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| Type 2 diabetes in adults: management (update) |

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| Health economic model report |

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| NICE Guideline  |

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| Methods, evidence and recommendations |

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| 01 September 2021 |

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| Draft for Consultation |
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| Commissioned by the National Institute for Health and Care Excellence |

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# Introduction

In 2015, NICE published a guideline on ‘Type 2 diabetes in adults: management’ ([NG28](https://www.nice.org.uk/guidance/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.

# Methods

## Model overview

### 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/m2
* 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.

### 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 UKPDS1 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](https://www.nice.org.uk/guidance/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.

### 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.

## Model structure

### 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 models2. 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. 20183 | Exclude – non-UK population |
| Cardiff | McEwan et al. 20154 | Exclude – industry funded |
| CDC/RTI  | Hoeger et al. 20095 | Exclude – non-UK population |
| ECHO – T2DM | Willis et al. 20136 | Exclude – industry funded |
| IQVIA CORE | Palmer et al. 2004 article7 | Include for further consideration |
| Michigan Model MMD | Zhou et al. 20058 | Exclude – non-UK population |
| PROSIT Model | Schramm et al. 20169 | Exclude – industry funded |
| SPHR Diabetes Model | Thomas et al. 201410 | Exclude – fixed treatment pathway, societal perspective |
| Treatment Transitions Model | Smolen et al. 201411 | Exclude – non-UK population |
| UKPDS OM2 | Hayes et al. 20131 | Include for further consideration |

Of the 10 diabetes models presented, the committee considered that the IQVIA CORE7 and UKPDS1 models were most suitable for use in the health economic analysis.

A full description of the UKPDS OM2 can be found in the Hayes et al. 2013 article1, 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 article7. 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](https://www.nice.org.uk/guidance/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.

### Implementation of UKPDS

Full details of the UKPDS OM2 are documented in the Hayes et al. 2013 paper1. 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 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. At the time of consultation these time-path equations are unpublished and so are academic in confidence. The original time-path equations used in the UKPDS OM1 are detailed in Clarke et al13 and extrapolated fewer risk factors (HbA1c, systolic blood pressure, total cholesterol : HDL cholesterol and smoking status).

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 paper1 . 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](https://www.nice.org.uk/guidance/ng28) used the UKPDS to model all comparators (see [NG28 Appendix F](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355) 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.

### 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.

###  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.

## Model inputs

### Baseline characteristics

UKPDS OM2 requires a baseline dataset containing demographics, clinical risk factors and pre-existing complications, detailed in Hayes et al.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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355) 3.3.1 for full details14). 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 Audit15 - 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 |

#### 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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355) 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.16reported 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 al16 |

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 model7 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.

#### 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**

| Variable | Initial therapy | First intensification  | Second intensification |
| --- | --- | --- | --- |
| 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/1.73m2) | 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 al16 | 16.30% | Adler et al16 | 22.6% | Adler et al16 |
| 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**

| Previous event\* | Initial therapy | First intensification  | Second intensification |
| --- | --- | --- | --- |
| 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 |
| 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* |

### 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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355) 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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355), 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.

#### 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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355) (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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355), 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.

#### 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 limited18 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. 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 HE010: 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 |
| 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* |

#### 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 HE011:**

| 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.

#### 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 HE012: 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* |

#### Hypoglycaemia

##### 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. 201919:

**Table HE013:**

| 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. 201720), 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 HE015:** **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 al19. 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](https://www.nice.org.uk/guidance/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 al19. 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 |

##### 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 HE016: 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 |
| 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* |

### Costs

#### Treatment costs

##### 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 Tariff22. 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 HE017: 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) | £952 |
| 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) | £954 |
| 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% |

##### 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 Tariff22. 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](https://www.nice.org.uk/guidance/ng17)). The treatment dosages were taken directly from [NG28](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355) 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 HE018: 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) |

#### 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 al23where 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 Disease24 with the UK Renal Registry25 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](https://renal.org/sites/renal.org/files/publication/file-attachments/22nd_UKRR_ANNUAL_REPORT_FULL.pdf), 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. 201926 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 HE019: Management and complication costs

| Input variables | Mean cost per year(£)\*  | Source/ Comments |
| --- | --- | --- |
| **Annual cost of CVD complications**  |
| MI 1st year | 8419 | Alva et al. 201523 - 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](https://renal.org/sites/renal.org/files/publication/file-attachments/22nd_UKRR_ANNUAL_REPORT_FULL.pdf), NICE guideline on Chronic Kidney Disease24 |
| 2nd + years | 8,332 |
| Blindness |
| 1st year | 3606 | Alva et al. 201523 |
| 2nd+ years | 1366 |
| Ulcer |
| Active ulcer | 3,520 | Kerr et al (2019)26  |
| Amputation  |  |  |
| 1st year | 14041 | Alva et al. 201523 |
| 2nd + years | 3902 |

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

#### 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](https://www.nice.org.uk/guidance/ng3)).

**Table HE020: 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](https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355)) 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](https://www.nice.org.uk/guidance/ng17)). The committee believed this value to be reasonable and noted that needles with a cost around than £5 per 100 were widely available.

**Table HE021: Modelled injections**

| Treatment | Daily Injections |
| --- | --- |
| NPH Insulin | 1 |
| Semaglutide (injectable) | 1 |
| 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 HE022: 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 HE023: 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  |

#### Hypoglycaemia costs

In the NICE guideline looking at type 1 diabetes in adults28, a detailed evaluation in the costs of managing hypoglycaemic events in type 1 diabetic patients was done, with information from Hammer et al. 200929 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. 201330 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 HE024: Hypoglycaemic costs

| Input variables | Mean cost per year\*  | Source/ Comments |
| --- | --- | --- |
| Non-severe hypoglycaemic events | 0 | Information from Geelhoed et al30 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 al29 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 (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 al31 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.  |

### Doses

The treatment doses were taken directly from [NG28](https://www.nice.org.uk/guidance/ng28), which used average doses from the included RCTs (NG28 Economic Appendix, Section 3.9).

#### 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 HE025: 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 |

#### 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 HE026: 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 |

#### 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 HE027: 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 |

### Utility values

#### 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. 201432), and a systematic review of utility values used in modelling of Type 2 diabetes (Beaudet et al. 201433). Committee opted to use the values from Beaudet et al. as these were aligned to the values used in the Type 1 diabetes insulin update28. 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 Report25 (Table 1.7); hemodialysis contributed 70% of the weighted average, peritoneal dialysis contributed 20.1% and renal transplant contributed 9.9%. 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.

**Table HE028: Quality of life parameters**

| Diabetic event | Utility value | Reference |
| --- | --- | --- |
| Baseline | 0.785 | Beaudet et al. (2014)33 |
| IHD | -0.09 |
| 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 |

#### 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 al34, Olofsson et al35 and Ridderstale et al36 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.

#### 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 diabetes28. 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 al37 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 al38 whose analysis was based on the same data set as Evans et al. Lauridson et al reported disutility equations of 0.0141x0.3393 for non-severe daytime hypoglycaemic events, with x being the rate of hypoglycaemic events.

#### Weight

A utility decrement of -0.0061 was assumed per 1 unit increase in BMI above 25kg/m2. This value was taken from Bagust et al. (2005)39 and is consistent with the approach taken for modelling weight in [NG28](https://www.nice.org.uk/guidance/ng28).

# Subgroup and sensitivity analyses

## 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/m2
* 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.

### BMI subgroup

The committee considered that people with a BMI of greater than 30kg/m2 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.

### 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.

### 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.

### 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.

## 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.

### 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.

### 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.

### 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.

### 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 HE029: 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% |

### 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.

### 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.

#### 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 + Suflonylurea)*** |
| 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 |
| 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 Guideline24 | 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 |
| 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 |
| 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 |
| Distutility 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 202122  |  |
| Canagliflozin (300mg) | £477 |  |
| Dapagliflozin (10mg) | £477 |  |
| Dulaglutide (1.5mg weekly) | £952 |  |
| Empagliflozin (25mg) | £477 |  |
| Ertugliflozin (15mg) | £383 |  |
| Exenatide (2mg weekly) | £954 |  |
| 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 202027  | Normal: μ=49 σ=4.9 |
| Band 8 Nurse hourly cost (£) | 59 ( 47 , 71) | PSSRU Unit Costs of Health and Social Care 202027  | 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 Pregnancy40  |  |
| 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.*

# 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.

## Base-case

Base case results followed a similar pattern across all analysed populations. SGLT2’s were the most cost-effective of the CVOTs across all populations, with dapagliflozin being the most cost-effective amongst the SGLT2s, being the only CVOT to have an ICER below £20,000. Both DPP-4’s and GLP-1’s were either dominated or had very large ICERs compared to the non-CVOT arm. DPP-4’s were largely more cost-effective 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.

### Initial therapy

Table HE031: CVOTs as replacements

| Drug | Cost (£) | QALY | Incremental cost (£) | Incremental QALYs | ICER |
| --- | --- | --- | --- | --- | --- |
| Alogliptin | £22,841  | 9.224 | £4,416  | -0.051 | Dominated |
| Linagliptin | £23,665  | 9.295 | £5,240  | 0.020 | £265,517 |
| Saxagliptin | £24,502  | 9.028 | £6,077  | -0.247 | Dominated |
| Sitagliptin | £24,153  | 9.323 | £5,728  | 0.048 | £119,284 |
| Dulaglutide | £31,090  | 9.424 | £12,666  | 0.149 | £85,134 |
| Exenatide | £31,238  | 9.353 | £12,813  | 0.078 | £164,207 |
| Liraglutide | £37,441  | 9.247 | £19,016  | -0.028 | Dominated |
| Lixisenatide | £27,585  | 8.944 | £9,160  | -0.331 | Dominated |
| Semaglutide (injection) | £30,958  | 9.414 | £12,533  | 0.139 | £90,451 |
| Semaglutide (oral) | £32,332  | 9.032 | £13,907  | -0.243 | Dominated |
| Pioglitazone | £19,705  | 9.249 | £1,280  | -0.026 | Dominated |
| Canagliflozin | £25,166  | 9.539 | £6,741  | 0.264 | £25,504 |
| Dapagliflozin | £24,423  | 9.615 | £5,998  | 0.339 | £17,670 |
| Empagliflozin | £24,710  | 9.510 | £6,285  | 0.235 | £26,730 |
| Ertugliflozin | £23,232  | 9.464 | £4,807  | 0.189 | £25,400 |

Table HE032: CVOTs as additions

| Drug | Cost  | QALY | Incremental cost | Incremental QALYs | ICER |
| --- | --- | --- | --- | --- | --- |
| Alogliptin |  £22,061  | 9.126 |  £4,496  | -0.061 | Dominated |
| Linagliptin |  £22,813  | 9.208 |  £5,248  | 0.021 | £249,251 |
| Saxagliptin |  £23,806  | 8.922 |  £6,241  | -0.265 | Dominated |
| Sitagliptin |  £23,387  | 9.217 |  £5,822  | 0.030 | £192,598 |
| Dulaglutide |  £30,188  | 9.344 |  £12,623  | 0.157 | £80,221 |
| Exenatide |  £30,481  | 9.247 |  £12,916  | 0.060 | £215,778 |
| Liraglutide |  £36,478  | 9.177 |  £18,913  | -0.010 | Dominated |
| Lixisenatide |  £26,543  | 8.898 |  £8,977  | -0.289 | Dominated |
| Semaglutide (injection) |  £30,130  | 9.309 |  £12,565  | 0.122 | £103,323 |
| Semaglutide (oral) |  £31,942  | 8.869 |  £14,377  | -0.318 | Dominated |
| Pioglitazone |  £19,212  | 9.083 |  £1,647  | -0.104 | Dominated |
| Canagliflozin |  £24,485  | 9.404 |  £6,920  | 0.217 | £31,914 |
| Dapagliflozin |  £23,399  | 9.548 |  £5,834  | 0.361 | £16,145 |
| Empagliflozin |  £23,785  | 9.427 |  £6,220  | 0.240 | £25,950 |
| Ertugliflozin |  £22,316  | 9.383 |  £4,751  | 0.196 | £24,274 |

### First intensification

Table HE033: CVOTs as replacements

| Drug | Cost  | QALY | Incremental cost  | Incremental QALYs | ICER |
| --- | --- | --- | --- | --- | --- |
| Alogliptin | £22,657 | 8.683 | £4,183 | -0.045 | Dominated |
| Linagliptin | £23,409 | 8.750 | £4,934 | 0.022 | £222,240 |
| Saxagliptin | £24,261 | 8.490 | £5,786 | -0.239 | Dominated |
| Sitagliptin | £23,933 | 8.774 | £5,458 | 0.046 | £118,518 |
| Dulaglutide | £30,483 | 8.873 | £12,009 | 0.145 | £82,736 |
| Exenatide | £30,647 | 8.803 | £12,173 | 0.074 | £163,702 |
| Liraglutide | £36,517 | 8.706 | £18,043 | -0.022 | Dominated |
| Lixisenatide | £27,112 | 8.416 | £8,637 | -0.313 | Dominated |
| Semaglutide (injection) | £30,470 | 8.876 | £11,995 | 0.148 | £81,100 |
| Semaglutide (oral) | £31,635 | 8.481 | £13,161 | -0.248 | Dominated |
| Pioglitazone | £19,780 | 8.699 | £1,306 | -0.029 | Dominated |
| Canagliflozin | £24,916 | 8.969 | £6,441 | 0.240 | £26,793 |
| Dapagliflozin | £24,158 | 9.048 | £5,684 | 0.320 | £17,787 |
| Empagliflozin | £24,435 | 8.938 | £5,961 | 0.210 | £28,395 |
| Ertugliflozin | £23,001 | 8.902 | £4,527 | 0.174 | £26,049 |

 Table HE034: CVOTs as additions

| Drug | Cost  | QALY | Incremental cost  | Incremental QALYs | ICER |
| --- | --- | --- | --- | --- | --- |
| Alogliptin |  £22,878  | 8.439 |  £4,266  | -0.063 | Dominated |
| Linagliptin |  £23,516  | 8.529 |  £4,905  | 0.027 | £180,999 |
| Saxagliptin |  £24,592  | 8.225 |  £5,980  | -0.277 | Dominated |
| Sitagliptin |  £24,181  | 8.523 |  £5,569  | 0.021 | £259,172 |
| Dulaglutide |  £30,486  | 8.667 |  £11,874  | 0.165 | £72,035 |
| Exenatide |  £30,864  | 8.555 |  £12,252  | 0.054 | £228,660 |
| Liraglutide |  £36,412  | 8.518 |  £17,800  | 0.016 | £1,114,410 |
| Lixisenatide |  £26,908  | 8.255 |  £8,297  | -0.247 | Dominated |
| Semaglutide (injection) |  £30,622  | 8.631 |  £12,010  | 0.129 | £92,797 |
| Semaglutide (oral) |  £32,349  | 8.151 |  £13,737  | -0.351 | Dominated |
| Pioglitazone |  £20,467  | 8.367 |  £1,855  | -0.135 | Dominated |
| Canagliflozin |  £25,297  | 8.695 |  £6,685  | 0.193 | £34,644 |
| Dapagliflozin |  £24,035  | 8.869 |  £5,423  | 0.367 | £14,756 |
| Empagliflozin |  £24,454  | 8.736 |  £ 5,842  | 0.234 | £24,975 |
| Ertugliflozin |  £23,026  | 8.699 |  £4,414  | 0.197 | £22,396 |

### Second intensification

Table HE035: CVOTs as replacements

| Drug | Cost  | QALY | Incremental cost  | Incremental QALYs | ICER |
| --- | --- | --- | --- | --- | --- |
| Alogliptin |  £23,704  | 7.833 |  £3,876  | -0.046 | Dominated |
| Linagliptin |  £24,350  | 7.905 |  £4,522  | 0.026 | £176,942 |
| Saxagliptin |  £25,203  | 7.637 |  £5,375  | -0.242 | Dominated |
| Sitagliptin |  £24,936  | 7.916 |  £5,108  | 0.037 | £139,652 |
| Dulaglutide |  £30,883  | 8.027 |  £11,055  | 0.148 | £74,699 |
| Exenatide |  £ 31,125  | 7.945 |  £11,298  | 0.066 | £171,084 |
| Liraglutide |  £36,453  | 7.882 |  £16,625  | 0.003 | £6,334,180 |
| Lixisenatide |  £27,630  | 7.614 |  £7,802  | -0.265 | Dominated |
| Semaglutide (injection) |  £31,067  | 8.030 |  £11,239  | 0.151 | £74,532 |
| Semaglutide (oral) |  £32,095  | 7.605 |  £12,267  | -0.274 | Dominated |
| Pioglitazone |  £21,314  | 7.822 |  £1,486  | -0.057 | Dominated |
| Canagliflozin |  £25,950  | 8.091 |  £6,122  | 0.212 | £28,922 |
| Dapagliflozin |  £25,030  | 8.198 |  £5,202  | 0.318 | £16,343 |
| Empagliflozin |  £25,329  | 8.080 |  £5,501  | 0.201 | £27,394 |
| Ertugliflozin |  £23,967  | 8.049 |  £4,140  | 0.170 | £24,322 |

Table HE036: CVOTs as additions

| Drug | Cost  | QALY | Incremental cost  | Incremental QALYs | ICER |
| --- | --- | --- | --- | --- | --- |
| Alogliptin |  £23,553  | 7.567 |  £3,949  | -0.064 | Dominated |
| Linagliptin |  £24,080  | 7.660 |  £4,475  | 0.028 | £157,990 |
| Saxagliptin |  £25,161  | 7.353 |  £5,557  | -0.278 | Dominated |
| Sitagliptin |  £24,814  | 7.645 |  £5,210  | 0.013 | £390,845 |
| Dulaglutide |  £30,483  | 7.801 |  £10,879  | 0.169 | £64,196 |
| Exenatide |  £30,952  | 7.678 |  £ 11,348  | 0.047 | £240,722 |
| Liraglutide |  £35,927  | 7.673 |  £16,323  | 0.042 | £391,861 |
| Lixisenatide |  £27,020  | 7.427 |  £7,416  | -0.204 | Dominated |
| Semaglutide (injection) |  £30,833  | 7.774 |  £11,229  | 0.142 | £78,902 |
| Semaglutide (oral) |  £32,431  | 7.251 |  £12,826  | -0.380 | Dominated |
| Pioglitazone |  £21,665  | 7.472 |  £2,061  | -0.160 | Dominated |
| Canagliflozin |  £25,972  | 7.796 |  £6,368  | 0.164 | £38,727 |
| Dapagliflozin |  £24,523  | 7.994 |  £4,918  | 0.363 | £13,548 |
| Empagliflozin |  £24,973  | 7.852 |  £5,369  | 0.220 | £24,376 |
| Ertugliflozin |  £23,616  | 7.820 |  £4,011  | 0.189 | £21,204 |

### 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 | 9 | 9 | 9 | 9 | 9 | 8 |
| Linagliptin | 8 | 7 | 7 | 6 | 7 | 6 |
| Saxagliptin | 12 | 12 | 12 | 13 | 13 | 13 |
| Sitagliptin | 7 | 8 | 8 | 8 | 8 | 7 |
| Dulaglutide | 10 | 10 | 11 | 10 | 10 | 10 |
| Exenatide | 13 | 13 | 13 | 12 | 12 | 12 |
| Liraglutide | 16 | 15 | 16 | 15 | 15 | 15 |
| Lixisenatide | 14 | 14 | 14 | 14 | 14 | 14 |
| Semaglutide (injection) | 11 | 11 | 10 | 11 | 11 | 11 |
| Semaglutide (oral) | 15 | 16 | 15 | 16 | 16 | 16 |
| Pioglitazone | 6 | 6 | 6 | 7 | 6 | 9 |
| Canagliflozin | 4 | 5 | 4 | 5 | 5 | 5 |
| Dapagliflozin | 1 | 1 | 1 | 1 | 1 | 1 |
| Empagliflozin | 5 | 4 | 5 | 4 | 4 | 4 |
| Ertugliflozin | 3 | 3 | 3 | 3 | 3 | 3 |

## Subgroup analyses

The tables below outline ICERs and net monetary benefit rankings (at £20,000) 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 remained the most cost-effectiveness across all subgroups. 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 a 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. Dapagliflozin continues to be the only CVOT to have an ICER below £20,000 in all subgroups, and hence remains as the most cost-effective treatment option.

### 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 | 9 | Dominated | 8 | Dominated | 9 | Dominated | 9 |
| Linagliptin | £185,349 | 8 | Dominated | 9 | £253,835 | 8 | £203,470 | 7 |
| Saxagliptin | Dominated  | 13 | Dominated | 12 | Dominated | 13 | Dominated | 13 |
| Sitagliptin | £106,167 | 7 | £85,445 | 7 | £114,125 | 7 | £127,721 | 8 |
| Dulaglutide | £71,385 | 11 | £65,338 | 11 | £69,112 | 10 | £87,684 | 10 |
| Exenatide | £128,525 | 12 | £113,955 | 13 | £128,188 | 12 | £170,510 | 12 |
| Liraglutide | Dominated  | 16 | £355,776 | 16 | Dominated | 16 | Dominated | 16 |
| Lixisenatide | Dominated  | 14 | Dominated  | 14 | Dominated  | 14 | Dominated | 14 |
| Semaglutide (injection) | £71,498 | 10 | £44,778 | 10 | £73,417 | 11 | £114,951 | 11 |
| Semaglutide (oral) | Dominated  | 15 | Dominated  | 15 | Dominated  | 15 | Dominated | 15 |
| Pioglitazone | £116,326 | 5 | £21,069 | 3 | £100,244 | 5 | Dominated | 6 |
| Canagliflozin | £20,769 | 3 | £21,666 | 4 | £20,988 | 3 | £24,270 | 5 |
| Dapagliflozin | £16,443 | 1 | £16,916 | 1 | £16,556 | 1 | £16,839 | 1 |
| Empagliflozin | £25,330 | 6 | £22,676 | 5 | £25,438 | 6 | £23,806 | 4 |
| Ertugliflozin | £22,525 | 4 | £33,510 | 6 | £22,821 | 4 | £22,772 | 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  | 9 | Dominated  | 8 | Dominated  | 9 | Dominated | 9 |
| Linagliptin | £181,635 | 7 | Dominated | 9 | £246,734 | 7 | £198,449 | 7 |
| Saxagliptin | Dominated  | 13 | Dominated  | 12 | Dominated  | 13 | Dominated  | 13 |
| Sitagliptin | £152,891 | 8 | £113,281 | 7 | £168,493 | 8 | £217,300 | 8 |
| Dulaglutide | £69,092 | 10 | £62,777 | 11 | £67,023 | 10 | £82,414 | 10 |
| Exenatide | £157,100 | 12 | £135,114 | 13 | £156,496 | 12 | £228,497 | 12 |
| Liraglutide | £3,504,735 | 15 | £275,683 | 15 | £2,855,842 | 15 | Dominated  | 15 |
| Lixisenatide | Dominated  | 14 | Dominated  | 14 | Dominated  | 14 | Dominated  | 14 |
| Semaglutide (injection) | £79,699 | 11 | £47,685 | 10 | £81,630 | 11 | £135,153 | 11 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated  | 6 | £75,098 | 6 | Dominated  | 6 | Dominated  | 6 |
| Canagliflozin | £24,923 | 5 | £25,041 | 4 | £25,132 | 5 | £30,357 | 5 |
| Dapagliflozin | £15,376 | 1 | £15,695 | 1 | £15,464 | 1 | £15,435 | 1 |
| Empagliflozin | £25,017 | 4 | £22,067 | 3 | £25,076 | 4 | £23,264 | 4 |
| Ertugliflozin | £22,008 | 3 | £31,441 | 5 | £22,283 | 3 | £21,952 | 3 |

### 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  | 9 | Dominated  | 8 | Dominated | 9 | Dominated  | 9 |
| Linagliptin | £140,587 | 7 | Dominated  | 9 | £363,173 | 8 | £185,291 | 7 |
| Saxagliptin | Dominated  | 13 | Dominated  | 12 | Dominated | 13 | Dominated  | 13 |
| Sitagliptin | £110,651 | 8 | £87,744 | 7 | £116,919 | 7 | £126,945 | 8 |
| Dulaglutide | £70,764 | 11 | £63,019 | 11 | £67,923 | 11 | £85,965 | 10 |
| Exenatide | £132,781 | 12 | £115,352 | 13 | £131,946 | 12 | £171,785 | 12 |
| Liraglutide | Dominated  | 16 | £385,874 | 16 | Dominated | 16 | Dominated  | 16 |
| Lixisenatide | Dominated  | 14 | Dominated  | 14 | Dominated | 14 | Dominated  | 14 |
| Semaglutide (injection) | £70,189 | 10 | £42,441 | 10 | £66,319 | 10 | £101,227 | 11 |
| Semaglutide (oral) | Dominated | 15 | Dominated  | 15 | Dominated | 15 | Dominated | 15 |
| Pioglitazone | Dominated  | 5 | £23,674 | 3 | £204,705 | 5 | Dominated  | 6 |
| Canagliflozin | £22,190 | 4 | £23,920 | 4 | £22,939 | 3 | £25,571 | 5 |
| Dapagliflozin | £16,551 | 1 | £17,878 | 1 | £16,972 | 1 | £16,979 | 1 |
| Empagliflozin | £26,835 | 6 | £26,293 | 5 | £27,857 | 6 | £25,087 | 4 |
| Ertugliflozin | £22,732 | 3 | £38,983 | 6 | £24,537 | 4 | £23,421 | 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 | 9 | Dominated | 8 | Dominated | 9 | Dominated | 9 |
| Linagliptin | £122,531 | 7 | Dominated | 9 | £263,975 | 7 | £153,134 | 6 |
| Saxagliptin | Dominated | 13 | Dominated | 12 | Dominated | 13 | Dominated | 13 |
| Sitagliptin | £221,947 | 8 | £142,327 | 7 | £246,451 | 8 | £301,735 | 8 |
| Dulaglutide | £62,864 | 10 | £57,370 | 10 | £60,718 | 10 | £74,315 | 10 |
| Exenatide | £172,601 | 12 | £146,081 | 13 | £171,452 | 12 | £243,498 | 12 |
| Liraglutide | £555,294 | 15 | £227,151 | 15 | £531,758 | 15 | £1,022,648 | 15 |
| Lixisenatide | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated  | 14 |
| Semaglutide (injection) | £79,368 | 11 | £45,838 | 11 | £74,342 | 11 | £119,629 | 11 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated | 6 | Dominated | 6 | Dominated | 6 | Dominated  | 7 |
| Canagliflozin | £27,464 | 5 | £29,470 | 5 | £28,544 | 5 | £32,593 | 5 |
| Dapagliflozin | £13,814 | 1 | £15,415 | 1 | £14,181 | 1 | £14,129 | 1 |
| Empagliflozin | £23,582 | 4 | £24,140 | 3 | £24,494 | 4 | £22,259 | 4 |
| Ertugliflozin | £19,742 | 2 | £32,252 | 4 | £21,169 | 3 | £20,289 | 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  | 9 | Dominated  | 8 | Dominated  | 9 | Dominated  | 9 |
| Linagliptin | £106,118 | 7 | Dominated  | 9 | £300,837 | 7 | £151,193 | 7 |
| Saxagliptin | Dominated  | 13 | Dominated  | 12 | Dominated  | 13 | Dominated  | 13 |
| Sitagliptin | £138,361 | 8 | £108,998 | 7 | £144,023 | 8 | £148,308 | 8 |
| Dulaglutide | £65,799 | 10 | £56,633 | 11 | £62,626 | 10 | £76,697 | 10 |
| Exenatide | £145,252 | 12 | £121,124 | 13 | £141,808 | 12 | £175,782 | 12 |
| Liraglutide | £1,046,000 | 15 | £262,166 | 15 | £791,498 | 15 | £3,377,498 | 15 |
| Lixisenatide | Dominated  | 14 | Dominated  | 14 | Dominated | 14 | Dominated | 14 |
| Semaglutide (injection) | £69,441 | 11 | £42,448 | 10 | £62,559 | 11 | £89,597 | 11 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated  | 6 | £46,163 | 4 | Dominated  | 6 | Dominated  | 6 |
| Canagliflozin | £24,721 | 4 | £26,039 | 5 | £25,591 | 4 | £26,974 | 5 |
| Dapagliflozin | £15,150 | 1 | £16,598 | 1 | £15,612 | 1 | £15,567 | 1 |
| Empagliflozin | £25,871 | 5 | £26,083 | 3 | £26,930 | 5 | £24,041 | 4 |
| Ertugliflozin | £21,077 | 3 | £34,694 | 6 | £23,240 | 3 | £21,782 | 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  | 9 | Dominated  | 9 | Dominated  | 9 | Dominated  | 8 |
| Linagliptin | £98,646 | 6 | Dominated  | 8 | £243,671 | 6 | £136,238 | 6 |
| Saxagliptin | Dominated  | 14 | Dominated  | 12 | Dominated  | 13 | Dominated  | 14 |
| Sitagliptin | £380,237 | 7 | £205,586 | 7 | £417,921 | 8 | £469,520 | 7 |
| Dulaglutide | £56,984 | 10 | £50,836 | 10 | £54,794 | 10 | £65,732 | 10 |
| Exenatide | £190,794 | 12 | £153,393 | 13 | £185,744 | 12 | £250,564 | 12 |
| Liraglutide | £289,677 | 15 | £166,180 | 15 | £270,891 | 15 | £372,298 | 15 |
| Lixisenatide | Dominated  | 13 | Dominated  | 14 | Dominated  | 14 | Dominated | 13 |
| Semaglutide (injection) | £72,389 | 11 | £44,076 | 11 | £65,240 | 11 | £96,461 | 11 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated  | 8 | Dominated  | 6 | Dominated  | 7 | Dominated  | 9 |
| Canagliflozin | £31,780 | 5 | £32,899 | 5 | £33,098 | 5 | £35,449 | 5 |
| Dapagliflozin | £12,591 | 1 | £14,200 | 1 | £13,020 | 1 | £12,974 | 1 |
| Empagliflozin | £23,071 | 4 | £23,912 | 3 | £24,083 | 4 | £21,602 | 4 |
| Ertugliflozin | £18,549 | 2 | £29,290 | 4 | £20,287 | 3 | £19,162 | 2 |

## Sensitivity analyses

The tables below outline ICERs and net monetary benefit rankings (at £20,000) 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.

### Utility decrement for injections (set to 0)

When the disutility from injections was set to 0, the cost-effectiveness of injected semaglutide improved across all subgroups and intensification levels as the sensitivity analysis did not account for any disutility experienced by patients when taking an injection. However, dapagliflozin remained the most cost-effective treatment option and the only one to have an ICER below £20,000.

#### 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 | 8 | Dominated | 10 | Dominated  | 10 |
| Linagliptin | £265,517 | 9 | £185,349 | 9 | Dominated | 9 | £253,835 | 9 | £203,470 | 8 |
| Saxagliptin | Dominated | 14 | Dominated | 15 | Dominated | 12 | Dominated | 14 | Dominated  | 14 |
| Sitagliptin | £119,284 | 8 | £106,167 | 8 | £85,445 | 7 | £114,125 | 8 | £127,721 | 9 |
| Dulaglutide | £62,210 | 12 | £54,387 | 11 | £65,338 | 11 | £53,115 | 11 | £63,559 | 12 |
| Exenatide | £96,442 | 13 | £82,696 | 13 | £113,955 | 13 | £82,644 | 13 | £98,583 | 13 |
| Liraglutide | £52,965 | 15 | £49,929 | 14 | £355,776 | 16 | £49,963 | 15 | £52,688 | 15 |
| Lixisenatide | £202,991 | 11 | £297,745 | 12 | Dominated | 14 | £259,940 | 12 | £168,856 | 11 |
| Semaglutide (injection) | £23,516 | 7 | £21,791 | 6 | £44,778 | 10 | £22,064 | 6 | £24,928 | 7 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 15 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated  | 6 | £116,326 | 5 | £21,069 | 3 | £100,244 | 5 | Dominated  | 6 |
| Canagliflozin | £25,504 | 4 | £20,769 | 3 | £21,666 | 4 | £20,988 | 3 | £24,270 | 5 |
| Dapagliflozin | £17,670 | 1 | £16,443 | 1 | £16,916 | 1 | £16,556 | 1 | £16,839 | 1 |
| Empagliflozin | £26,730 | 5 | £25,330 | 7 | £22,676 | 5 | £25,438 | 7 | £23,806 | 4 |
| Ertugliflozin | £25,400 | 3 | £22,525 | 4 | £33,510 | 6 | £22,821 | 4 | £22,772 | 3 |

#### 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 | £222,240 | 8 | £140,587 | 8 | Dominated | 10 | £363,173 | 9 | £185,291 | 8 |
| Saxagliptin | Dominated | 14 | Dominated | 15 | Dominated | 13 | Dominated | 14 | Dominated | 14 |
| Sitagliptin | £118,518 | 9 | £110,651 | 9 | £87,744 | 8 | £116,919 | 8 | £126,945 | 9 |
| Dulaglutide | £60,919 | 12 | £54,030 | 11 | £49,772 | 11 | £52,437 | 11 | £62,656 | 12 |
| Exenatide | £96,346 | 13 | £84,488 | 13 | £78,284 | 14 | £84,316 | 13 | £99,089 | 13 |
| Liraglutide | £52,356 | 15 | £49,749 | 14 | £45,792 | 15 | £49,779 | 15 | £52,198 | 15 |
| Lixisenatide | £199,267 | 11 | £255,182 | 12 | £291,366 | 12 | £236,477 | 12 | £164,866 | 11 |
| Semaglutide (injection) | £22,958 | 4 | £21,702 | 5 | £20,012 | 3 | £21,662 | 5 | £24,337 | 6 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated | 7 | Dominated | 6 | £23,674 | 4 | £204,705 | 6 | Dominated | 7 |
| Canagliflozin | £26,793 | 5 | £22,190 | 4 | £23,920 | 5 | £22,939 | 3 | £25,571 | 5 |
| Dapagliflozin | £17,787 | 1 | £16,551 | 1 | £17,878 | 1 | £16,972 | 1 | £16,979 | 1 |
| Empagliflozin | £28,395 | 6 | £26,835 | 7 | £26,293 | 6 | £27,857 | 7 | £25,087 | 4 |
| Ertugliflozin | £26,049 | 3 | £22,732 | 3 | £38,983 | 7 | £24,537 | 4 | £23,421 | 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 | £176,942 | 8 | £106,118 | 8 | Dominated | 10 | £300,837 | 8 | £151,193 | 8 |
| Saxagliptin | Dominated | 15 | Dominated | 15 | Dominated | 13 | Dominated | 15 | Dominated | 15 |
| Sitagliptin | £139,652 | 9 | £138,361 | 9 | £108,998 | 8 | £144,023 | 9 | £148,308 | 9 |
| Dulaglutide | £56,426 | 12 | £51,067 | 11 | £45,699 | 12 | £49,221 | 11 | £57,563 | 12 |
| Exenatide | £99,133 | 13 | £89,589 | 13 | £81,080 | 14 | £88,534 | 13 | £100,685 | 13 |
| Liraglutide | £48,796 | 14 | £46,604 | 14 | £43,284 | 15 | £46,372 | 14 | £48,456 | 14 |
| Lixisenatide | £125,102 | 11 | £131,122 | 12 | £133,002 | 11 | £126,725 | 12 | £112,244 | 11 |
| Semaglutide (injection) | £22,626 | 4 | £21,748 | 4 | £20,110 | 3 | £21,523 | 4 | £23,850 | 6 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | Dominated | 7 | Dominated | 7 | £46,163 | 5 | Dominated | 7 | Dominated | 7 |
| Canagliflozin | £28,922 | 6 | £24,721 | 5 | £26,039 | 6 | £25,591 | 5 | £26,974 | 5 |
| Dapagliflozin | £16,343 | 1 | £15,150 | 1 | £16,598 | 1 | £15,612 | 1 | £15,567 | 1 |
| Empagliflozin | £27,394 | 5 | £25,871 | 6 | £26,083 | 4 | £26,930 | 6 | £24,041 | 4 |
| Ertugliflozin | £24,322 | 3 | £21,077 | 3 | £34,694 | 7 | £23,240 | 3 | £21,782 | 3 |

### 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.

#### 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 | 8 | Dominated | 9 | Dominated | 8 | Dominated | 9 | Dominated | 9 |
| Linagliptin | £378,688 | 9 | £226,265 | 8 | Dominated | 10 | £346,302 | 8 | £261,253 | 8 |
| Saxagliptin | Dominated | 11 | Dominated | 13 | Dominated | 11 | Dominated | 13 | Dominated | 11 |
| Sitagliptin | £59,569 | 7 | £57,580 | 7 | £51,255 | 7 | £59,939 | 7 | £61,425 | 7 |
| Dulaglutide | £110,127 | 13 | £86,233 | 11 | £76,726 | 12 | £82,671 | 11 | £115,041 | 13 |
| Exenatide | £104,549 | 12 | £89,773 | 12 | £81,843 | 13 | £89,569 | 12 | £106,847 | 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) | £71,095 | 10 | £58,744 | 10 | £38,891 | 9 | £60,115 | 10 | £86,149 | 10 |
| Semaglutide (oral) | Dominated | 14 | Dominated | 14 | Dominated | 14 | £1,931,880 | 14 | Dominated | 14 |
| Pioglitazone | £7,303 | 1 | £5,478 | 1 | £7,460 | 1 | £5,713 | 1 | £7,952 | 1 |
| Canagliflozin | £18,073 | 2 | £15,593 | 2 | £16,651 | 2 | £15,757 | 2 | £17,364 | 2 |
| Dapagliflozin | £23,478 | 4 | £20,901 | 4 | £20,720 | 4 | £21,029 | 4 | £22,064 | 4 |
| Empagliflozin | £30,864 | 6 | £28,583 | 6 | £24,571 | 5 | £28,693 | 6 | £26,926 | 6 |
| Ertugliflozin | £30,698 | 5 | £26,164 | 5 | £42,856 | 6 | £26,540 | 5 | £26,861 | 5 |

#### 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 | 8 | Dominated | 9 | Dominated | 8 | Dominated | 8 | Dominated | 9 |
| Linagliptin | £300,741 | 9 | £163,571 | 8 | Dominated | 10 | £671,326 | 9 | £235,391 | 8 |
| Saxagliptin | Dominated | 11 | Dominated | 13 | Dominated | 11 | Dominated | 12 | Dominated | 11 |
| Sitagliptin | £57,996 | 7 | £57,004 | 7 | £51,225 | 7 | £58,880 | 7 | £59,784 | 7 |
| Dulaglutide | £107,958 | 12 | £87,030 | 11 | £74,181 | 12 | £82,334 | 11 | £114,145 | 13 |
| Exenatide | £102,574 | 13 | £90,038 | 12 | £81,505 | 13 | £89,680 | 13 | £105,536 | 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) | £64,601 | 10 | £57,419 | 10 | £36,896 | 9 | £54,724 | 10 | £77,398 | 10 |
| Semaglutide (oral) | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 |
| Pioglitazone | £7,599 | 1 | £5,976 | 1 | £8,017 | 1 | £6,401 | 1 | £8,261 | 1 |
| Canagliflozin | £18,519 | 2 | £16,162 | 2 | £17,834 | 2 | £16,651 | 2 | £17,850 | 2 |
| Dapagliflozin | £24,188 | 4 | £21,649 | 4 | £22,601 | 4 | £22,283 | 4 | £22,748 | 4 |
| Empagliflozin | £33,588 | 6 | £31,060 | 6 | £29,350 | 5 | £32,448 | 6 | £28,928 | 6 |
| Ertugliflozin | £32,202 | 5 | £26,905 | 5 | £54,974 | 6 | £29,664 | 5 | £28,190 | 5 |

#### 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 | 8 | Dominated | 9 | Dominated | 8 | Dominated | 8 | Dominated | 9 |
| Linagliptin | £236,565 | 9 | £122,163 | 8 | Dominated | 10 | £588,016 | 9 | £191,187 | 8 |
| Saxagliptin | Dominated | 11 | Dominated | 13 | Dominated | 11 | Dominated | 13 | Dominated | 13 |
| Sitagliptin | £56,621 | 7 | £56,185 | 7 | £52,337 | 7 | £57,525 | 7 | £58,045 | 7 |
| Dulaglutide | £101,582 | 12 | £85,688 | 11 | £68,975 | 12 | £79,784 | 11 | £105,475 | 11 |
| Exenatide | £98,126 | 13 | £88,531 | 12 | £79,097 | 13 | £87,298 | 12 | £99,714 | 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) | £59,047 | 10 | £55,626 | 10 | £36,435 | 9 | £50,994 | 10 | £68,641 | 10 |
| Semaglutide (oral) | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 |
| Pioglitazone | £8,874 | 1 | £7,573 | 1 | £8,917 | 1 | £7,946 | 1 | £9,446 | 1 |
| Canagliflozin | £18,531 | 2 | £16,488 | 2 | £18,057 | 2 | £17,046 | 2 | £17,662 | 2 |
| Dapagliflozin | £23,493 | 4 | £21,235 | 4 | £22,313 | 4 | £21,916 | 4 | £21,864 | 4 |
| Empagliflozin | £33,742 | 6 | £31,430 | 6 | £30,398 | 5 | £32,899 | 6 | £28,598 | 6 |
| Ertugliflozin | £31,332 | 5 | £26,033 | 5 | £52,016 | 6 | £29,668 | 5 | £27,082 | 5 |

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

When the disutility from BMI was set to 0, SGLT2’s remained the most cost-effective class of treatment in all type 2 diabetes patients across the three stages of intensifications considered where CVOT’s were used as replacements. However the cost-effectiveness of dapagliflozin did increase to marginally above £20,000. 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.

#### 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 | 9 | Dominated | 9 | Dominated | 8 | Dominated | 9 | Dominated | 9 |
| Linagliptin | £199,440 | 7 | £150,336 | 7 | Dominated | 9 | £192,407 | 7 | £162,202 | 7 |
| Saxagliptin | Dominated | 11 | Dominated | 12 | Dominated | 10 | Dominated | 12 | Dominated | 11 |
| Sitagliptin | £119,284 | 8 | £106,167 | 8 | £85,445 | 7 | £114,125 | 8 | £127,721 | 8 |
| Dulaglutide | £108,241 | 10 | £87,168 | 10 | £77,786 | 11 | £83,719 | 10 | £112,400 | 10 |
| Exenatide | £302,927 | 13 | £201,190 | 13 | £164,204 | 13 | £200,027 | 13 | £325,090 | 12 |
| Liraglutide | Dominated | 15 | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 15 |
| Lixisenatide | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 |
| Semaglutide (injection) | £370,359 | 12 | £181,304 | 11 | £66,067 | 12 | £192,180 | 11 | £2,795,348 | 13 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 15 | Dominated | 15 | Dominated | 15 | Dominated | 16 |
| Pioglitazone | £25,618 | 3 | £12,768 | 1 | £12,524 | 1 | £13,175 | 1 | £35,396 | 3 |
| Canagliflozin | £30,842 | 5 | £24,300 | 4 | £24,671 | 4 | £24,537 | 4 | £29,063 | 5 |
| Dapagliflozin | £20,766 | 2 | £19,124 | 2 | £19,277 | 2 | £19,244 | 2 | £19,636 | 1 |
| Empagliflozin | £37,214 | 6 | £34,521 | 6 | £28,578 | 5 | £34,627 | 6 | £31,814 | 6 |
| Ertugliflozin | £39,377 | 4 | £33,076 | 5 | £60,517 | 6 | £33,591 | 5 | £33,463 | 4 |

#### 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 | 9 | Dominated | 9 | Dominated | 8 | Dominated | 9 | Dominated | 9 |
| Linagliptin | £173,734 | 7 | £119,396 | 7 | Dominated | 9 | £247,852 | 7 | £150,241 | 7 |
| Saxagliptin | Dominated | 11 | Dominated | 13 | Dominated | 10 | Dominated | 12 | Dominated | 11 |
| Sitagliptin | £118,518 | 8 | £110,651 | 8 | £87,744 | 7 | £116,919 | 8 | £126,945 | 8 |
| Dulaglutide | £104,395 | 10 | £86,236 | 10 | £74,507 | 11 | £81,942 | 10 | £109,580 | 10 |
| Exenatide | £300,712 | 13 | £211,612 | 12 | £166,836 | 13 | £208,827 | 13 | £329,174 | 12 |
| Liraglutide | Dominated | 15 | Dominated | 15 | Dominated | 16 | Dominated | 16 | Dominated | 15 |
| Lixisenatide | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 |
| Semaglutide (injection) | £247,596 | 12 | £172,559 | 11 | £60,422 | 12 | £146,521 | 11 | £628,220 | 13 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 15 | Dominated | 15 | Dominated | 16 |
| Pioglitazone | £30,230 | 3 | £16,893 | 2 | £13,976 | 1 | £16,345 | 1 | £43,945 | 3 |
| Canagliflozin | £32,686 | 5 | £26,233 | 4 | £27,606 | 4 | £27,177 | 4 | £30,893 | 5 |
| Dapagliflozin | £20,926 | 2 | £19,280 | 1 | £20,540 | 3 | £19,806 | 2 | £19,825 | 1 |
| Empagliflozin | £40,487 | 6 | £37,394 | 6 | £34,603 | 5 | £39,280 | 6 | £34,118 | 6 |
| Ertugliflozin | £41,097 | 4 | £33,585 | 5 | £84,376 | 6 | £37,786 | 5 | £34,968 | 4 |

#### 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 | 9 | Dominated | 9 | Dominated | 8 | Dominated | 9 | Dominated | 9 |
| Linagliptin | £144,612 | 7 | £93,552 | 7 | Dominated | 9 | £216,637 | 7 | £126,903 | 7 |
| Saxagliptin | Dominated | 12 | Dominated | 13 | Dominated | 11 | Dominated | 12 | Dominated | 11 |
| Sitagliptin | £139,652 | 8 | £138,361 | 8 | £108,998 | 7 | £144,023 | 8 | £148,308 | 8 |
| Dulaglutide | £91,949 | 10 | £79,002 | 10 | £65,747 | 10 | £74,357 | 10 | £94,989 | 10 |
| Exenatide | £324,655 | 13 | £244,091 | 12 | £178,618 | 13 | £233,299 | 13 | £342,054 | 13 |
| Liraglutide | Dominated | 15 | Dominated | 15 | £1,800,964 | 15 | Dominated | 15 | Dominated | 15 |
| Lixisenatide | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 | Dominated | 14 |
| Semaglutide (injection) | £190,684 | 11 | £166,237 | 11 | £60,202 | 12 | £126,700 | 11 | £334,253 | 12 |
| Semaglutide (oral) | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 | Dominated | 16 |
| Pioglitazone | £161,552 | 3 | £83,776 | 3 | £21,021 | 3 | £44,812 | 3 | Dominated | 3 |
| Canagliflozin | £35,658 | 6 | £29,672 | 5 | £30,345 | 4 | £30,722 | 5 | £32,753 | 6 |
| Dapagliflozin | £18,977 | 1 | £17,445 | 1 | £18,896 | 1 | £17,991 | 1 | £17,944 | 1 |
| Empagliflozin | £38,456 | 5 | £35,615 | 6 | £34,274 | 5 | £37,398 | 6 | £32,184 | 5 |
| Ertugliflozin | £37,108 | 4 | £30,197 | 4 | £67,155 | 6 | £34,927 | 4 | £31,537 | 4 |

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

**Table HE053**

| Treatment | ICER including SAE | Base-case ICER |
| --- | --- | --- |
| Alogliptin | Dominated | Dominated |
| Linagliptin | £177,961 | £176,942 |
| Saxagliptin | Dominated | Dominated |
| Sitagliptin | £137,172 | £139,652 |
| Dulaglutide | £71,690 | £74,699 |
| Exenatide | £179,844 | £171,084 |
| Liraglutide | £54,090,888 | £6,334,180 |
| Lixisenatide | Dominated | Dominated |
| Semaglutide (injection) | £79,822 | £74,532 |
| Semaglutide (oral) | Dominated | Dominated |
| Pioglitazone | Dominated | Dominated |
| Canagliflozin | £27,345 | £28,922 |
| Dapagliflozin | £16,094 | £16,343 |
| Empagliflozin | £27,463 | £27,394 |
| Ertugliflozin | £24,981 | £24,322 |

### 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 : Effect of adjustment for cardiovascular mortality



For most treatments, 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.

**Table HE054**

|  | Pre adjustment Base-Case ICER | Post-adjustment CV-adjusted ICER | Pre-adjustment Base-caseRank @20k | Post-adjustment CV-adjustedRank @20k |
| --- | --- | --- | --- | --- |
| Alogliptin | Dominated | £21,595 | 9 | 5 |
| Linagliptin | £176,942 | £58,531 | 7 | 7 |
| Saxagliptin | Dominated | Dominated | 13 | 12 |
| Sitagliptin | £139,652 | Dominated | 8 | 9 |
| Dulaglutide | £74,699 | £50,983 | 10 | 10 |
| Exenatide | £171,084 | £61,155 | 12 | 11 |
| Liraglutide | £6,334,180 | £66,627 | 15 | 16 |
| Lixisenatide | Dominated | Dominated | 14 | 15 |
| Semaglutide (injection) | £74,532 | Dominated | 11 | 14 |
| Semaglutide (oral) | Dominated | £29,113 | 16 | 13 |
| Pioglitazone | Dominated | Dominated | 6 | 8 |
| Canagliflozin | £28,922 | £28,366 | 5 | 6 |
| Dapagliflozin | £16,343 | £21,209 | 1 | 4 |
| Empagliflozin | £27,394 | £15,989 | 4 | 1 |
| Ertugliflozin | £24,322 | £19,039 | 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 £15,989 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 became dominated 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 £21,595. This change is driven by the difference in incremental QALYs which increases from -0.047 to 0.451 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).

### Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was run for the second intensification - replace population. Due 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 : Cost effectiveness plane for treatments on a class level



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 second 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 £30,000 whereas injectable semaglutide has a 7% chance – the highest for all GLP-1s.

**Table HE055: Proportion of ICERs falling under threshold (class)**

| Treatment | ICER <20k | ICER <30k |
| --- | --- | --- |
| DPP4 | 2.25% | 8.25% |
| SGLT-2 | 42.75% | 63.75% |
| GLP-1 | 0% | 2.2% |
| Pioglitazone | 37% | 39% |
| GLP-1 (oral) | 0% | 0% |

**Table HE056: Proportion of ICERs falling under threshold (individual)**

| Treatment | ICER <20k | ICER <30k |
| --- | --- | --- |
| Alogliptin | 7% | 10% |
| Canagliflozin | 33% | 51% |
| Dapagliflozin | 74% | 92% |
| Dulaglutide | 0% | 4% |
| Empagliflozin | 25% | 50% |
| Ertugliflozin | 39% | 62% |
| Exenatide | 0% | 0% |
| Linagliptin | 2% | 18% |
| Liraglutide | 0% | 0% |
| Lixisenatide | 0% | 0% |
| Pioglitazone | 37% | 39% |
| Saxagliptin | 0% | 0% |
| Semaglutide (injection) | 0% | 7% |
| Semaglutide (oral) | 0% | 0% |
| Sitagliptin | 0% | 5% |

# Discussion

## 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. 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.

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 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.

## Strengths and limitations of the analysis

### 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.

### 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).

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.

# 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.

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.

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Appendices

1. 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. 20131 . 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



1. 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.



