National Institute for Health and Care Excellence

Final

Type 1 and 2 diabetes in adults: diagnosis and management

Economic modelling for periodontal treatment in adults with type 1 and type 2 diabetes

NICE guideline NG17, NG28

Economic model report

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Contents

HE1 Introduction

Given the costs and impact on health-related quality of life associated with the long-term complications of type 1 and type 2 diabetes and unstable HbA1c control, the cost-effectiveness of non-surgical periodontal treatment versus 'usual care or no active treatment' was identified by the guideline committee as an area of priority for economic analysis. Usual care or no active treatment is defined as a placebo or supragingival prophylaxis which can include scaling only or/and polish, oral hygiene instruction; education or support sessions to improve self-help or self-awareness of oral hygiene in line with the clinical review.

The review question addressed in this analysis is:

- In adults with type 1 and type 2 diabetes, is it cost-effective to introduce non-surgical periodontal treatment?

The decision problem addressed by this analysis is summarised in Table HE001, with the full protocol for the clinical review available in appendix A of the evidence review for the guideline update.

In the economic literature review, only one cost-utility analysis (CUA) was identified, looking at the cost-effectiveness of periodontal treatment to improve glycaemic control in adults with type 2 diabetes in the UK[1]. The study found that periodontal treatment appeared cost-effective compared with usual care if the improvements in HbA1c can be maintained. However, the analysis was only based on patients with type 2 diabetes, and therefore the committee agreed there was additional value in conducting original modelling to include people with type 1 diabetes.

Table HE001: Health economic decision problem

Population	Adults (aged 18 years and older) with type 1 and type 2 diabetes
Intervention	Non-surgical periodontal treatment
Comparator	Usual care or no active treatment
Outcomes	Costs QALYs

HE2 Methods

HE2.1 Model overview

The previously published IQVIA CORE Diabetes model (CDM) version 9.5, which has been validated against clinical and epidemiological data, was used for the analysis. This was decided due to the need for a model accounting for the long-term complications of diabetes within a lifetime time horizon, as agreed upon by the guideline committee. Given the complexity of modelling diabetes and the timeline constraints associated with this clinical guideline development, the committee agreed this was a more robust approach than attempting to develop a new model framework from scratch.

The CDM is a Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. The model can be run over different time horizons including the lifetime of a patient. The model allows for transition probabilities and management strategies to be differentiated by type of diabetes. Following the modelling structure and input parameters of the CDM, we modelled type 1 and type 2 diabetes separately. Diabetes type specific data were used for baseline characteristics, diabetes progression and complications.

It has been found that treating patients with type 1 and type 2 diabetes for periodontitis has an additional benefit of lowering HbA1c. Therefore, an economic analysis was undertaken to evaluate the cost-effectiveness of non-surgical periodontal treatment.

HE2.1.1 Population(s)

The primary analysis looked at a cohort of adults representing average individuals with type 1 or type 2 diabetes with a diagnosis of periodontitis.

HE2.1.2 Interventions

The analysis simulates non-surgical periodontal treatment, which includes:

- Scaling and root planing (SRP)
- SRP plus antimicrobials
- SRP plus antimicrobial mouth rinse

The committee agreed that combining the effectiveness data of SRP, SRP plus antimicrobials and SRP plus antimicrobial mouth rinse was appropriate, since the clinical review (evidence review X) found no significant difference across different types of treatment. Therefore, the main interest of the analysis is to compare non-surgical periodontal treatment with usual care or no active treatment without differentiating types of periodontal treatment. Usual care or no active treatment is defined as a placebo or supragingival prophylaxis which can include scaling only or/and polish, oral hygiene instruction; education or support sessions to improve self-help or self-awareness of oral hygiene in line with the clinical review.

HE2.1.3 Type of evaluation, time horizon, perspective, discount rate, cycle length

A time horizon of 80 years was used in the base case since this was deemed sufficient to consider lifetime costs and outcomes of all the patients in the model (note that the IQVIA CDM model requires the number of years to be specified to define a time horizon). An 80-year time horizon was chosen to be consistent with the previous modelling using the CDM in diabetes and to be consistent across type 1 and type 2 diabetes. This time horizon was also chosen to ensure that no patients would live past the end of the model, this will mean the long-term benefits of the treatment are captured. Shorter time horizons were tested but given

the small number of patients that would survive longer than a 50-year time horizon it is likely that the difference between 80 years and 50 years would be very small. Costs and quality-adjusted life years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects. The cycle length of the model is one year, there was a couple of reasons for this. Diabetes is a long-term condition with complications that develop over a patient's lifetime therefore a year was deemed as an appropriate cycle length, periodontal treatment is also a longer term treatment that is unlikely to result in a lot of variation of the person's HbA1c. Also, the CDM only has an option of a year as a cycle length and therefore if it was deemed that a shorter cycle length was required then it would not be possible to use the CDM.

HE2.2 Model structure

The IQVIA CDM is a tool used to simulate disease progression in type 1 and type 2 diabetes patients over their lifetime. The model has been previously validated[2] against epidemiological and clinical studies and could account for long-term diabetes related complications across a time horizon extending to the lifetime of the patient. A more detailed description of IQVIA CDM has been published by Palmer et al[3].

The IQVIA CDM can account for a range of interventions aimed at diabetes related complications. These include intensive or conventional insulin therapy, oral hypoglycaemic medications, screening and treatment strategies for microvascular complications, treatment strategy for end stage complications and multifactorial interventions.

Diabetes progression with the IQVIA CDM is simulated using a series of interlinked, inter-dependent sub-models which simulate the following complications:

- angina
- myocardial infarction
- congestive heart failure
- stroke
- peripheral vascular disease
- diabetic retinopathy
- macular oedema
- cataract
- hypoglycaemia
- ketoacidosis
- lactic acidosis
- nephropathy and end-stage renal disease
- neuropathy
- foot ulcer
- amputation
- non-specific mortality

The Markov sub models listed above use time, state, and diabetes type-dependent probabilities from published sources. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables[3].

HE2.3 Parameters

Model input parameters in the IQVIA CDM model are grouped under the following databases:

1. Cohort
2. Economics

- Costs
- Quality of life

3. Treatment
    - Treatment effects of periodontal treatments
    - Treatment algorithm - a sequence of alternative treatments in the event a treatment is discontinued
    - Treatment costs
4. Clinical
5. Other Management

The default model input parameters for type 1 and type 2 diabetes in the IQVIA CDM model were validated with the committee and, if found appropriate, were used. In a scenario where more reliable or recent UK specific sources were identified, these were used instead. Table HE002 to Table HE012 list the input parameters used in our analysis, with details about the sources, calculations and rational for selection listed in the sections below.

Where parameter values other than the IQVIA CDM default values were used, these were identified using the standard methods listed in the NICE guideline manual. These include taking values from established routine national data sources, identifying relevant published studies through citation searching of the studies identified through the cost-effectiveness literature review, targeted literature searches, and through studies identified by committee members.

HE2.3.1 Cohort parameters

HE2.3.1.1 Baseline cohort characteristics

Within the IQVIA CDM model the baseline population needs to be defined in terms of patient's demographics, baseline risk factors, and pre-existing complications. These characteristics were sourced from a range of UK specific type 1 and type 2 diabetes populations (and aimed to be representative of the full population of people with diabetes in the UK). Characteristics not reported in these sources were either set at default IQVIA CDM or kept at 0 due to a lack of data representative of UK population values (this generally applies to proportions of people having suffered a previous event that would likely to be uncommon in the age range of the starting population simulated). The baseline cohort characteristics used alongside their sources are listed in Table HE002.

The REPOSE trial[4], which was used to source a number of the baseline characteristics listed below, is a cluster randomised trial of 267 adults with type 1 diabetes in the UK who were recruited from November 2011 to December 2012 and reported detailed baseline data for a range of the characteristics needed to populate the model. The inclusion criteria included requiring participants to be aged 18 or over and have had type 1 diabetes for at least 12 months at the time of undertaking a DAFNE course. Hence the baseline population of the trial was judged similar to that of our review question. This study was identified through a targeted search of HTA reports on type 1 diabetes, undertaken due to the fact that HTA reports tend to give more detail on baseline characteristics than are present in a standard journal article.

A number of baseline characteristics listed below for people with type 2 diabetes were sourced from the dataset from the Health Improvement Network (THIN) that included 3.7 million people from 427 UK GP practices[5]. About 131,000 people with type 2 diabetes were selected from the THIN dataset using READ codes, and the baseline characteristics were drawn from people at the time of their first insulin therapy.

We have used these baseline characteristics to simulate a cohort of 1,000 patients using the IQVIA CDM. Note that for characteristics where the standard deviation was kept at 0, the

mean values were kept static when patient cohort was simulated. The simulated patient cohort also does not take into account correlations between risk factors.

Table HE002: Baseline cohort characteristics

Baseline characteristic	Mean	SD	Source/ Comments
Patient demographics			
Age (years)	46.43 (T1) 65.41(T2)	12.13 (T1) 13.67 (T2)	National Diabetes Audit 2019-20[6] Type 1 and 2 Diabetes Report: age and duration of diabetes were calculated by obtaining weighted averages since they were reported for categories of patients, rather than as a single mean age.
Duration of Diabetes (years)	21 (T1) 9 (T2)	13.48 (T1) 5.57 (T2)	
Prop. Male	0.569 (T1) 0.559 (T2)	n/a (T1) n/a (T2)	
Baseline risk factors			
HbA1c (%)	9.1 (T1)	1.7 (T1)	REPOSE[4] – a cluster randomised trial of 267 adults with type 1 diabetes in the UK recruited from November 2011 to December 2012. Conversion to mmol/mol: mean 75.96mmol/mol.
	7.6 (T2)	1.5 (T2)	Baseline HbA1c (%) values as one of the current risk factors for people with second intensification taken from Table 20 of NICE guideline NG28; originally sourced from THIN data[5]. Conversion to mmol/mol: mean 59.57mmol/mol.
Systolic blood pressure (mmHg)	131.3 (T1)	16.3 (T1)	REPOSE[4]
	133.1 (T2)	15.7 (T2)	THIN data[5]: blood pressure (mmHg) values for patients with first insulin therapy
Diastolic blood pressure (mmHg)	80 (T1, T2)	0 (T1, T2)	IQVIA CDM default value[7]
Total Cholesterol (mg/dL)	90 (T1)	16.2 (T1)	REPOSE[4]; Conversion to mmol/l: mean 2.33mmol/l; SD 0.42mmol/l.
	168.34 (T2)	38.22 (T2)	Baseline total cholesterol values (mean 4.36mmol/l; SD 0.99mmol/l) as one of the current risk factors for people with second intensification taken from Table 20 of NICE guideline NG28; originally sourced from THIN data[5]; converted to mg/dL.
High density cholesterol (mg/dL)	28.8 (T1)	7.2 (T1)	REPOSE[4]; Conversion to mmol/l: mean 0.74mmol/l; SD 0.19mmol/l.
	44.85 (T2)	12.56 (T2)	THIN data[5]: HDL values (mean: 1.16mmol/l; SD: 0.33mmol/l) for patients with first insulin therapy; converted to mg/dL.
Low density cholesterol (mg/dL)	50.4 (T1)	16.2 (T1)	REPOSE[4]; Conversion to mmol/l: mean 1.30mmol/l; SD 0.42mmol/l.
	91.00 (T2)	36.21 (T2)	THIN data[5]: LDL values (mean: 2.36mmol/l; SD: 0.94mmol/l) for patients with first insulin therapy; converted to mg/dL.
Triglyceride (mg/dL)	25.2 (T1)	18 (T1)	REPOSE[4]; Conversion to mmol/l: mean 0.28mmol/l; SD 0.20mmol/l.

Baseline characteristic	Mean	SD	Source/ Comments
	147.00 (T2)	0 (T2)	IQVIA CDM default value[7]; Conversion to mmol/l: mean 1.66mmol/l
Body mass index (kg/m^2)	27.2 (T1)	5 (T1)	REPOSE[4]
	31.24 (T2)	0.2 (T2)	THIN data[5]: calculated from weight (kg) and height (m) values for patients with first insulin therapy
estimated glomerular filtration rate (ml/min/1.72m^2)	78.58 (T1)	13.24 (T1)	REPOSE[4] - calculated by obtaining weighted averages since they were reported for categories of patients
	68.20 (T2)	21.6 (T2)	THIN data[5]: eGFR values for patients with first insulin therapy
Haemoglobin (gr/dl)	14.5 (T1, T2)	0 (T1, T2)	IQVIA CDM default value[8]
White blood cell count (10^6/ml)	6.8 (T1)	0 (T1)	IQVIA CDM default value[8]
	7.9 (T2)	2.1 (T2)	THIN data[5]: White blood cell count for patients with first insulin therapy
Heart rate (bpm)	72 (T1, T2)	0 (T1, T2)	IQVIA CDM default value[8]
Waist to hip ratio	0.93 (T1)	0 (T1)	IQVIA CDM default value[8]
	0.96 (T2)	0.08 (T2)	Health Survey for England 2017 & 2018[9] – calculated from the subset of individuals with type 2 diabetes
Waist circumference	87.84 (T1)	n/a (T1)	IQVIA CDM default value[8]
	107.02 (T2)	n/a (T2)	Health Survey for England 2017 & 2018[9] – calculated from the subset of individuals with type 2 diabetes
Urinary Albumin creatinine ratio (mg/mmol)	4.78 (T1)	10.19 (T1)	REPOSE[4] - calculated by obtaining weighted averages since they were reported for categories of patients
	3.10 (T2)	0 (T2)	IQVIA CDM default value[10]
Serum Creatinine (mg/dL)	1.10 (T1, T2)	0 (T1, T2)	IQVIA CDM default value[10]; Conversion to µmol/L: mean 97.24 µmol/l.
Serum Albumin (g/dl)	3.90 (T1, T2)	0 (T1, T2)	IQVIA CDM default value[10]; Conversion to g/l: mean 39g/l.
Prop. Smoker	0.192 (T1)	n/a (T1)	REPOSE[6]
	0.131 (T2)	n/a (T2)	National Diabetes Audit 2019-20[6] – calculated from the subset of individuals with type 2 diabetes
Cigarettes/ day	15 (T1, T2)	0 (T1, T2)	Health Survey for England 2017 & 2018[9] – calculated from the subset of individuals with type 2 diabetes
Alcohol consumption (Oz/week)	7.70 (T1, T2)	0 (T1, T2)	WHO status report on alcohol 2018[11] (converted from l/year to oz/week)
Prop. Physical activity	0.620 (T1)	0 (T1)	Health Survey for England 2017 & 2018[9] – calculated from the subset of individuals with type 1 diabetes
	0.612 (T2)	0 (T2)	Health Survey for England 2017 & 2018[9] – calculated from the subset of individuals with type 2 diabetes
Fasting glucose	180.72 (T1, T2)	0 (T1, T2)	IQVIA CDM default value

Baseline characteristic	Mean	SD	Source/ Comments
Prop. Family history stroke	0.044 (T1, T2)	0 (T1, T2)	IQVIA CDM default value
Prop. Family history CHD	0.147 (T1, T2)	0 (T1, T2)	IQVIA CDM default value
Prop. China Northern region	n/a (T1, T2)	n/a (T1, T2)	n/a
Prop. China rural area	n/a (T1, T2)	n/a (T1, T2)	n/a
Racial characteristics			
Prop. White/ other	0.942 (T1) 0.824 (T2)	n/a	National Diabetes Audit 2019-20[6] Type 1 Diabetes Report
Prop. Black	0.023 (T1) 0.045 (T2)	n/a	
Prop. Asian/ Pacific islander	0.035 (T1) 0.131 (T2)	n/a	
Baseline CVD complications			
Prop. MI	0.022 (T1)	0 (T1)	REPOSE[4]
	0.036 (T2)	0 (T2)	THIN data[5]: proportion of patients with first insulin therapy prior to time point when myocardial infarction occurred
Prop. Angina	0.012 (T1)	0 (T1)	REPOSE[4]
	0 (T2)	0 (T2)	IQVIA CDM default value[12]
Prop. Peripheral vascular disease	0 (T1, T2)	0 (T1, T2)	Assumption
Prop. Stroke	0.003 (T1)	0 (T1)	REPOSE[4]
	0.017 (T2)	0 (T2)	THIN data[5]: proportion of patients with first insulin therapy prior to time point when stoke occurred
Prop. Heart failure	0.006 (T1)	0 (T1)	REPOSE[4]
	0.030 (T2)	0 (T2)	THIN data[5]: proportion of patients with first insulin therapy prior to time point when congestive heart failure occurred
Prop. Atrial Fibrillation	0 (T1, T2)	0 (T1, T2)	Assumption
Prop. Left venitucular hypertrophy	0 (T1, T2)	0 (T1, T2)	Assumption
Baseline renal complications			
Prop. Microalbuminuria (MA)	0.12 (T1)	0 (T1)	REPOSE[4]
	0.313 (T2)	0 (T2)	IQVIA CDM default value[7]
Prop. Gross proternuria (GPR)	0.045 (T1)	0 (T1)	REPOSE[4]
	0.077 (T2)	0 (T2)	IQVIA CDM default value[7]
Prop. End stage renal disease (ESRD)	0 (T1, T2)	0 (T1, T2)	Assumption
Baseline retinopathy complications			
Prop. Background retinopathy (BDR)	0.348 (T1)	0 (T1)	REPOSE[4]
	0.331 (T2)	0 (T2)	IQVIA CDM default value[13]
Prop. Proliferative diabetic retinopathy (PDR)	0.093 (T1)	0 (T1)	REPOSE[4]
	0.071 (T2)	0 (T2)	IQVIA CDM default value[14]
Prop. Severe vision loss (SVL)	0 (T1, T2)	0 (T1, T2)	Assumption
Baseline macular edema			
Prop. Macular Edema	0 (T1, T2)	n/a (T1, T2)	Assumption

Baseline characteristic	Mean	SD	Source/ Comments
Baseline cataract			
Prop. Cataract	0 (T1, T2)	n/a (T1, T2)	Assumption
Baseline foot ulcer complications			
Prop. History of ulcer	0 (T1, T2)	n/a (T1, T2)	Assumption
Prop. History of amputation	0 (T1, T2)	n/a (T1, T2)	Assumption
Baseline neuropathy			
Prop. Neuropathy	0.071 (T1)	n/a (T1)	REPOSE[4]
	0.430 (T2)	n/a (T2)	IQVIA CDM default value[15]

HE2.3.1.2 Mortality

The IQVIA CDM offers four options to account for mortality within the model. These include the non-combined mortality approach where event and health state specific mortality are used to estimate fatal events (there is a lack of clarity about how non-event specific mortality is accounted for in this option), 2 UK specific approaches; the UKPDS 68 and UKPDS 82 approaches, and the Western Australia mortality approach where the data was sourced from an Australian population. Given that the UKPDS 68 and UKPDS 82 approaches were from UK specific populations, these were considered in more detail.

The UKPDS 68 approach uses 2 separate equations to predict the 1st and subsequent year mortality risks for diabetes related complications using information from the UKPDS population. This approach requires non-specific mortality risks stratified by ethnicity, gender, and age to be uploaded manually. However, given the unavailability of disease specific mortality (which is required to calculate non-specific mortality) by these stratifications for the relevant population in the UK, this approach was not used.

The UKPDS 82 approach uses four separate equations to estimate the incidence of death following “no history and no event”, “no history and event”, “history and no event”, and “history and event”. With it being clear that the excess mortality in the UKPDS 82 approach is reflective of a UK type 2 diabetes population due to it being sourced from the UKPDS, the UKPDS 82 approach was used. For type 1 diabetes, the committee agreed there was no robust evidence to suggest that event specific and non-event specific mortality differed from type 2 diabetes (e.g. the mortality associated with having a stroke would be expected to be similar, regardless of whether the person has type 1 or type 2 diabetes, assuming their other characteristics are similar).

HE2.3.2 Economics

HE2.3.2.1 Cost

Default values for costs of chronic and recurrent conditions, and complication costs in the IQVIA CDM model were updated to reflect those of contemporary clinical practice in the UK. Costs for medicines were taken from the NHS Drug Tariff[16], whilst costs associated with complications were sourced from other relevant NICE guidelines if available, or otherwise from either published papers or based on committee knowledge. No indirect costs were included in the analysis with these parameters set to 0 in the IQVIA CDM, as the indirect costs that can be included in the IQVIA CDM fall outside the NICE reference case.

The values used for resource use and costs are listed in Table HE003 with their relevant sources. All costs from earlier than 2020/21 were inflated to 2020/21 values using the Unit Costs of Health and Social Care 2021 by personal social services research unit (PSSRU 2021)[17]. For the probabilistic analysis values were altered within a range of plus/minus 10%. Note that IQVIA CDM only allows for a single measure of variability across all cost parameters.

Table HE003: Management and complication costs

Input variables	Mean cost per year*	Source/ Comments
Management costs		
Statins	£27.38	Atorvastatin 80 mg tablets x 28 days (unit price: £2.10) - NHS Electronic Drug Tariff June 2021[16]
Aspirin	£16.43	Aspirin 75 mg tablets x 28 days (unit price: £1.26) - NHS Drug Electronic Tariff June 2021[16]
ACE-I/ARB	£22.84	Weighted (by use as reported by Prescription Cost Analysis data March 2021[18]) average costs of: ACE-I/ARB (Source: NHS Electronic Drug Tariff June 2021[16]) Enalapril (10mg x 28; Unit price: £7.04) Lisinopril (10mg tablets x 28; Unit price: £1.08) Perindopril arginine (10mg tablets x 30; Unit price: £10.65) Ramipril (10mg tablets x 30; Unit price: £1.42) Candesartan (8mg tablets x 28; Unit price: £1.54) Eprosartan (600mg tablets x 28; Unit price: £18.16) Losartan (50mg tablets x 28; Unit price: £1.45) Telmisartan (40mg tablets x 28; Unit price: £2.69)
Screening for micro-albuminuria	£4.31	Cost of ACR/PCR testing from Kerr et al (2012)[19] who sourced patient numbers from Quality and Outcomes Framework (QOF) for General Practice and costs from PSSRU[17]
Screening for gross proteinuria	£4.31	
Stopping ACE-I/ARB due to AEs	£39.23	Assumed as the cost of a GP visit as sourced from unit costs of health and social care 2020[20]
Eye Screening	£60.36	Local estimate provided via an ophthalmologist involved in the guideline on the 25th of January 2021 (no published data were available for this parameter).
Annual cost of CVD complications		
MI 1st year	£4,142	NICE Cardiovascular disease risk guideline, CG181 The guideline calculates costs for management of CVD complications during the first 6 months for event states and 1-year post-event states. Costs calculated by using information from NHS Drug Tariff[16], procedure costs from NHS Reference costs, PSSRU Unit Costs of Health & Social Care[20] and the British National Formulary. Assumptions made: 1st year costs were assumed to be cost of first 6 months in event state plus half of 1-year post event state costs. 2nd year costs were assumed to be 1-year post-event state costs. Cost of stroke death within 30 days was assumed to be the cost of a cardiovascular death as reported in CG181. Assumed that one third of angina episodes are stable, and two thirds unstable, based on expert opinion in NG17. This assumption was validated by the committee, with no objections raised. Peripheral arterial disease (PAD) costs from CG181 assumed to be the same as PVD costs.
MI 2nd+ years	£875	
Angina 1st year	£7,112	
Angina 2nd+ years	£320	
CHF 1st year	£3,992	
CHF 2nd+ years	£2,883	
Stroke 1st year	£4,629	
Stroke 2nd+ years	£172	
stroke death within 30 days	£1,303	
PVD 1st year	£1,351	
PVD 2nd+ years	£587	
Renal Complications		

Input variables	Mean cost per year*	Source/ Comments
Haemodialysis 1st year	£34,778	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Haemodialysis 2nd + years	£34,778	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Peritoneal dialysis	£30,209	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Peritoneal dialysis 2nd + years	£30,209	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Renal transplant (1st year)	£22,300	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Renal transplant (2nd year)	£8,467	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Acute events		
Non-severe hypoglycaemic events	0	Information from Geelhoed et al[21] 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	£376	Based on information from Hammer et al[22] who reported results from 101 T1D 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 HCP) 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 al[23] 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 et al[22]. Although these costs were derived from a population of people with T1D, the committee agreed there was unlikely to be a significant difference in the cost of managing a hypoglycaemic event between people with T1D and T2D. **Note:** The IQVIA CDM offers inputs for a second class of severe hypoglycaemic events to account for severe hypoglycaemic events which required medical assistance (if it is decided to keep these separate from events not requiring medical assistance). However, as we have decided to keep severe hypoglycaemic events which required

Input variables	Mean cost per year*	Source/ Comments
		medical assistance and did not require medical assistance in the same category to match the way the cost data were reported, this was kept at 0.
Cost of eye disease		
Laser treatment	£147	NHS Reference Costs 2018/19[24] Currency code BZ86B - Non-surgical ophthalmology with interventions.
Cataract operation	£942	NHS Reference Costs 2018/19[24] Currency codes: BZ84A/BZ84B/BZ84C (Phacoemulsification Cataract Extraction and Lens Implant - CC Score 4+, 2-3, 0-1)
Following cataract operation	£206	NHS Reference Costs 2018/19[24] Currency code: WF01A (Non-admitted face to face attendance, ophthalmology follow-up)
Blindness - year of onset	£7,693	NICE Glaucoma guideline, NG81 Cost calculated by calculating costs of blind registration, low vision rehabilitation, community care, and residential care. These costs are then multiplied by the proportion of patients experiencing blindness who use these services. .
Blindness - following years	£7,432	
Cost of neuropathy/ foot-ulcer/ amputation		
Neuropathy 1st year	£37.10	Duloxetine (Zentiva) 60mg x 28 days priced at £2.77 (source: NHS Electronic Drug Tariff[16])
Neuropathy 2nd year onwards	£37.10	
Active ulcer	£3,577	Kerr et al (2019)[25] - The cost of diabetic foot ulcers and amputations to the NHS in England. HES data (2014-15) used to calculate relevant inpatient activity, with costs of these activities calculated using reference costs.
Amputation event	£8,577	NICE Diabetic foot problems guideline, NG19 Amputation costs sourced from NHS reference costs. Amputation event costs calculated by combining amputations with and without major complications by using reported information on the probability an amputation is major.
Post amputation	£26,093	NICE Peripheral arterial disease guideline, CG147 Reported as the annual cost of care in subsequent years. Costs included: care home costs (£986/ week), community care costs (£296/ week), and wheelchair costs.

**Older costs have been inflated to current prices*

HE2.3.2.2 Quality of life parameters

Quality of life parameters were set at default IQVIA CDM parameters values (Table HE004).

Sources for impact of quality of life by severe and non-severe hypoglycaemic events were identified by looking at primary sources for quality-of-life parameters from our systematic review of economic evidence. The most commonly used sources in the literature were studies by Currie et al[26] and Evans et al[27].

Currie et al[26] sourced information from two surveys conducted in 2000 and 2004 among 1,305 respondents with diabetes. Impact on quality of life was measured using the EQ-5D instrument with the fear of hypoglycaemia measured using the Hypoglycaemia Fear Survey

(HFS). Results were based on a multivariate analysis with pooled data used to explore the relationship between frequency of hypoglycaemic events and fear of hypoglycaemia (HFS values). Then the HFS values in conjunction with other independent variables was used to predict the EQ-5D values. Currie et al[26] reported results for severe, symptomatic, and nocturnal hypoglycaemic events with symptomatic events defined as mild or moderate event that did not require external assistance. However, the impact of QoL by nocturnal events were not reported by severity. Therefore, results from this study were not considered to fulfil all the desirable criteria for this analysis.

Evans et al[27] performed a web-based 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. 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 QoL 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. The IQVIA CDM allows to account 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) and for this information from Lauridson et al[28] was used as it was based on the same data set as Evans et al[27].

No quality of life benefit or decrement due to change in oral health was included in this analysis. This is due to a number of reasons including the benefit of periodontal treatment to oral health does not last long enough to be incorporated in the one-year cycle of our model. Additionally, the EQ-5D, the preferred measure of the National Institute of Health and Care Excellence (NICE), is not sensitive enough to capture a benefit of improved oral health, while there is no reliable mapping algorithms to translate a disease specific measure (e.g. Oral Health Impact Profile) to the EQ-5D. This is a conservative approach and would likely favour usual care, if periodontal treatment is cost-effective then it is likely that periodontal treatment would be more cost-effective than calculated.

Table HE004: Quality of life values

Input variables	Mean utility	se	Source/ Comment
No complications	0.839 (T1)	0.0048 (T1)	Default value in IQVIA CDM which was sourced from Peasgood et al.[29]
	0.785 (T2)	0.007 (T2)	Default value in IQVIA CDM which was sourced from Beaudet et al[30]
Disutility of MI event	-0.055(T1, T2)	0.005(T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Clarke et al[31]. QoL post MI was assumed to be baseline utility minus disutility of MI from Beaudet et al[30]. A similar calculation was done to obtain QoL post stroke and post amputation.
Utility post MI	0.078 (T1) 0.73 (T2)	0.007 (T1) 0.009 (T2)	
Utility CHF	0.6770 (T1, T2)	0.01 (T1, T2)	
Disutility of Stroke event	-0.164 (T1, T2)	0.008 (T1, T2)	
Utility post Stroke event	0.675 (T1) 0.621 (T2)	0.009 (T1) 0.011 (T2)	
Disutility amputation event	-0.280 (T1, T2)	0.011 (T1, T2)	
Utility post amputation	0.559 (T1) 0.505 (T2)	0.012 (T1) 0.013 (T2)	

Input variables	Mean utility	se	Source/ Comment
Utility PVD	0.7240 (T1, T2)	0.008 (T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Bagust et al[32]
Utility gross proteinuria	0.7370 (T1, T2)	0.008 (T1, T2)	
Utility neuropathy	0.7010 (T1, T2)	0.008 (T1, T2)	
Disutility of ulcer	-0.1700 (T1, T2)	0.0189 (T1, T2)	
Utility haemodialysis	0.6210 (T1, T2)	0.029 (T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Wasserfallen et al[33]
Utility peritoneal dialysis	0.5810 (T1, T2)	0.03 (T1, T2)	
Utility background diabetic retinopathy (BDR)	0.7450 (T1, T2)	0.021 (T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Fenwick et al[34]
Utility BDR wrongly treated	0.7450 (T1, T2)	0.022 (T1, T2)	
Utility macular edema	0.7450 (T1, T2)	0.021 (T1, T2)	
Utility renal transplant	0.7620 (T1, T2)	0.118 (T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Kiberd et al[35]
Utility cataract	0.7690 (T1, T2)	0.016 (T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Lee et al[36]
Utility proliferative diabetic retinopathy (PDR) laser treatment	0.7150 (T1, T2)	0.022 (T1, T2)	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30].
Utility PDR no laser	0.7150 (T1, T2)	0.022 (T1, T2)	
Utility angina	0.6950 (T1, T2)	0.01 (T1, T2)	
Utility microalbuminuria	0.7850 (T1, T2)	0.007 (T1, T2)	
Disutility NSHE daytime	-0.005 (T1, T2)	0.00077 (T1, T2)	UK patients from a TTO survey in five countries (UK, USA, Canada, Germany & Sweden) from Evans et al[27].This study was based hypothetical health states, with the description of health states to all respondents (T1D, T2D and non-diabetic) being the same (meaning even people with T2D were not asked to report on how bad their own events are, but how bad it would be to suffer the hypothetical event described). It should be noted that this approach leads to larger estimates of QoL loss than when people are asked to rate their own events (mainly due to adaptation effects – people tend to get used to the events they suffer and so how
Disutility NSHE nocturnal	-0.008 (T1, T2)	0.00102 (T1, T2)	
Disutility SHE daytime	-0.062 (T1, T2)	0.00433 (T1, T2)	
Disutility SHE nocturnal	-0.066 (T1, T2)	0.00485 (T1, T2)	

Input variables	Mean utility	se	Source/ Comment
			bad they feel they are can reduce over time, even if the events themselves are just as bad). The descriptions of these health states were derived from a survey of 247 UK patients with diabetes. Hence given that all respondents answered the TTO survey based on the described hypothetical health states, no differences should be assumed between categories of patients. A more important distinction to make is that of results between specific countries, given the differences in the perception of a full health states between countries. Hence given that this analysis is done for a UK population, the UK specific value set was used. Note that the lower CI for NSHE nocturnal was reported as 0.06 which was assumed to be an error, and 0.006 was used when calculating the standard error
Disutility for 1 unit increase in BMI above 25 kg/m^2	-0.0061 (T1, T2)	n/a	Default value in IQVIA CDM - sourced from Bagust et al[32]

HE2.3.3 Treatments

HE2.3.3.1 Treatment effects of periodontal treatments

Treatment effects for the outcomes listed below were based on the clinical evidence review as informed by an updated Cochrane review for this topic (see evidence review X).

Reduction in HbA1c levels

The reduction in HbA1c levels, calculated as the mean change from baseline are listed in Table HE005. For type 1 diabetes, the mean change for usual care was taken from the economic modelling undertaken for comparing different insulin therapies, using the numbers estimated for detemir twice daily insulin, as that was the primary treatment recommended in the guideline. Some of the studies included participants using continuous subcutaneous insulin infusion, but the committee agreed it was appropriate to model a population of people starting with multiple daily insulin injections, since this is how most people with type 1 diabetes start treatment, and therefore represents the point at which the initial decision on whether to offer periodontal treatments needs to be made. For type 2 diabetes, the mean change for usual care was taken from the economic modelling undertaken for pharmacological management of type 2 diabetes, using the numbers estimated for Metformin-NPH insulin, as this was agreed to be reasonably reflective of people at the time of their first insulin injection.

The estimated differences between usual care and periodontal treatment (evidence review X) were then applied to this baseline value for usual care to estimate changes in HbA1c after periodontal treatments. We took an average across four treatment comparison subgroups, as there was no significant difference across them based on the clinical review. The studies also reported outcomes using different follow-up periods: 3 months, 6 months and 12 months. There was only one 12-month study that showed a larger reduction in HbA1c compared with 3-month and 6-month studies. As the CDM defines a one-year cycle length, the committee felt that instead of using the 12-month estimate, it is more appropriate to take an average of all studies since it would give us a more conservative estimate. If periodontal treatment is to come out cost-effective, there would be more confidence with the result. In addition, the

same difference between usual care and periodontal treatment was used for type 1 and type 2 diabetes, as the clinical review only identified one study that included type 1 diabetes which was a mix of type 1 and type 2 patients. Given the limited type 1 evidence, the committee agreed to combine both types of diabetes together to obtain an overall estimate of treatment effect.

The mean changes, shown in Table HE005, are the values that are entered into the CDM. These values take into account the compliance and response rates of patients to periodontal treatments from Solowiej-Wedderburn et al[1]. The committee noted that not all patients could attend appointments regularly for maintenance following the initial periodontal treatment, especially among people with diabetes. Following Solowiej-Wedderburn et al[1], we assumed that only patients who complied and responded to treatment would achieve the HbA1c benefit, with a 30% compliance rate and 87% response rate. Therefore, in the base case, about 26.1% of patients benefit from periodontal treatment and improve diabetic control.

Although there was no evidence of the treatment effect after 12 months, the committee agreed that the one-year benefit in HbA1c is very likely to maintain over time due to patients receiving maintenance and re-treatment when necessary. In the sensitivity analysis, we also tested a scenario when the improvement of HbA1c waning over time and the difference between periodontal treatment arm and usual arm would disappear.

Table HE005: Reduction in HbA1c levels

Treatments	Change in HbA1c	Se	Source
Periodontal treatments (T1)	-0.566	0.017	Clinical review
Usual care (T1)	-0.454	0.117	REPOSE[4]
Periodontal treatments (T2)	-0.647	0.017	Clinical review
Usual care (T2)	-0.535	0.117	NG28

Hypoglycaemic events

There was no clinical evidence of periodontal treatment effecting the patient's HbA1c. The committee felt that periodontal treatment would not affect the number of hypoglycaemic events, and therefore, the number of events were set as zero in the CDM. This is due to periodontal treatment being a long-term treatment that does not cause rapid changes in HbA1c.

HE2.3.3.2 Treatment algorithm

The IQVIA CDM allows to define a treatment algorithm for each intervention in the event of treatment failure. However, since the failure of periodontal treatment is not defined by diabetes-related outcomes, we did not consider treatment failure in the treatment algorithm but incorporated rates of compliance and response to the treatment in the in the HbA1c change.

HE2.3.3.3 Treatment costs

The reimbursement of dental treatment within England is currently based on a treatment banding system. Dental practices receive reimbursement based on contracted units of dental activity (UDAs) associated with each treatment band. Solowiej-Wedderburn et al[1] highlighted that the reimbursement based on UDAs may not fully reflect the actual cost to the dental practice. Our base case analysis follows the method used by Solowiej-Wedderburn et al[1] in which treatment costs were calculated as the duration of time multiplied by the unit cost,

depending on the level of staff who carry out the treatment. We tested the UDA approach in the sensitivity analyses (see Section HE3.2).

Since the cost analysis is based on an NHS & PSS perspective, we only consider costs incurred by the health care sector and public sectors and deduct patient co-payments from the total cost of the treatment. Patient co-payments vary by treatment band and were calculated as the cost of treatment paid by paying patients multiplied by the proportion of patients who need to pay, sourced from NHS digital 2021 dentist statistics[37]. The average amount of patient co-payments by treatment band is presented in Table HE006, using the patient costs from PSSRU[17] multiplied by the proportion of paying adults sourced from NHS digital[37]. The reason the dentist co-payments were deducted when in other cost-effectiveness analyses prescription charges are not deducted was due to the co-payment varying by treatment whereas the prescription charge does not vary by treatment and is the same regardless of the treatment.

Table HE006: Patient co-payment

Treatment band	Cost to patients	Proportion of paying adults	Average co-pay
1	£23.80	82%	£19.63
2	£65.20	72%	£48.32
3	£282.80	53%	£148.57

Non-surgical treatment costs

We calculated the cost for non-surgical periodontal treatment using the assumptions presented in Table HE007 , following Solowiej-Wedderburn et al[1]. In the base case, it was assumed that periodontal treatment would be delivered in two 60-minute sessions by a primary practice dentist. This would be followed by a 30-minute appointment with the hygienist (equivalent to a band 5 nurse) every 3 months and a 60-minute retreatment conducted by a primary practice dentist every 3 years. According to Solowiej-Wedderburn et al[1], the initial periodontal treatment was conducted by an experienced periodontal expert with a unit cost of the dentist providing performer (practice partner) as reported in the PSSRU[17]. However, the committee advised that within the NHS, it is more likely for a less experienced periodontist to deliver care, and therefore in our analysis we used the unit cost of an NHS dentist performer from the PSSRU[20]. This assumption was later tested in the sensitivity analysis. The rest of our analysis followed the resource use assumptions made by Solowiej-Wedderburn et al[1].

Table HE007: non-surgical periodontal treatment resource use

Treatment phase	Resource provider	Duration (minutes)	Frequency
Initial periodontal treatment	NHS dentist performer	120	Once
Maintenance	Hygienist	30	Every three months
Re-treatment	NHS dentist performer	60	Every three years

Unit costs for each hour of patient contact are presented in Table HE008. Since dental costs were not updated in the latest version of PSSRU[17], we took the 2019/20 cost figures from PSSRU[20] and inflated it to 2021. According to the committee, the 2019/20 figures are considered as more appropriate here since dentists are not part of the agenda for change in pay scale and are unlikely to receive the same pay rise as nurses.

Table HE008: Cost and resource use non-surgical periodontal treatment

Resource	Cost per hour of patient contact	Source
Dentist providing performer	£200	PSSRU[17]
Dentist performer only	£135	PSSRU[17]
Hygienist	£64	PSSRU[17]

In addition to periodontal treatments, patients also require treatments for tooth loss repair. The resource use and distribution of treatment type are based on the assumptions used in Solowiej-Wedderburn et al[1], which gives a weighted average cost of £118.17 for treating tooth loss after deducting patient co-payments (Table HE009).

Table HE009: Tooth loss replacement

Procedure	Duration (minutes)	Labour cost	Laboratory cost	Total cost	Treatment band	Distribution
Extraction only	20	£45	£0	£45	2	15%
Resin-bonded bridge	80	£180	£75	£255	3	45%
Removable partial denture	100	£225	£100	£325	3	40%

The tooth loss rate depends on whether patients comply with maintenance therapy and carry out the required oral hygiene practices to promote treatment benefits. Following Solowiej-Wedderburn et al[1], compliant patients were assumed to suffer from tooth loss at an annual rate of 0.036, while non-compliant patients were assumed to require tooth loss repair at an annual rate of 0.19.

The annual costs of treatments used in the base case are presented in Table HE010. They were entered separately for year 1 and years two onwards as required by the CDM.

Table HE010: Cost of treatment base case

Treatment category	Cost year 1	Cost year 2 onwards
Initial treatment	£221.99	
Maintenance treatment	£23.53	£14.86
Retreatment	£0.00	£8.68
Tooth loss repair	£16.99	£16.99
Total	**£262.51**	**£40.54**

Usual care treatment costs

Patients receiving usual care are assumed to only receive treatment for tooth loss repair as part of routine treatment. Treatment in the usual care arm was assumed to be £22.45 per year based on the higher rate of tooth loss.

HE2.3.4 Clinical

The clinical module with the IQVIA CDM contains data that describes the natural history of diseases. Default parameters for both type 1 and type 2 diabetes were used in this module. The clinical parameters and the clinical progression parameters (transitional probabilities) used in the default version are explained in more detail in the IQVIA CDM manual.

Whilst default parameters in the clinical module were used, decision relating to the clinical module were required to be made across other modules. Decisions to be made in the treatment module included choosing the progression equations for HbA1c, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL, HDL, triglycerides, BMI, eGFR and waste to hip ratio in the treatment module (in our analysis the clinical database option which was the only to source information from a type 1 diabetes population was used), and risk adjustments for statins and ACE-I/ARB were used (selected option "yes").

HE2.3.5 Other management

Table HE011 lists the input parameters used for proportions of patients who were managed for various chronic and recurrent conditions.

Table HE011: Other management parameters (T1, T2)

Input parameter	Mean	Source/ comments
Concomitant medications		
Proportion on aspirin for primary prevention	0.59	Sourced from EUROASPIRE II Study group and Kotseva et al[38,39]
Proportion on statins for primary prevention	0.474	
Proportion on ACE-inhibitors for primary prevention	0.213	
Proportion on aspirin for secondary prevention	0.887	Sourced from Kotseva et al[38,39]
Proportion on statins for secondary prevention	0.841	
Proportion on ACE-inhibitors for secondary prevention	0.755	
Screening and patient management proportions		
Proportion screened for eye disease	1.00	No UK data, assumed to be standard management, in line with the UK diabetes eye screening programme
Proportion screened for renal disease	1.00	Assumed as recommended by NICE CG66, and should reflect current practice
Proportion receiving intensive insulin after MI	1.00	Sourced from Bydureon NICE TA submission
Others		
Sensitivity of eye screening	80%	Sourced from Lopes-Bastida[40]
Specificity of eye screening	97%	
Sensitivity of gross proteinuria screening	85%	
Sensitivity of micro albuminuria screening	75%	Sourced from Cortes-Sanabria[41]
Specificity of micro albuminuria screening	97%	

HE2.4 Sensitivity analyses

No evidence was identified from the clinical review suggesting differences in treatment effectiveness in different patient subgroups (for example by ethnicity or age) and therefore no sensitivity analyses were conducted looking at these subpopulations.

HE2.4.1 Deterministic sensitivity analyses

A number of deterministic sensitivity analyses were performed to test for the robustness of our base case results. These include:

1. **Severe periodontitis:**
   In the base case, we only considered patients with mild periodontitiss, while according to Kassebaum et al[42], about 11.2% of the periodontal patients were severe cases. The proportion might be even higher among people with diabetes. In this scenario, we assumed that people with severe periodontitis are likely to incur a higher health care cost. After discussion with the committee, we agreed that the initial treatment for severe patients would take 5 hours (3 more hours compared to the base case assumption), and an additional 2 hours of retreatment would be required in the first year. In addition, the maintenance treatment would be delivered by a dentist rather than a hygienist. Notice here, due to a lack of clinical effectiveness data on severe cases, we only considered an increase in treatment cost while assuming the same treatment benefit as the base case.

2. **UDA costing approach:**
   As explained above, UDA is the current reimbursement system for NHS dentists. Both initial periodontal treatment and retreatment are considered as band 2 and receive 3 UDAs, which costs approximately £75[1]. The maintenance treatment was considered as band 1 and receive 1 UDA, costing approximately £25. Therefore, the annual costs of periodontal treatment were £55.97 for year 1 and £28.20 for year 2 onwards, and the cost of usual care was estimated to be £25.22.

3. **Dentist providing performer:**
   In this scenario, we assume that a more experienced dentist would provide the initial periodontal treatment, following Solowiej-Wedderburn et al[1]. This increased the first-year cost to £380.50.

4. **Time horizons: 50, 25, 10 and 5 years**
   In this scenario, we reduced the time horizon down from 80 years in the base case to 50, 25, 10 and 5 years.

5. **No patient co-payment**
   As suggested by the committee, we assumed no patient co-payment for periodontal treatment in this scenario to see whether the treatment remains cost-effective if the NHS covers 100% of the costs.

6. **Compliance rate down to 11%**
   We reduced the proportion of patients who comply to the treatment down to 11%. The value was chosen as it was the minimum value for compliance in Solowiej-Wedderburn et al[1].

7. **Response down to 50%**
   We reduced the proportion of patients who respond to the treatment down to 50%. The value was chosen as it was the minimum value for response in Solowiej-Wedderburn et al[1].

8. **Benefit of treatment reduces**
   In this scenario, even if the patient is fully compliant and responds to the treatment, the treatment benefit would reduce over time and be equivalent to usual care in about 15 years. This is an extreme assumption as the committee believe that as long as the

patient is compliant and responds to the treatment, they are likely to retain at least some of the benefit.

HE2.4.2 Probabilistic sensitivity analyses

The IQVIA CDM allows for a probabilistic analysis to account for the uncertainty surrounding the model input parameters listed above. The probability distributions around each parameter are set by default in the IQVIA CDM, as explained in the document available in the IQVIA CDM website. When the probabilistic version of the model is run, values are randomly selected simultaneously for each model input parameter from its respective probability distribution. These values are then used to calculate the respective costs and QALYs. This was repeated 1000 times (1000 bootstraps) for the base case, and then mean costs and QALYs calculated across those samples.

The following variables were left deterministic, due to the IQVIA CDM not accounting for uncertainty surrounding them:

- Costs of monitoring devices
- The cost-effectiveness threshold (defined as fixed by NICE)

Note that the deterministic version of IQVIA CDM also has an element of stochastic variability in it due to a baseline cohort of 1000 patients being simulated to run the economic analysis on.

HE3 Results

HE3.1 Base-case cost–utility results

The base case results (Table HE012, Table HE013) showed that periodontal treatment was cost-effective compared with usual care at a threshold of £20,000 per QALY for both type 1 and type 2 diabetes. For type 1 diabetes, periodontal treatment dominated usual care as it was less costly and more effective than usual care.

Table HE012: Base-case cost–utility results, Type 1

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER
Usual care	44,048	12.741			
Periodontal treatment (T1)	42,977	12.796	-1,070	0.055	Dominates

Table HE013: Base-case cost–utility results, Type 2

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER
Usual care	10,840	7.895			
Periodontal treatment (T2)	11,087	7.917	247	0.022	11,375

** The costs and QALYs in the table are rounded and the ICER is calculated using the exact values, therefore the ICER in the table is slightly different*

HE3.2 Deterministic sensitivity analysis

Results of the sensitivity analyses performed are shown in Table HE014 and Table HE015.

Table HE014: Summary findings of deterministic sensitivity analyses, Type 1

Sensitivity analyses	Costs (£)		QALYs		ICER (£)
	UC	PT	UC	PT	
Base case	44,048	42,977	12.741	12.796	PT dominates
Severe periodontitis	44,048	43,115	12.741	12.796	PT dominates
UDA costing approach	44,097	42,567	12.741	12.796	PT dominates
Dentist providing performer	44,048	43,091	12.741	12.796	PT dominates
50-year time horizon	43,862	42,832	12.725	12.775	PT dominates
25-year time horizon	27,228	26,855	10.888	10.917	PT dominates
10-year time horizon	6,559	6,743	6.035	6.044	21,115
5-year time horizon	2,287	2,570	3.372	3.375	74,542
No patient co-payment	44,553	43,889	12.741	12,796	PT dominates
Compliance down to 11%	44,048	43,995	12.741	12.759	PT dominates
Response down to 50%	44,048	43,625	12.741	12.777	PT dominates
Benefit of treatment reduces	50,167	50,104	12.581	12.600	PT dominates

** UC – usual care, PT – periodontal treatment*

** The costs and QALYs in the table are rounded and the ICER is calculated using the exact values, therefore the ICER in the table is slightly different*

The sensitivity analyses results for type 1 diabetes (Table HE014) show that periodontal treatment remains cost-effective for most scenarios. It was only when reducing the time

horizon to 10 years and below that periodontal treatment appeared not cost-effective. This is due to the fact that the treatment prevents more costly complications later in life. As treatment benefit is likely to last over time when patients stick to the maintenance treatment and retreatment, we are more interested in the long-term cost-effectiveness of the treatment, and therefore the results should not affect our conclusion.

Table HE015: Summary findings of deterministic sensitivity analyses, Type 2

Sensitivity analyses	Costs (£)		QALYs		ICER (£)
	UC	PT	UC	PT	
Base case	10,840	11,087	7.895	7.917	11,375
Severe periodontitis	10,840	11,195	7.895	7.917	16,353
UDA costing approach	10,873	10,755	7.895	7.917	PT dominates
Dentist providing performer	10,840	11,201	7.895	7.917	16,628
50-year time horizon	10,842	11,088	7.895	7.916	11,654
25-year time horizon	10,103	10,334	7.736	7.747	21,816
10-year time horizon	4,713	5,012	5.212	5.219	48,131
5-year time horizon	2,223	2,504	3.066	3.066	312,178
No patient co-payment	11,136	11,698	7.895	7.917	25,906
Compliance down to 11%	10,840	11,068	7.895	7.903	29,880
Response down to 50%	10,840	11,190	7.895	7.908	27,311
Benefit of treatment reduces	11,094	11,426	7.892	7.896	197,553

** UC – usual care, PT – periodontal treatment*

** The costs and QALYs in the table are rounded and the ICER is calculated using the exact values, therefore the ICER in the table is slightly different*

The sensitivity analyses results for type 2 diabetes are shown in Table HE015. Except from the shorter time horizon scenarios as the type 1 results, the cost-effectiveness of the periodontal treatment was sensitive to the removal of patients' co-payment, lower compliance rate and response rate, and reduction of treatment benefit over time. When assuming everyone is exempt from dental charges, the ICER is over the £20,000 threshold. This is an extreme scenario and unlikely to happen in the near future. However, it indicates that with a small increase in the proportion of people who are eligible for exemption from dental charges, the treatment would still remain cost-effective. With lower rates of compliance and response to the treatment, the ICERs also exceed the £20,000 threshold. According to the committee, both rates are extremely low and should be considered as very conservative assumptions based on their experience. Therefore, the result should not affect our recommendations. Lastly, the ICER becomes extremely large when assuming the benefit of treatment reducing over time. However, the committee felt that if the patient is compliant and responding to the treatments, it is unlikely that they will lose all benefits in lower HbA1c as they continue to receive maintenance treatments and retreatments. Therefore, although periodontal treatment was not cost-effective under this scenario, it is unlikely to represent practice and should not affect the cost-effectiveness of the treatment.

HE3.3 Probabilistic sensitivity analysis

Probabilistic sensitivity results were reported below in Table HE016, and the cost-effectiveness acceptability curves (CEAC) are shown in Figure HE001 and Figure HE002.

Table HE016: Summary findings of probabilistic sensitivity analyses

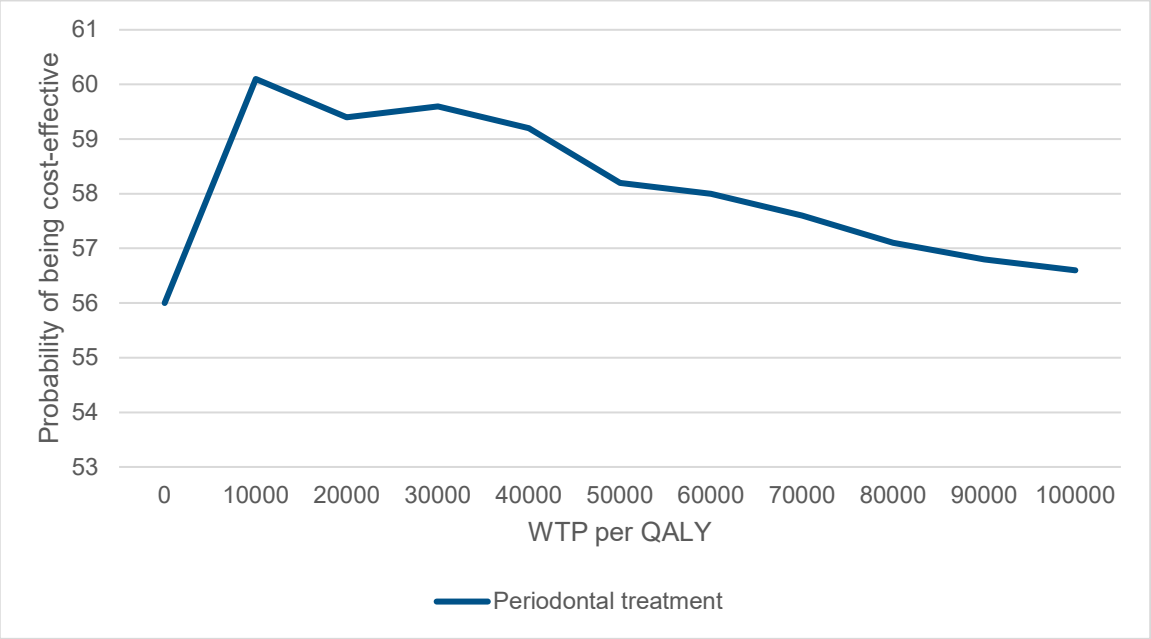
Sensitivity analyses	Costs (£)		QALYs		ICER
	UC	PT	UC	PT	
Type 1	50,825	49,782	12.057	12.083	PT dominates

Sensitivity analyses	Costs (£)		QALYs		ICER
	UC	PT	UC	PT	
Type 2	14,529	14,721	7.536	7.556	9,360

** UC – usual care, PT – periodontal treatment*

** The costs and QALYs in the table are rounded and the ICER is calculated using the exact values, therefore the ICER in the table is slightly different*

Figure HE001: Cost-effectiveness acceptability curve in probabilistic sensitivity analyses (Type 1)



The CEAC for type 1 diabetes (Figure HE001) is different from the familiar shape of monotonically increasing ones since the probability of periodontal treatment being cost-effective decreases with willingness-to-pay (WTP) when WTP exceeds £10,000 or so. This is due to periodontal treatment being cost saving compared to usual care when taking into account long-term cost of diabetes-related complications. However, the associated QALY gain due to the treatment was relatively small, and therefore, in some iterations in PSA, usual care may appear more effective than periodontal treatment (as shown in the ICER scatter plot Figure HE002). As the total cost of both intervention and control arms are slightly below £15,000, the probability of periodontal treatment being cost-effective drops around the value and decreases further with increasing WTPs. At the £20,000 cost-effectiveness threshold, periodontal treatment is about 60% likely to be cost-effective.

Figure HE002: ICER Scatterplot (Type 1)

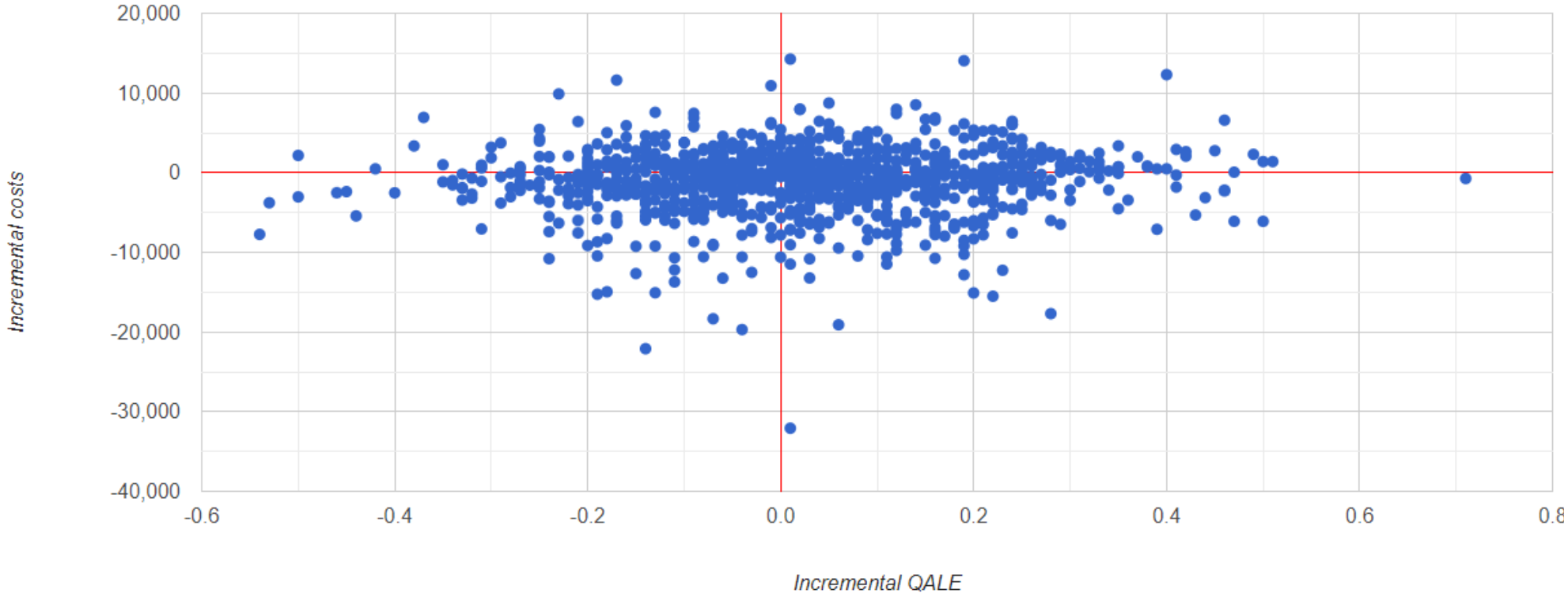
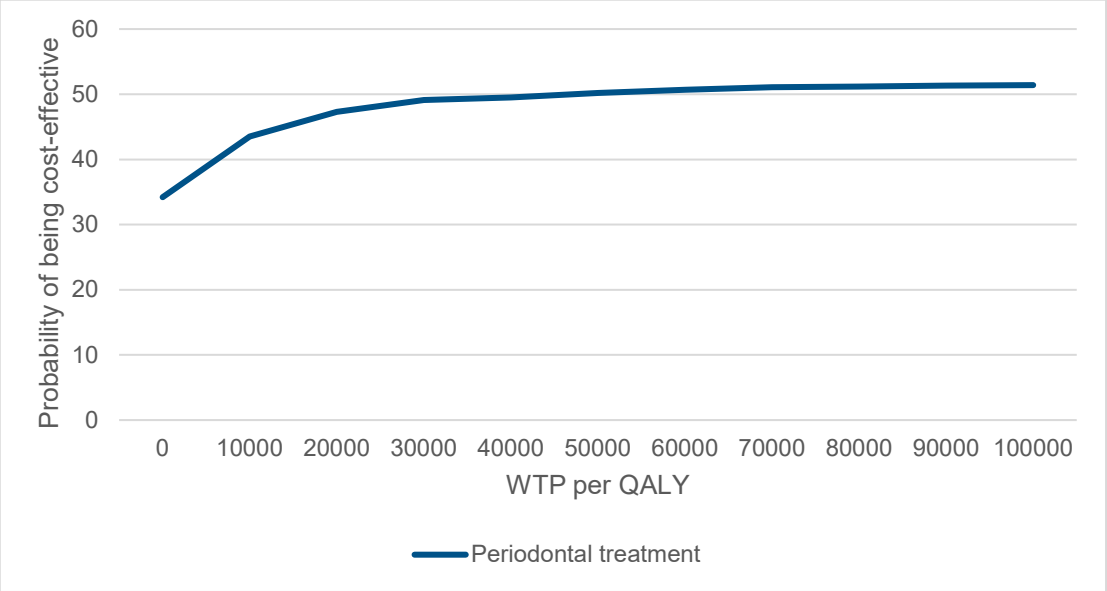


Figure HE003: Cost-effectiveness acceptability curve in probabilistic sensitivity analyses (Type 2)



The cost-effectiveness acceptability curve for type 2 diabetes (Figure HE003) shows that at the £20,000 willingness to pay threshold, periodontal treatment has around 47% likelihood of being cost-effective. Both probabilities are relatively low, indicating some uncertainty around the cost-effectiveness results.

HE3.4 Discussion

HE3.4.1 Principal findings

In the base case, periodontal treatment was found to be cost-effective compared with usual care for both type 1 and type 2 diabetes. The sensitivity analyses show that periodontal treatment remained cost-effective across most scenarios, apart from the ones with shorter time horizons (10 years and below). The cost-effectiveness results for patients with type 2 diabetes were also sensitive to changes in compliance rate, response rate and when the benefit of treatment reduces over time. The committee agreed that these were all very conservative scenarios and did not reflect the current practice. Therefore, periodontal treatment was still considered to be cost-effective among people with diabetes.

HE3.4.2 Weaknesses of the analysis

One of the weaknesses of this analysis is that it did not take into account any dental outcome related to the periodontal treatment. There are a number of reasons: 1) our model structure did not contain a dental module that can be used to model the costs and consequences along the periodontal pathway of intervening with treatment in a diabetic cohort; 2) the commonly adopted utility measure, EQ-5D, is not sufficient to capture the processes and outcomes of dental care due to its insensitivity and short health state durations; 3) there are also no good mapping algorithms to translate disease specific measures (e.g. Oral Health Impact Profile) onto utility values. Given that the periodontal treatment appears highly cost-effective in our base case analysis, the inclusion of any potential oral health benefit will further increase its cost-effectiveness and will not influence our conclusions.

HE3.4.3 Comparison with other CUAs

Compared with Solowiej-Wedderburn et al[1], our results are generally in line with their study since we both found that periodontal treatment was cost-effective compared to usual care or no active treatment, and the results were mostly sensitive to the proportion of people who are compliant and respond to the treatment. We extended their analysis to people with type 1 diabetes using the IQVIA CDM and included more diabetes-related complications in the model. In addition, our results showed that the ICERs of the treatment were even smaller than that from Solowiej-Wedderburn et al[1], mainly due to the fact that we considered the long-term cost savings from more types of diabetes-related complications.

HE3.5 Conclusions

Given the current clinical and economic evidence, periodontal treatment is cost-effective when compared to usual care for both type 1 and type 2 diabetes. The results are robust in the majority of the sensitivity analyses however, there is considerable uncertainty as shown by the probabilistic sensitivity analyses.

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