56,855	8	7
Saxagliptin	Dominated	Dominated	13	13
Sitagliptin	£130,822	Dominated	9	10
Dulaglutide	£72,742	£49,400	11	11
Exenatide	£161,775	£58,441	12	12
Liraglutide	£1,984,769	£62,930	15	16
Lixisenatide	Dominated	Dominated	14	15
Semaglutide (injection)	£24,453	£83,522	6	9
Semaglutide (oral)	Dominated	£27,715	16	14
Pioglitazone	Dominated	Dominated	7	8
Canagliflozin	£27,851	£27,316	5	6
Dapagliflozin	£16,088	£21,233	1	4
Empagliflozin	£26,958	£15,427	4	1
Ertugliflozin	£24,052	£18,637	3	2

Oral semaglutide and empagliflozin had cardiovascular mortality hazard ratios that differed most greatly from the indirectly modelled rates. In this scenario empagliflozin is associated with an ICER of £15,427 as is ranked first in terms of net monetary benefit at £20,000. Oral semaglutide is no longer dominated in the CV-adjusted scenario however due to the high cost of treatment and the increased underlying rates of MI and unstable angina resulting in high ongoing costs and low QALYs, the ICER is above £20,000. Two other treatments had notably different results; injectable semaglutide and alogliptin. Injectable semaglutide had an ICER above £80,000 in the CV-adjusted scenario as despite strongly reducing rates of cardiovascular events, the reduction in cardiovascular mortality reported in the trial was very modest and hence calibrating the model to match it reduces the treatment's cost-effectiveness. Alogliptin went from being dominated to being associated with an ICER of £20,705. This change is driven by the difference in incremental QALYs which increases from -0.047 to 0.471 when the model is calibrated to the cardiovascular mortality observed in the EXAMINE trial; the hazard ratio changes from 1.01 to 0.79 with this adjustment. The difference between the approaches is pronounced in this instance because the point estimates from the EXAMINE trial suggested that alogliptin worsened some cardiovascular outcomes whilst still improving cardiovascular mortality (for example, the hazard ratio for heart failure from EXAMINE is 1.07 and the hazard ratio for MI is 1.08). Whilst the cost-effectiveness estimates for alogliptin improved using this approach there would be other treatments in which the cost-effectiveness estimates would worsen under this approach. Although there was uncertainty around which approach to modelling cardiovascular mortality was more appropriate, the committee preferred on balance not to calibrate the model to align to the cardiovascular mortality observed in the trials (see section 2.3.2.3).

4.3.6 Impact on quality of life from diabetic events

A sensitivity analysis was run where the impact on quality of life from specific diabetic events were sourced from Alva et al[32] for the second intensification replacement pathway. A single pathway was chosen for the sensitivity analysis due to model run time constraints, given that the interpretation of cost-effectiveness results did not differ significantly across pathways in

the base case. As shown by the table below, results from this analysis did not differ from our original analysis across all pathways and subgroups.

Second intensification

Table HE055: CVOTs as replacements

Drug	All T2 patients		High cardiovascular risk – no prior event		High cardiovascular risk –prior event		All high cardiovascular risk		High BMI	
Alogliptin	Dominated	10	Dominated	10	Dominated	9	Dominated	10	Dominated	10
Linagliptin	£236,691	8	£119,910	8	Dominated	10	£601,076	8	£192,943	8
Saxagliptin	Dominated	13	Dominated	13	Dominated	12	Dominated	13	Dominated	13
Sitagliptin	£135,449	9	£134,858	9	£91,703	8	£135,915	9	£144,450	9
Dulaglutide	£68,548	11	£61,145	11	£50,672	11	£57,619	11	£70,266	11
Exenatide	£153,729	12	£133,049	12	£101,893	13	£127,221	12	£157,770	12
Liraglutide	£1,220,857	15	£636,597	15	£180,968	15	£480,569	15	£1,040,579	15
Lixisenatide	Dominated	14	Dominated	14	Dominated	14	Dominated	14	Dominated	14
Semaglutide (injection)	£24,098	6	£23,245	6	£19,661	2	£22,550	5	£25,573	6
Semaglutide (oral)	Dominated	16	Dominated	16	Dominated	16	Dominated	16	Dominated	16
Pioglitazone	Dominated	7	Dominated	7	£26,947	4	Dominated	7	Dominated	7
Canagliflozin	£26,882	5	£23,249	4	£22,766	5	£23,665	4	£25,121	5
Dapagliflozin	£15,853	1	£14,744	1	£15,522	1	£15,077	1	£15,091	1
Empagliflozin	£26,621	4	£25,235	5	£24,349	6	£26,058	6	£23,314	4
Ertugliflozin	£24,004	3	£20,762	3	£34,203	7	£22,935	3	£21,431	3

4.3.7 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was run for the second intensification - replace for the total and high CV populations. Reasons as to why this pathway was chosen is outlined in Section 3.2.7. This was further supported by the fact that conclusions from results in the deterministic analysis did not differ significantly between pathways. Due to the volume of treatments and long model run times each treatment was simulated 100 times. As cost-effectiveness results did not differ substantially between intensification levels or populations this analysis is likely to be broadly representative of all treatment stages and populations.

The results of the probabilistic are shown on the cost-effectiveness plane below. For legibility treatments from the same class are grouped by colour although individual treatment results are given in the table below.

Figure 2: Cost effectiveness plane for treatments on a class level for the total population

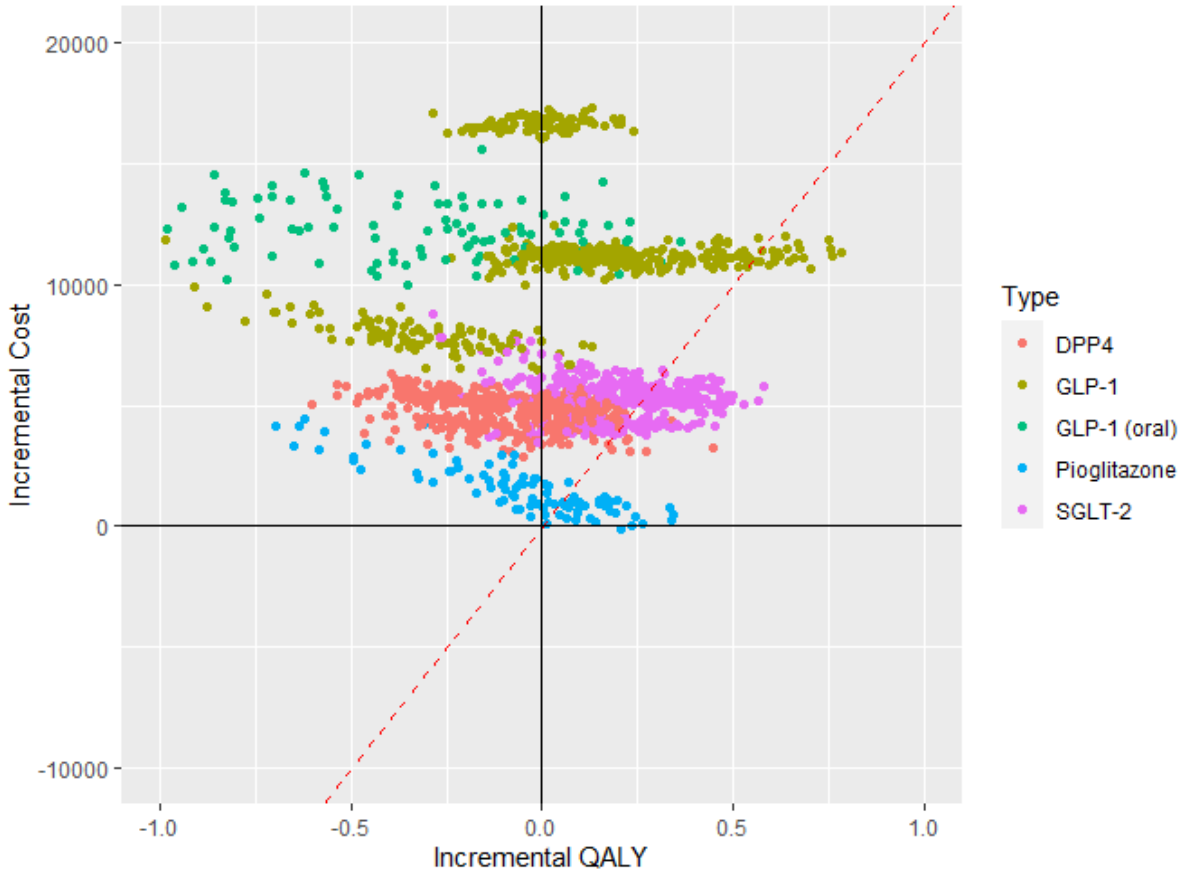
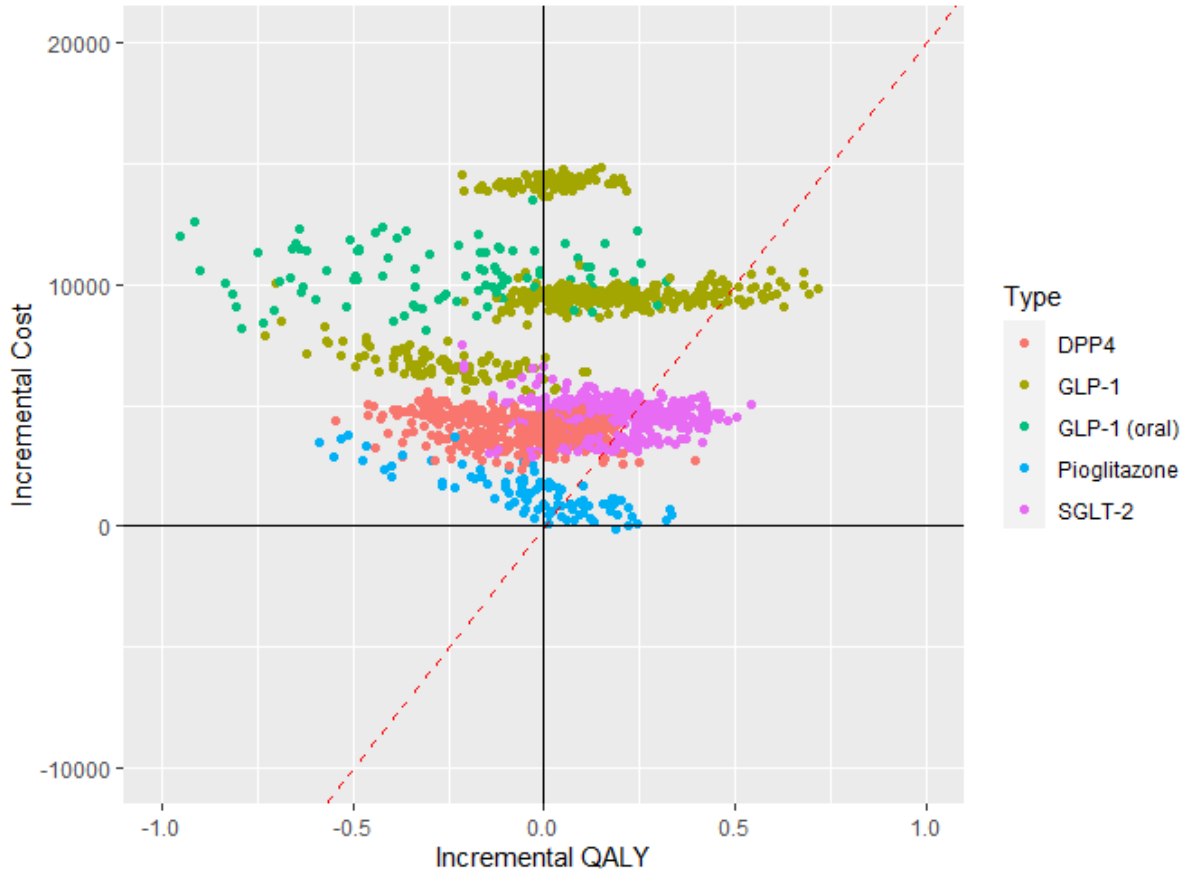


Figure 3: Cost effectiveness plane for treatments on a class level for the high CV population



The PSA results demonstrate the considerable uncertainty associated with the hazard ratios from the CVOT trials. With the uncertainty being primarily confined to the x-axis (QALYs). The dashed red line corresponds to an ICER of £20,000 compared with the baseline, no-CVOT treatment.

The tables below show the proportion of PSA runs that are associated with an ICER below £20,000 and £30,000 compared with the no-CVOT baseline.

The first table shows the results when treatments are grouped by class. The class with the highest probability of being associated with ICERs below £30,000 is the SGLT2 inhibitors. Other classes have a much lower likelihood, and with the exception of pioglitazone, have single digit percentage probabilities of being associated with an ICER below £30,000. The probabilities by class do not change significantly when limiting the analysis to the High CV population as shown by the second table.

The third table shows the likelihood of each individual treatment being cost-effective when compared with the baseline no-CVOT treatment. The SGLT2 inhibitors are consistent in being associated with reasonable likelihoods of ICERs less than £20,000. The DPP-4 inhibitors have a low probability of ICERs less than £20,000. There is some variation in the results for GLP-1s with some treatments such as exenatide having a 0% probability of being associated with an ICER below £20,000 whereas injectable semaglutide, the most cost-effective of the GLP1s, had a 22% chance of having an ICER below £20,000. Here again, there were no significant differences in results when limiting the analysis to the High CV population.

Table HE056: Proportion of ICERs falling under threshold (class) for total population

Treatment	ICER <20k	ICER <30k
SGLT-2	43.25%	65.00%
DPP4	2.25%	9.00%
GLP-1	4.40%	13.00%
Pioglitazone	39.00%	40.00%
GLP-1 (oral)	0.00%	0.00%

Table HE057: Proportion of ICERs falling under threshold (class) for high CV population

Treatment	ICER <20k	ICER <30k
SGLT-2	46.50%	68.25%
DPP4	2.25%	9.50%
GLP-1	5.00%	13.80%
Pioglitazone	41.00%	43.00%
GLP-1 (oral)	0.00%	0.00%

Table HE058: Proportion of ICERs falling under threshold (individual) for the total population

Treatment	ICER <20k	ICER <30k
Alogliptin	7%	11%
Linagliptin	2%	18%
Saxagliptin	0%	0%
Sitagliptin	0%	7%
Dulaglutide	0%	5%
Exenatide	0%	0%
Liraglutide	0%	0%
Lixisenatide	0%	0%
Semaglutide (injection)	22%	60%
Semaglutide (oral)	0%	0%
Pioglitazone	39%	40%
Canagliflozin	34%	54%
Dapagliflozin	76%	93%
Empagliflozin	25%	50%
Ertugliflozin	38%	63%

Table HE059: Proportion of ICERs falling under threshold (individual) for the High CV population

Treatment	ICER <20k	ICER <30k
Alogliptin	7%	12%
Linagliptin	2%	17%
Saxagliptin	0%	0%
Sitagliptin	0%	9%
Dulaglutide	0%	7%

Treatment	ICER <20k	ICER <30k
Exenatide	0%	0%
Liraglutide	0%	0%
Lixisenatide	0%	0%
Semaglutide (injection)	25%	62%
Semaglutide (oral)	0%	0%
Pioglitazone	41%	43%
Canagliflozin	37%	61%
Dapagliflozin	79%	95%
Empagliflozin	26%	51%
Ertugliflozin	44%	66%

5 Discussion

5.1 Discussion of results

The committee had initially chosen to include individual drugs in the analysis to explore the possibility of within-class differences in cost-effectiveness. However, results were broadly clustered based on drug class across all analyses, with the only notable difference being in the sensitivity analysis exploring cardiovascular mortality. The committee considered that making class-based recommendations could provide clinicians with more treatment options to tailor to individual patient characteristics and make recommendations more robust to future changes in available diabetes drugs. On this basis, the committee primarily considered the results on a class level.

In the base-case analysis, drugs belonging to the SGLT2 class were associated with the lowest ICERs compared with no CVOT treatment. Across all subgroups in the base-case dapagliflozin is the SGLT2 most commonly associated with an ICER of less than £20,000. The CVOT trials for DPP4 inhibitors do not show cardiovascular benefits observed in other drug classes and due to their additional cost are associated with ICERs over £20,000 compared with no CVOT drug. While injectable GLP-1s were associated with event hazard ratios of less than one for some cardiovascular events, they also had the highest acquisition cost and were also associated with a disutility related to injections. This leads to them being associated with a lower QALY gain and higher costs than the SGLT2s when compared to the no CVOT arm. The only GLP-1 to have ICERs in the range of £20,000 to £30,000 was injectable semaglutide. Oral semaglutide was associated with more MI events and a high hypoglycaemia rate which again, led to a higher cost and fewer QALYs than the SGLT2s. Pioglitazone is associated with increased hypoglycaemia rates leading to an overall QALY loss against no CVOT. When the hypoglycaemia QALY decrement is removed pioglitazone becomes associated with the lowest ICER against no CVOT.

Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. They also noted uncertainty in the clinical evidence for semaglutide, as a result of inconsistencies in the trial outcomes for these treatments (see Evidence Review A for further details). Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors.

Four subgroups and a total cohort were modelled in order to assess the cost-effectiveness across different cardiovascular risk profiles. While the ICERs differ between subgroups and treatments typically become most cost-effective in a higher risk population the differences are small. This is explained by the lower life expectancy in the higher risk subgroups, who

are also subject to higher background mortality leading to reduced life expectancy over which QALY benefits resulting from lower cardiovascular events would be realised.

In-year events, such as hypoglycaemia related decrements, are significant drivers of the model. In a high cardiovascular risk population the absolute rate of cardiovascular events is low (with around 2 events per 100 patient years observed in the highest-risk CVOTs) whereas the in-year decrements are applied every year to all living patients leading to a large overall influence on the model results.

Due to the nature and design of the CVOT trials the hazard ratios applied in the model are typically very broad with confidence intervals frequently crossing 1. Modelling these values results in considerable uncertainty in the effectiveness of the treatment and any drug with a non-significant hazard ratio greater than 1 will be associated with higher event rates for this outcome. Despite this, the probabilistic sensitivity analysis shows reasonable clustering of treatments within class.

Multiple sensitivity analyses are presented which have a larger impact on model results than between subgroup differences. Removing hypoglycaemic events has the effect of making pioglitazone highly cost-effective, whereas other drugs typically gain or lose a proportion of their QALYs with no clear within-class trends. Removing the QALYs associated with injections leads to a QALY gain for the injectable GLP-1s, with injectable semaglutide being associated with the lowest ICER. However, in all other analyses the higher cost of GLP-1s compared with SGLT2s prevents them from being associated with the lowest ICERs. Removing the quality of life impact of BMI change has a small overall impact however as GLPL-1s are associated with the highest weight loss they lose more QALYs in this scenario than other treatments.

In the base-case analysis the cardiovascular mortality was not calibrated to match the CVOT outcomes to provide between-trial consistency. A sensitivity analysis was run to assess the impact that calibration to CVOT trials cardiovascular mortality HR would have on the results. In this scenario the majority of treatments show very little change in the net monetary benefit rankings, suggesting that the approach of modelling cardiovascular mortality indirectly through cardiovascular events is a reasonable approximation of the cardiovascular mortality observed in most of the trials. The cardiovascular mortality modelled in the base-case fell outside the confidence intervals of the trials for empagliflozin and oral semaglutide (see section 2.3.2.3). In the sensitivity analysis, empagliflozin and ertugliflozin was associated with an ICER below £20,000 compared with no CVOT. Oral semaglutide was associated with significantly more QALYs than in the base case analysis but despite the increased QALYs oral semaglutide is not associated with an ICER below £20,000 due to the high hypoglycaemia rates and increased rates of unstable angina and MI. The modelled cardiovascular mortality for alogliptin fell within the trial confidence intervals but the cost-effectiveness results for alogliptin were much lower in the sensitivity analysis than in the base-case (see section 3.2.5), although the ICER was still over £20,000. The ICER of injectable semaglutide which was in the range of £20,000 to £30,000, rose to above £80,000 in the CV-adjusted scenario as despite strongly reducing rates of cardiovascular events, the reduction in cardiovascular mortality reported in the trial was very modest and hence calibrating the model to match it reduces the treatment's cost-effectiveness.

Both assumptions (that differences in cardiovascular mortality are mediated through differences in rates of cardiovascular events, or that they are not) are currently unprovable with the available data, and therefore the committee considered the practical implications of each choice. In particular, they noted that the cardiovascular outcomes trials, whilst large, were not powered to detect differences in cardiovascular mortality, and therefore there was considerable uncertainty around those results (since rates of cardiovascular events are necessarily higher than rates of cardiovascular mortality, the data on vents will necessarily be more precise). They therefore felt the data on cardiovascular event rates were more robust, and thus favoured an approach to modelling mortality based on those data. The

committee did, however, consider both sets of results when making recommendations, and in particular noted they would have more confidence in a treatment that was shown to be cost-effective under both sets of assumptions, than one where the cost-effectiveness was very sensitive to the choice of assumption.

5.2 Strengths and limitations of the analysis

5.2.1 Strengths

This model assesses a large number of treatments options for drugs with and without CVOTs in a single model incorporating the best available evidence for all treatment types.

By incorporating population data from THIN, the analysis models an accurate and representative Type 2 diabetes population, preserving the correlations between risk factors and modelling a cohort of several thousand patients.

Converting the outputs of the UKPDS risk equations to a multi-state model demonstrates a flexible approach which fully incorporate the results of CVOTs into an economic model with full adaptability to match trial results, augmenting the traditional individual patient simulations frequently used in diabetes modelling.

The use of the UKPDS risk equations to generate a comparator arm against which CVOT treatments can be compared allows the consistent modelling of treatments across classes while preserving the progression of competing events, morbidity and mortality informed by the UKPDS equations.

5.2.2 Limitations

For treatments with a CVOT the model used the clinical effectiveness outputs generated from the clinical CVOT review. Despite the scale of these trials many of the event hazard ratios have confidence intervals which contained one. This resulted in the modelling of point estimates of non-significant outcomes which are associated with considerable uncertainty. This is most clearly demonstrated in spread of incremental costs and QALYs in the probabilistic sensitivity analysis (PSA).

In our analysis, the timing of intensification of treatments were not specific to each treatment arm, as differences in HbA1c between treatments not accounted for due to the analysis sourcing treatment effects on CV outcomes directly from CVOT trials. This may result in small inaccuracies in the time patients may stay on treatment pathways and the impact on the results was considered to be minor. Furthermore, treatment intensification was stratified by time of diagnosis as this was the only variable by which treatment intensification could be stratified in the THIN database. Whilst this is a limitation in our analysis stemming from using the THIN database to source baseline characteristics, the THIN data set was the most representative of a contemporary UK diabetic population reporting a wide range of baseline characteristics and hence deemed the most suitable to inform the baseline population. Other limitations of using the THIN include arguments that the dataset may of too recent a population, given that the time path risk equations used to extrapolate the SoC arm come from an older UKPDS population. However there were no significant differences between baseline characteristics such as HbA1c levels in the THIN population used in this guideline update and that of NG28.

When accounting for in the impact on quality of life due to diabetic events, a decrement in quality of life was assumed at the year of the event. But no changes in quality of life were assumed in subsequent years due to the original event. This may either over or underestimate the impact on quality of life of complications depending on the nature of complications. Question specifically raised on a potential reversal of a disutility due to an

ulcer in subsequent years was discussed by the committee, with the committee coming to the conclusion that this is unlikely to be the case.

Our analysis has not accounted for the impact of treatment discontinuation, which might not be reflective of real world practice. The committee noted there was uncertainty over the likely rates of treatment discontinuation in clinical practice, but importantly there was also uncertainty over the duration of treatment effect, and how long this would persist for. They agreed it would be inappropriate to include the impact of reduced costs through discontinuation, but not the impact of reduced efficacy, both from discontinuations after the trial time horizon, but also from possible reduced efficacy in people still on treatment. Given these uncertainties, the committee agreed an appropriate approach was to model lifetime use of the drugs which, whilst it will not 100% accurately reflect practice, will at least mean the impacts of discontinuation and treatment effect waning are treated consistently, in the absence of evidence to take a different approach.

The outcomes included in the analysis, confirmed by the committee, were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. As such, the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes such as HbA1c. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust.

There were many other areas of uncertainty within this model which would benefit from probabilistic sensitivity analysis however due to the volume of treatment combined with long model runtimes only one PSA for one patient population is presented.

While the model is capable of full flexibility and calibration to hit any CVOT outcome in order to provide a consistent approach we are required to make assumptions about which events the model should be calibrated to hit. This is a balance between accuracy in matching CVOT trials exactly against providing a consistent basis by which all treatments can be compared. A sensitivity analysis calibrating to trial cardiovascular mortality is provided in order to quantify the effect different assumptions may have had on model outputs.

6 Conclusions

This economic analysis was based on information from the clinical review of evidence from the CVOT trials, and a range of other model input parameters including costs and quality of life which were sourced following input from the committee. The analysis was stratified by treatment stage and by whether CVOT drugs were added to or replacing components of a non-CVOT regimen. Multiple subgroups were considered, including subgroups based on people with prior cardiovascular events and people at high risk of cardiovascular events. Sensitivity analyses were used to explore the likely direction and size of changes to ICERs if parameters associated with substantial uncertainty were removed from the analysis.

In almost all analyses, SGLT2s were likely to be the most cost-effective class of drug studied in the CVOT trials; the only notable exception to this were the estimates for pioglitazone in the sensitivity analysis exploring hypoglycaemia (where the disutility from hypoglycaemic events was set to 0). In the base case analyses, ICER estimates for SGLT2s varied from £18,802 to £39,092 depending on the individual drug, treatment stage and population being modelled. In our PSA, SGLT2s as class had the highest probability of being cost-effective. The only other treatment to have ICERs between £20,000 and £30,000 was injectable semaglutide. However, ICERs of injectable semaglutide rose above £80,000 in the sensitivity analysis where differences in CV mortality risks were sourced from CVOTs. The differences in ICERs between the two analyses coupled with the low population sizes of GLP-1 trials informing our analyses raised further doubts about the cost-effectiveness of injectable semaglutide.

This analysis represents a flexible approach to modelling in Type 2 diabetes that incorporates surrogate evidence and evidence from the CVOT trials. Due to wide confidence intervals in around estimates from the CVOT studies there is substantial parameter uncertainty associated with some of the model inputs, and this translates to uncertainty in the model estimates. Nonetheless, this model provides economic evidence for the cost effectiveness of drugs studies in the CVOT trials when used to prevent cardiovascular and diabetic outcomes in a range of populations.

7 References

1. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS Outcomes Model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia*. 2013;56(9):1925-1933. doi:10.1007/s00125-013-2940-y

2. Mt Hood Diabetes Challenge Network. Published 2021. https://www.mthooddiabeteschallenge.com/

3. Shao H, Fonseca V, Stoecker C, Liu S, Shi L. Novel risk engine for diabetes progression and mortality in USA: building, relating, assessing, and validating outcomes (BRAVO). *Pharmacoeconomics*. 2018;36(9):1125-1134.

4. McEwan P, Ward T, Bennett H, Bergenheim K. Validation of the UKPDS 82 risk equations within the Cardiff Diabetes Model. *Cost Eff Resour Alloc*. 2015;13(1):1-7.

5. Press RTI. Validation of the CDC-RTI Diabetes Cost-Effectiveness Model. Published online 2009.

6. Willis M, Asseburg C, He J. Validation of economic and health outcomes simulation model of type 2 diabetes mellitus (ECHO-T2DM). *J Med Econ*. 2013;16(8):1007-1021.

7. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and costeffectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*. 2004;20(sup1):S5-S26.

8. Zhou H, Isaman DJM, Messinger S, et al. A computer simulation model of diabetes progression, quality of life, and cost. *Diabetes Care*. 2005;28(12):2856-2863.

9. Schramm W, Sailer F, Pobiruchin M, Weiss C. PROSIT Open Source Disease Models for Diabetes Mellitus. In: *ICIMTH*. ; 2016:115-118.

10. Thomas C, Watson P, Squires H, Chilcott J, Brennan A. Validation of the SPHR Diabetes Prevention Model. *Value Heal*. 2014;17(7):A556.

11. Smolen HJ, Murphy DR, Gahn JC, Yu X, Curtis BH. The evaluation of clinical and cost outcomes associated with earlier initiation of insulin in patients with type 2 diabetes mellitus. *J Manag Care Pharm*. 2014;20(9):968-984.

12. NHS. The Health Improvement Network. Published online 2020.

13. Leal J, Alva M, Gregory V, et al. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). *Diabet Med*. 2021;38(10):e14656.

14. NICE. NG28 - Type 2 diabetes in adults: management (appendix F). Published online 2015. https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355

15. Diabetes UK. National Diabetes Audit. Published online 2019. https://www.diabetes.org.uk/professionals/position-statements-reports/statistics?gclid=CjwKCAjw_JuGBhBkEiwA1xmbRaE_gtlb7CsDf4OgMkqCx-iOuqy7-KZfJ9IfZFWF0nnP7s-Vi4IY6RoC5F4QAvD_BwE

16. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;63(1):225-232.

17. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *Jama*. 2019;322(12):1155-1166.

18. Si L, Willis MS, Asseburg C, et al. Evaluating the ability of economic models of diabetes to simulate new cardiovascular outcomes trials: a report on the Ninth Mount Hood Diabetes Challenge. *Value Heal*. 2020;23(9):1163-1170.

19. Dunkley AJ, Fitzpatrick C, Gray LJ, et al. Incidence and severity of hypoglycaemia in type 2 diabetes by treatment regimen: A UK multisite 12-month prospective observational study. *Diabetes, Obes Metab*. 2019;21(7):1585-1595.

20. Wang H, Donnan PT, Leese CJ, et al. Temporal changes in frequency of severe hypoglycemia treated by emergency medical services in types 1 and 2 diabetes: a population-based data-linkage cohort study. *Clin diabetes Endocrinol*. 2017;3(1):1-8.

21. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*. 2008;31(11):2086-2091.

22. NHS. NHS Electronic Drug Tariff. Published 2021. http://www.drugtariff.nhsbsa.nhs.uk/#/00789028-DC/DC00788719/Part VIIIA products L

23. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). *Diabet Med*. 2015;32(4):459-466.

24. NICE. Chronic kidney disease: assessment and management (update). Published online 2021. https://www.nice.org.uk/guidance/indevelopment/gid-ng10118

25. UK Renal Association. UK Renal Association 22nd Annual Report. Published online 2018. https://renal.org/audit-research/annual-report

26. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. *Diabet Med*. 2019;36(8):995-1002.

27. PSSRU. Unit Costs of Health and Social Care 2020. Published online 2020. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

28. NICE. Type 1 diabetes in adults: diagnosis and management (update). Published online 2021. https://www.nice.org.uk/guidance/indevelopment/gid-ng10159

29. Hammer M, Lammert M, Mejías SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. *J Med Econ*. 2009;12(4):281-290.

30. Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weitgasser R, Lahtela J, Jensen MM, Östenson C-G. Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work-time loss, and wellbeing in insulin-treated patients with diabetes in seven European countries. *J Med Econ*. 2013;16(12):1453-1461.

31. Heller SR, Frier BM, Hersløv ML, Gundgaard J, Gough SCL. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. *Diabet Med*. 2016;33(4):471-477.

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

33. Beaudet A, Clegg J, Thuresson P-O, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value Heal*. 2014;17(4):462-470.

34. Evans M, Jensen HH, Bøgelund M, Gundgaard J, Chubb B, Khunti K. Flexible insulin dosing improves health-related quality-of-life (HRQoL): a time trade-off survey. *J Med Econ*. 2013;16(11):1357-1365.

35. Olofsson S, Norrlid H, Persson U. Preferences for improvements in attributes associated with basal insulin: a time trade-off and willingness-to-pay survey of a diabetic and non-diabetic population in Sweden. *J Med Econ*. 2016;19(10):945-958.

36. Ridderstråle M, Evans LM, Jensen HH, et al. Estimating the impact of changes in HbA 1c, body weight and insulin injection regimen on health related quality-of-life: a time trade off study. *Health Qual Life Outcomes*. 2016;14(1):1-10.

37. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health Qual Life Outcomes*. 2013;11(1):90.

38. Lauridsen JT, Lønborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. *Qual Life Res*. 2014;23(9):2645-2650.

39. Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. *Health Econ*. 2005;14(3):217-230.

40. NICE. Diabetes in pregnancy: management from preconception to the postnatal period (NG3). Published online 2020. https://www.nice.org.uk/guidance/ng3

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Appendices

Appendix A: R implementation of UKPDS appendix

UKPDS OM2 is the most recent version of a long-established surrogate model; it is described in detail in Hayes et al. 2013[1] . UKPDS was used to model treatments for which there was no CVOT evidence and provide an anchor for the CVOT multi-state model (MSM). Surrogate level models outputs give a greater insight into the relationship between events, event histories and mortality – information which cannot be deduced from survival curves alone. The current official version of UKPDS does not provide the output in the format we required, nor does it give the ability to fix the sequence of random numbers to generate the event equation bootstraps.

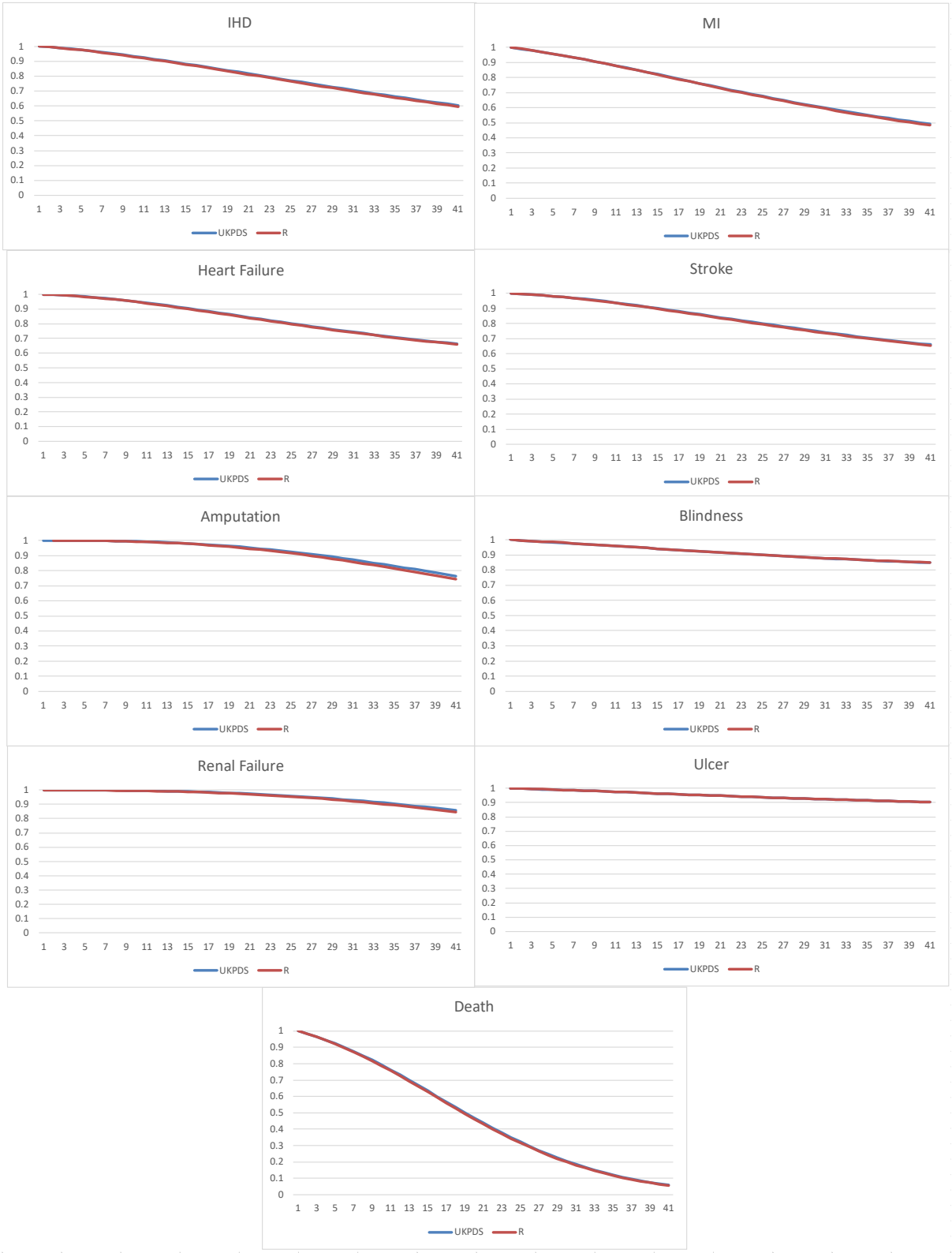
As a result of these requirements we developed our own implementation of the UKPDS risk equations using R. Our model uses the UKPDS OM2 risk equations and we obtained the bootstraps and risk factor time-path equations directly from Oxford. These were provided directly by the UKPDS team, who also assisted with technical validation of the risk equations. The time-path equations are currently academic in confidence.

To ensure acceptable model run times it was necessary to make a slight change to the official version of UKPDS. In the official implementation of UKPDS each year, for each patient the event equations (MI, Stoke etc.) are run in a random order. In the implementation the events are ordered randomly each year, but that order is preserved for every patient. In the main analysis each cohort is run 100 times for 50 bootstraps (5000 loops) and although the order each year is fixed for all patients in each loop, it will vary across the 5000 loops leading to any potential bias (e.g from MI2 always occurring after MI1) being smoothed out (as there will be an equal number of cases where MI2 occurs before MI1).

In order to ensure technical accuracy of the model, the R implementation was compared with the official UKPDS implementation. 20,000 patients were modelled at first intensification, run 100 times representing one bootstrap of the base case analysis. As the official UKPDS implementation did not have the functionality to apply the time-path equations, risk factors were held constant throughout the model run. As it was not possible to run a defined sequence of bootstraps the mean values were used for event equations. Outputs of the analysis are shown in Figure A1.

The R model showed excellent consistency with the official UKPDS implementation. Slight differences were noted towards the end of the model run (where the number at risk is much lower and hence first order uncertainty is increased) for rare events such as renal failure and amputation.

Figure A1: Graph to show consistency of R implementation of UKPDS with official implementation in prediction of cardiovascular events



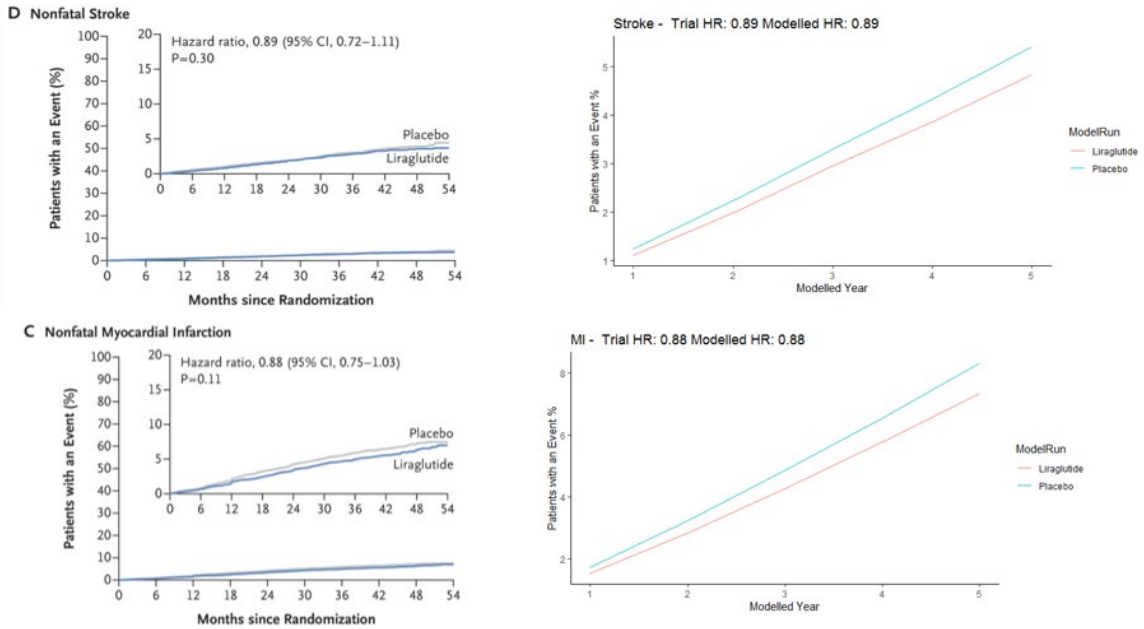
Appendix B: Comparison of UKPDS and CVOT trials

As outlined in Section 2.2.1, the non-CVOT standard care arm was modelled using the UKPDS rather than being modelled using data from the comparator arms from the CVOT trials. The reasons for this were two-fold:

1. The standard care arms in the CVOT trials had less applicability to the population being considered in this guideline update (all people with Type 2 diabetes) as they are restricted to people with high cardiovascular risk.
2. The treat-to-target design of the CVOTs meant that the treatments given in the standard care arm were not comparable to the treatments given in the standard care + CVOT drug arm.

To explore whether the UKPDS was a suitable alternative for the modelling of the standard care arm, a validation exercise was conducted to compare the predictions from the UKDPS to the predictions from the standard care arm in a CVOT trial. The standard care arm from the LEADER trial exploring liraglutide was chosen as an example standard care arm. The population simulated in the UKPDS were from the 'high cardiovascular risk' subgroup as this was considered to be best aligned to the LEADER trial population. The comparison could not account for differences in the distribution of background treatments between the trial and those modelled in the UKPDS.

The UKPDS incidence rates in the high cardiovascular risk subgroup are similar to those observed in CVOT trials. In the LEADER trial the cumulative incidence for nonfatal stroke at 48 months was around 4%. UKPDS predicted around 5% for a combination of fatal and nonfatal stroke. In the LEADER trial the cumulative incidence for nonfatal MI was around 6% and UKPDS predicted 8% for a combination of fatal and nonfatal MI. These results show that the UKPDS incidence rates are comparable with rates observed in the CVOTs, suggesting that the UKPDS has good external validity for predicting 'real world' event rates.



A strength of UKPDS was its ability to generate differing baseline event rates dependent on the modelled population which would not have been possible if the model was based on evidence from CVOT trials alone. When UKPDS is run with the total diabetic population

(which includes a high proportion of people defined as high cardiovascular risk) the resulting incidence rates are given below. For both stroke and MI the incidence rates are around 30% lower than in the high CV risk subgroup alone.