National Institute for Health and Care Excellence

Draft for consultation

Type 1 diabetes in adults: diagnosis and management

Insulin therapy

NICE guideline NG17

Economic model report

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Draft for Consultation

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Funding
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HE1 Introduction

Given the costs and impact on health-related quality of life associated with the long-term complications of type I diabetes and unstable HbA1c control, the comparison of long-acting insulins and associated regimens (once or twice daily) was identified by the Guideline Committee as an area of priority for economic analysis.

In 2015 NICE published a guideline titled "Type 1 diabetes in adults: diagnosis and management" (NG17) which evaluated the cost-effectiveness of long-acting insulins and insulin regimens. This analysis will update a similar analysis that informed the recommendations published in 2015.

The review question addressed in this analysis is:

- In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus Neutral Protamine Hagedorn (NPH)) and frequency of administration for optimal diabetic control?

Long-acting insulins considered include biosimilars which have entered the market since the 2015 guideline. Only differences in costs of biosimilars were taken into consideration in the economic analysis, with treatment effects assumed to be the same as the reference medicine. This is in line with the position statement adopted by NICE for how biosimilars should be addressed in technology appraisals.

The decision problem this analysis is designed to address in summarised in Table HE001, with the full protocol for the clinical review available in appendix M of the evidence review for the guideline update.

In the economic literature review 27 cost-utility analyses (CUAs) were identified looking at the cost-effectiveness of long-acting insulins in adults with type 1 diabetes. The type of CUA conducted could be broadly separated into two groups: Twelve short-terms CUAs[1–12] with a one-year time horizon considering only hypoglycaemic events as an adverse event, and fifteen long-term CUAs[13–27], all of which used the CORE model (or models developed based on the CORE model) with a lifetime time horizon, considering all long-term complications associated with type 1 diabetes, except Warren et al[17] which used a model developed to predict the cost and QALYs associated with hypoglycaemic complications over a period of 9 years (with other long-term complications only considered in alternative analysis). All but three[14,17,25] of the CUAs included in the review were industry funded. Of the 27 CUAs included, ten[2,3,11–14,17,18,26,27] were UK based.

Six CUAs[14,15,17,19,25,27] compared the cost-effectiveness of glargine vs NPH with all barring a CUA by Cameron et al[25] reporting results favouring glargine. Similarly, from the twelve CUAs[2,4,7,8,14,16,18,22–26] comparing detemir vs NPH, only the CUA by Cameron et al[25] reported results favouring NPH. Cameron et al[25] was an independent analysis funded by Health Canada. 2 CUAs compared detemir vs glargine; results from NG17[14] which reported an ICER of £7,940 / QALY for detemir (twice daily) vs glargine (once daily), and glargine (once daily) dominating detemir (once daily), and a study by Valentine et al[16] reported results favouring detemir. Only results from NG17[14] reported an analysis for degludec vs detemir, showing that both detemir once daily and twice daily dominated degludec once daily.

Eight CUAs[3,5,6,9–12,14] compared degludec vs glargine with all of them barring the economic evaluation performed in NG17 reporting results favouring degludec. Three CUAs[1,2,12] also extended the analysis to compare degludec against biosimilars of glargine, by substituting the input parameters for the price of glargine with that of the biosimilars, with results again favouring degludec. Three other CUAs[13,20,21] compared degludec vs glargine/detemir/other basal insulins, with all three reporting results favouring degludec. Only one CUA (NG17[14]) compared degludec vs detemir, with results favouring both detemir once daily and detemir twice daily when compared to detemir once daily.

Of the 27 economic analyses in the literature, only NG17[14] compared all available insulin therapies and insulin regimens in a single framework. Hence, the committee agreed an update to the modelling used in NG17 was the most suitable way to approach this question.

Table HE001: Health economic decision problem

Population	Adults (aged 18 years and older) with type 1 diabetes
Intervention	Long-acting insulins (once daily and twice daily regimens)
Comparator	Compared to each other or to the same long-acting insulin in a different regimen
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 on 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 type 1 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 lifetime 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 allows for transition probabilities and management strategies to be differentiated by type of diabetes. In our analysis, type 1 diabetes data was used where available.

In addition to reducing the occurrence of short-term complications such as hypoglycaemic events, more effective insulin regimens can also improve the stability of HbA1c levels, hence reducing long-term complications. Therefore, an economic analysis was undertaken to evaluate the cost-effectiveness of basal insulin regimens, taking into account the benefits of lowering HbA1c levels and reducing severe and non-severe hypoglycaemic events.

HE2.1.1 Population(s)

The primary analysis looked at a cohort of adults representing average individuals with type 1 diabetes in the UK. In the subgroup analysis, cohorts defined by particular risk factors were considered.

HE2.1.2 Interventions

The following insulin therapies were compared against each other (based on those regimens for which evidence was identified in the clinical review):

- Insulin Detemir (once daily)
- Insulin Detemir (twice daily)
- Insulin Glargine U100 (once daily)
- Insulin Glargine U300 (once daily)
- Insulin Degludec (once daily)
- NPH (once daily)
- NPH (twice daily)
- Insulin Abasaglar (once daily) – glargine biosimilar
- Insulin Semglee (once daily) – glargine biosimilar

The daily doses (both basal and bolus) for each arm were calculated using mean differences from NMAs of the included RCTs (see section 2.3.3.3). Daily doses for biosimilars of glargine were assumed to be the same as insulin glargine U100, since they were biosimilars for insulin glargine U100. The dose would be given in divided doses for comparators with higher dosing frequency (twice daily compared to once daily). The Glargine U100 twice daily insulin regimen was also not included in the economic analysis as there were no trials reporting its treatment effects for severe hypoglycaemic events, which the committee agreed were a key component to include.

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

A time horizon of 80 years was used in the base case since this was deemed sufficient to consider lifetime costs and outcomes (note that the IQVIA CDM model requires the number of years to be specified to define a time horizon). 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.

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 type 1 diabetes version of the model has been previously validated[28] against epidemiological and clinical studies of type 1 diabetes. A more detailed description of IQVIA CDM has been published by Palmer et al[29].

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[29].

The IQVIA CDM was chosen for this analysis as it is a pre-validated model which accounts for long-term diabetes related complications across a time horizon extending to the lifetime of the patient.

HE2.3 Parameters

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

1. Cohort
2. Economics
    - Costs

- Quality of life

3. Treatment
    - Treatment effects of insulin therapy
    - 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 diabetes in the IQVIA CDM 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 HE018 list the input parameters used in our analysis, with detail 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 guidelines manual. These include taking values from established routine national data sources, and 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 patients demographics, baseline risk factors, and pre-existing complications. These characteristics were sourced from a range of UK specific type 1 diabetes populations (and aimed to be representative of the full population of people with type 1 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 be 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[30] trial 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 though 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.

We have used these baseline characteristics to simulate a cohort of 1000 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			

Baseline characteristic	Mean	Sd	Source/ Comments
Age (years)	47.09	15.6	National Diabetes Audit 2018-19[31]
Duration of Diabetes (years)	19	13.23	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.
Prop. Male	0.565	n/a	
Baseline risk factors			
HbA1c (%)	9.1	1.7	REPOSE[30] – a cluster randomised trial of 267 adults with type 1 diabetes in the UK recruited from November 2011 to December 2012.
Systolic blood pressure (mmHg)	131.3	16.3	REPOSE[30]
Diastolic blood pressure (mmHg)	80	0	IQVIA CDM default value
Total Cholesterol (mg/dL)	90	16.2	REPOSE[30]
High density cholesterol (mg/dL)	28.8	7.2	REPOSE[30]
Low density cholesterol (mg/dL)	50.4	16.2	REPOSE[30]
Triglyceride (mg/dL)	25.2	18	REPOSE[30]
Body mass index (kg/m^2)	27.2	5	REPOSE[30]
estimate glomerular filtration rate (ml/min/1.72m^2)	78.58	13.24	REPOSE[30] - calculated by obtaining weighted averages since they were reported for categories of patients
Haemoglobin (gr/dl)	14.5	0	IQVIA CDM default value
White blood cell count (10^6/ml)	6.8	0	IQVIA CDM default value
Heart rate (bpm)	72	0	IQVIA CDM default value
Waist to hip ratio	0.93	0	IQVIA CDM default value
Waist circumference	87.84	0	IQVIA CDM default value
Urinary Albumin creatinine ration (mg/mmol)	4.78	10.19	REPOSE[30] - calculated by obtaining weighted averages since they were reported for categories of patients
Serum Creatinine (mg/dL)	1.1	0	IQVIA CDM default value
Serum Albumin (g/dl)	3.9	0	IQVIA CDM default value
Prop. Smoker	0.192	n/a	REPOSE[30]
Cigarettes/ day	9	n/a	Adult smoking habits in Great Britain 2019[32]
Alcohol consumption (Oz/week)	1.63	n/a	WHO status report on alcohol 2018[33] (converted from l/year to oz/week)
Prop. Physical activity	0.218	n/a	IQVIA CDM default value
Fasting glucose	180.72	n/a	IQVIA CDM default value
Prop. Family history stroke	0.0436	n/a	IQVIA CDM default value
Prop. Family history CHD	0.1474	n/a	IQVIA CDM default value
Prop. China Northern region	n/a	n/a	n/a
Prop. China rural area	n/a	n/a	n/a
Racial characteristics			
Prop. White/ other	0.930	n/a	National Diabetes Audit 2018-19[31]
Prop. Black	0.027	n/a	
Prop. Asian/ Pacific islander	0.043	n/a	
Baseline CVD complications			
Prop. MI	0.022	n/a	REPOSE[30]
Prop. Angina	0.012	n/a	REPOSE[30]

Baseline characteristic	Mean	Sd	Source/ Comments
Prop. Peripheral vascular disease	0	n/a	Assumption
Prop. Stroke	0.003	n/a	REPOSE[30]
Prop. Heart failure	0.006	n/a	REPOSE[30]
Prop. Atrial Fibrillation	0	n/a	Assumption
Prop. Left venitucular hypertrophy	0	n/a	Assumption
Baseline renal complications			
Prop. Microalbuminuria (MA)	0.12	n/a	REPOSE[30]
Prop. Gross proternuria (GPR)	0.045	n/a	REPOSE[30]
Prop. End stage renal disease (ESRD)	0	n/a	Assumption
Baseline retinopathy complications			
Prop. Background retinopathy (BDR)	0.348	n/a	REPOSE[30]
Prop. Proliferative diabetic retinopathy (PDR)	0.093	n/a	REPOSE[30]
Prop. Severe vision loss (SVL)	0	n/a	Assumption
Baseline macular edema			
Prop. Macular Edema	0	n/a	Assumption
Baseline cataract			
Prop. Cataract	0	n/a	Assumption
Baseline foot ulcer complications			
Prop. History of ulcer	0	n/a	Assumption
Prop. History of amputation	0	n/a	Assumption
Baseline neuropathy			
Prop. Neuropathy	0.071	n/a	REPOSE[30]

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 population due it being sourced from the UKPDS, the UKPDS 82 approach was used. While the UKPDS is a type 2 diabetes population, the committee agreed there was no robust evidence to suggest that event specific and non-event specific mortality

differed between type 1 and type 2 diabetes patients (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 were updated to reflect those of contemporary clinical practise in the UK. Costs for medicines were taken from the NHS Drug Tariff, 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 2019/20 were inflated to 2019/20 values using the Unit Costs of Health and Social Care 2019[34]. 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	£25.55	Atorvastatin 80 mg x 28 days (unit price: £1.96) - NHS Electronic Drug Tariff March 2021[35]
Aspirin	£17.99	Aspirin 75 mg x 28 days (unit price: £1.38) - NHS Drug Electronic Tariff March 2021[35]
ACE-I/ARB	£18.62	Weighted (by use as reported by Prescription Cost Analysis data November 2020[36]) average costs of: ACE-I/ARB (Source: NHS Electronic Drug Tariff March 2021[35]) Enalapril (10mg x 28; Unit price: £1.94) Lisinopril (10mg x 28; Unit price: £1.01) Perindopril (10mg x 30; Unit price: £10.65) Ramipril (10mg x 30; Unit price: £1.2) Candesartan (8mg x 28; Unit price: £1.85) Eprosartan (600mg x 28; Unit price: £18.16) Losartan (50mg x 28; Unit price: £1.96) Telmisartan (40mg x 28; Unit price: £4.14)
Screening for micro-albuminuria	£4.25	Cost of ACR/PCR testing from Kerr et al (2012)[37] who sourced patient numbers from Quality and Outcomes Framework (QOF) for General Practice and costs from PSSRU
Screening for gross proteinuria	£4.25	
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[34]
Eye Screening	£54.37	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	£4,076	

Input variables	Mean cost per year*	Source/ Comments
MI 2nd+ years	£861	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, procedure costs from NHS Reference costs, PSSRU Unit Costs of Health & Social Care 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.
Angina 1st year	£6,999	
Angina 2nd+ years	£315	
CHF 1st year	£3,928	
CHF 2nd+ years	£2,837	
Stroke 1st year	£4,555	
Stroke 2nd+ years	£169	
stroke death within 30 days	£1,283	
PVD 1st year	£1,329	
PVD 2nd+ years	£578	
Renal Complications		
Haemodialysis 1st year	£33,579	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Haemodialysis 2nd + years	£33,579	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)	£21,012	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Renal transplant (2nd year)	£8,332	Estimate sourced from 2021 update of the NICE chronic kidney disease guideline
Acute events		
Non-severe hypoglycaemic events	0	Information from Geelhoed et al[38] 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	£370	Based on information from Hammer et al[39] 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

Input variables	Mean cost per year*	Source/ Comments
		study by Heller et al[40] 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. **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 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	£145	NHS Reference Costs 2018/19 Currency code BZ86B - Non-surgical ophthalmology with interventions.
Cataract operation	£927	NHS Reference Costs 2018/19 Currency codes: BZ84A/BZ84B/BZ84C (Phacoemulsification Cataract Extraction and Lens Implant - CC Score 4+, 2-3, 0-1)
Following cataract operation	£203	NHS Reference Costs 2018/19 Currency code: WF01A (Non-admitted face to face attendance, ophthalmology follow-up)
Blindness - year of onset	£7,570	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	£7,314	
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[35])
Neuropathy 2nd year onwards	£37.10	
Active ulcer	£3,520	Kerr et al (2019)[41] - 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	£8,440	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	£25,677	NICE Peripheral arterial disease guideline, CG147

Input variables	Mean cost per year*	Source/ Comments
		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, except in the case of the impact on quality of life from severe and non-severe hypoglycaemic events (which were expected to be key drivers of the model).

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[42] and Evans et al[43].

Currie et al[42] sourced information from 1,305 respondents with diabetes to 2 surveys conducted in 2000 and 2004. Impact on quality of life was measured using the EQ-5D instrument with the fear of hypoglycaemia measured using the HFS survey. 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 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[43] 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[44] was used as it was based on the same data set as Evans et al[43].

The impact on quality of life from multiple flexible dosing regimens was not included in the model. The committee initially agreed this was an important issue to address, under the assumption there would potentially be a quality of life benefit associated with needing fewer injections, and therefore a specific search was made for papers providing data on this issue. A study by Evans et al[45] has reported findings on the impact of flexible dosing and multiple injection insulin regimens on quality of life, and did include estimates from people with both type 1 and type 2 diabetes. However, the results were not reported by type of diabetes. The committee believed the impact on quality of life from multiple injections and flexible dosing regimens are likely to differ between type 1 and type 2 patients due to the younger average age of type 1 patients, and the difference between the conditions (such as comorbidities, and the number of injections needs per day and other medicines being taken). Hence this was not incorporated in our analysis. The committee also noted this study did not consider whether any potential quality of life differences would persist permanently, or whether there

would be adaptation effects (meaning the quality of life associated with the different options converged over time as people became used to the regimen they were using). They noted this would also be a relevant factor to consider in any future quality of life studies conducted.

All inputs used to measure the quality of life of patients with their relevant sources are listed in Table HE004.

Table HE004: Quality of life values

Input variables	Mean utility	se	Source/ Comment
No complications	0.8390	0.0048	Default value in IQVIA CDM which was sourced from Peasgood et al[46] – obtained from the T1D population who undertook a DAFNE course (2009-12) at baseline and 2 subsequent years. Information collected using EQ-5D, EQ-VAS and SF-12 instruments. Baseline utility values calculated form the EQ-5D cohort.
Disutility of MI event	-0.055	0.005	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47]. Within this systematic review, these relevant parameters were sourced from Clarke et al[48]. QoL post MI was assumed to be baseline utility minus disutility of MI from Beaudet et al. A similar calculation was done to obtain QoL post Stroke and post amputation.
Utility post MI	0.784	0.0069	
Utility CHF	0.6770	0.01	
Disutility of Stroke event	-0.164	0.008	
Utility post Stroke event	0.675	0.0093	
Utility post amputation	0.559	0.012	
Disutility amputation event	-0.280	0.011	
Utility PVD	0.7240	0.008	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47]. Within this systematic review, these relevant parameters were sourced from Bagust et al[49]
Utility gross proteinuria	0.7370	0.008	
Utility neuropathy	0.7010	0.008	
Disutility of ulcer	-0.1700	0.0189	
Utility haemodialysis	0.6210	0.029	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47]. Within this systematic review, these relevant parameters were sourced from Wasserfallen et al[50]
Utility peritoneal dialysis	0.5810	0.03	
Utility background diabetic retinopathy (BDR)	0.7450	0.021	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47]. Within this systematic review, these relevant parameters were sourced from Fenwick et al[51]
Utility BDR wrongly treated	0.7450	0.022	
Utility macular edema	0.7450	0.021	
Utility renal transplant	0.7620	0.118	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47]. Within this systematic review, these relevant parameters were sourced from Kiberd et al[52]
Utility cataract	0.7690	0.016	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47]. Within this systematic review, these relevant parameters were sourced from Lee et al[53]

Input variables	Mean utility	se	Source/ Comment
Utility proliferative diabetic retinopathy (PDR) laser treatment	0.7150	0.022	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[47].
Utility PDR no laser	0.7150	0.022	
Utility angina	0.6950	0.01	
Utility microalbuminuria	0.7850	0.007	
Disutility NSHE daytime	-0.005	0.00077	UK patients from a TTO survey in five countries (UK, USA, Canada, Germany & Sweden) from Evans et al[43]. 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 T1D 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 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 NSHE nocturnal	-0.008	0.00102	
Disutility SHE daytime	-0.062	0.00433	
Disutility SHE nocturnal	-0.066	0.00485	
Disutility for 1 unit increase in BMI above 25 kg/m^2	-0.0061	n/a	Default value in IQVIA CDM - sourced from Bagust et al[49]

HE2.3.3 Treatments

HE2.3.3.1 Treatment effects of insulin therapy

Treatment effects for the outcomes listed below were based on the network meta-analyses (NMA) performed on the clinical evidence identified from the systematic review (see appendix E of the evidence review for the guideline update). The results of these NMAs are outlined in more detail in appendix K of the same evidence review. From the NMA, insulin regimens where the frequency of insulin was not defined (eg: NPH once/twice daily) were not included in the economic analysis.

Reduction in HbA1c levels

The reduction in HbA1c levels, calculated as the mean change from baseline are listed in Table HE005. These absolute changes were calculated from the relative changes provided by the NMA by performing a random effects meta-analysis on all the individual study arms reporting data on detemir twice daily (chosen as the primary treatment recommended in NG17), and then applying the relative effects estimated from the NMA to that baseline absolute value for detemir twice daily.

The listed values were then applied to the baseline HBA1c level (9.1%). Full details of the NMA from which these values were derived is given in appendix K.

Table HE005: Reduction in HbA1c levels

Insulin	Change in HbA1c[a]	Se
Detemir twice daily	-0.4544	0.1174
NPH twice daily	-0.3605	0.1297
Detemir once daily	-0.3712	0.1495
NPH once daily	-0.2555	0.1745
Glargine U100 once daily	-0.4767	0.1711
Degludec U100 once daily	-0.3955	0.2221
Glargine U300 once daily	-0.4614	0.3297

(a) Median of the posterior distribution from the NMA

Severe hypoglycaemic events

To account for the uncertainty surrounding results of the NMA on severe hypoglycaemic events (many of the median point estimates were substantial, but often the results were not statistically significant at a 95% level due to the high levels of uncertainty), three scenarios were considered when calculating severe hypoglycaemic event rates to be used in the economic analysis.

Scenario 1:

Severe hypoglycaemic event rates were calculated by applying the odds ratios obtained from the NMA of severe hypoglycaemic events in appendix K to the rate of severe hypoglycaemic event rates in the detemir twice daily arm. The rate of detemir twice daily was obtained by synthesising the rates of severe hypoglycaemic event rates (obtained from the systematic review of clinical evidence in appendix E) using a random effects meta-analysis. Severe hypoglycaemic event rates (per 100 patient years) used in scenario 1 are listed in table HE006. Scenario 1 essentially uses all available information on hypoglycaemic event rates from the NMA when calculating hypoglycaemic event rates.

Table HE006: Severe hypoglycaemic event rates (scenario 1)

Insulin	Event rate (per 100 patient years)[a]
Detemir twice daily	30.17
NPH twice daily	34.29
Glargine U100 once daily	65.7
Detemir once daily	57.21
NPH once daily	68.61
Degludec U100 once daily	57.17
Glargine U300 once daily	91.82

(a) Median of the posterior distribution from the NMA

Scenario 2:

In scenario 2, the proportion of severe hypoglycaemic events in all hypoglycaemic events across all studies (and all treatments) included in the systematic review of clinical evidence in appendix E was estimated using a random effects model. Severe hypoglycaemic event rates (table HE007) were then calculated by applying these proportions to all hypoglycaemic event rates. All hypoglycaemic event rates had been calculated by applying the odds ratios obtained from the NMA in appendix K to the rate of hypoglycaemic event rates in the detemir twice daily arm (the rate of detemir twice daily calculated by synthesising data from all individual trials reporting information on detemir twice daily using a random effect model). Scenario 2 does not make use of the NMA for severe hypoglycaemic event rates, and only uses the results from the NMA for all hypoglycaemic event rates (which contains less uncertainty as rates of all hypoglycaemic events are higher than rates of severe hypoglycaemic events, meaning there is more data in the analysis). Note that the event rate for detemir twice daily is higher in scenario 2 when compared to scenario 1 as it is calculated by multiplying the synthesised value of all hypoglycaemic event rates in detemir twice daily arms reporting all hypoglycaemic event rates by the proportion of severe hypoglycaemic events in all hypoglycaemic events (calculated by synthesising information from detemir twice daily arms reporting severe hypoglycaemic and all hypoglycaemic events).

Table HE007: Severe hypoglycaemic event rates (scenario 2)

Insulin	Event rate (per 100 patient years)[a]
Detemir twice daily	36.53
NPH twice daily	42.50
Glargine U100 once daily	49.67
Detemir once daily	40.81
NPH once daily	50.65
Degludec U100 once daily	45.68
Glargine U300 once daily	50.26

(a) Median of the posterior distribution from the NMA

Scenario 3:

In scenario 3, severe hypoglycaemic events in each insulin regimen were assumed to be the same as those in the detemir twice daily arm (table HE008). Scenario 3 does not use any information from the NMAs for either severe hypoglycaemic events or all hypoglycaemic events when calculating hypoglycaemic event rates in the economic analysis.

Table HE008: Severe hypoglycaemic event rates (scenario 3)

Insulin	Event rate (per 100 patient years)
Detemir twice daily	30.17
NPH twice daily	30.17
Glargine U100 once daily	30.17
Detemir once daily	30.17
NPH once daily	30.17
Degludec U100 once daily	30.17
Glargine U300 once daily	30.17

Non-severe hypoglycaemic events

Non-severe hypoglycaemic event rates in scenarios 1 (table HE009) and 2 (table HE010) were calculated by subtracting severe hypoglycaemic rates in tables HE006 and HE007 from all hypoglycaemic event rates. Absolute all hypoglycaemic event rates were calculated by

applying the odds ratios obtained from the NMA in appendix K to a random effect meta-analysis on the detemir twice daily all hypoglycaemic rates reported in individual trials. Even though rates of all hypoglycaemic events are the same in scenarios 1 and 2, because severe hypoglycaemic rates are different, this leads to small differences in rates of non-severe hypoglycaemic events.

In scenario 3, non-severe hypoglycaemic event rates (table HE011) in al insulin regimens were assumed to be the same as the non-severe hypoglycaemic event rates for detemir twice daily in scenario 1.

Table HE009: Non-severe hypoglycaemic event rates (scenario 1)

Insulin	Event rate (per 100 patient years)[a]
Detemir twice daily	2616.83
NPH twice daily	3045.71
Glargine U100 once daily	3533.3
Detemir once daily	2899.79
NPH once daily	3601.39
Degludec U100 once daily	3252.83
Glargine U300 once daily	3550.18

(a) Median of the posterior distribution from the NMA

Table HE010: Non-severe hypoglycaemic event rates (scenario 2)

Insulin	Event rate (per 100 patient years)[a]
Detemir twice daily	2610.47
NPH twice daily	3037.50
Glargine U100 once daily	3549.33
Detemir once daily	2916.19
NPH once daily	3619.35
Degludec U100 once daily	3264.32
Glargine U300 once daily	3591.74

(a) Median of the posterior from the NMA

Table HE011: Non-severe hypoglycaemic event rates (case scenario 3)

Insulin	Event rate (per 100 patient years)
Detemir twice daily	2616.83
NPH twice daily	2616.83
Glargine U100 once daily	2616.83
Detemir once daily	2616.83
NPH once daily	2616.83
Degludec U100 once daily	2616.83
Glargine U300 once daily	2616.83

Nocturnal hypoglycaemic events

Proportion of nocturnal hypoglycaemic events in all hypoglycaemic event were extracted from the studies included in the systematic review of clinical studies (appendix E). An NMA (appendix K) was then performed to calculate the relative effects of the proportion of nocturnal hypoglycaemic events in all hypoglycaemic events. These relative effects were then applied to the proportion of nocturnal hypoglycaemic events in the detemir twice daily arm (obtained by performing a random effects meta-analysis on all the individual study arms

reporting data on detemir twice daily) to obtain the absolute proportion of nocturnal hypoglycaemic events in each insulin regimen (table 12) These proportions were used in conjunction with severe and non-severe hypoglycaemic events shown above to calculate the severe nocturnal and non-severe nocturnal hypoglycaemic events in our economic analysis. Insufficient data was available in the RCTs to be able to separately estimate proportions of severe and non-severe events that are nocturnal, and therefore the same proportion was applied to both.

Table HE012: Proportion of nocturnal hypoglycaemic event rates

Insulin	Proportion of nocturnal hypoglycaemic events
Detemir twice daily	0.1396
NPH twice daily	0.1839
Glargine U100 once daily	0.1569
Detemir once daily	0.2
NPH once daily	0.2215
Degludec U100 once daily	0.1081
Glargine U300 once daily	0.1417

(a) Median of the posterior distribution from the NMA

HE2.3.3.2 Treatment algorithm

The IQVIA CDM allows to define a treatment algorithm for each intervention in the event of treatment failure. Given the lack of evidence of differences between insulin regimens with regard to the discontinuation of treatments, no treatment failure was assumed in this analysis. The committee noted that people discontinuing from one insulin would need to go on to another one, and therefore without evidence of differential discontinuation rates this would not affect the ordering of effectiveness or cost-effectiveness of the treatments.

HE2.3.3.3 Treatment costs

Prices of insulin were obtained from the NHS electronic drug tariff[31]. In cases where prices were not available in the NHS electronic drug tariff, the NHS indicative price was sourced from the British National Formulary (BNF). The price per unit was then calculated for available products (products were selected with guidance from the committee on ones used in practice for type 1 diabetes) and the weighted average price was obtained by weighting the prices by quantities prescribed as per Prescription Cost Analysis (PCA) data[36]. The calculation and the weighted average prices are listed in table HE013. Based on committee advice, a single average cost per unit was estimated for bolus insulin, and this same cost per unit was used regardless of which basal insulin the person was using.

Table HE013: Prices of insulins

Type of insulin	Product	Unit price (£)	Ml	units /ml	price/ unit	Quantity	Weighted average price/unit
Basal Insulin							
NPH	Humulin I 3x5ml cartridges[a]	19.08	15	100	0.012 72	31,503	0.01430
	Humulin I KwikPen 5x3ml pre-filled disposable pens[a]	21.70	15	100	0.014 47	205,469	
	Insulatard (Insulin isophane human): 5X 3ml cartridges[b]	22.90	15	100	0.015 27	55,723	

Type of insulin	Product	Unit price (£)	Ml	units /ml	price/ unit	Quantity	Weighted average price/unit
	Insulatard Innolet 5x3ml[b] pens	20.40	15	100	0.013 60	27,929	
	Insuman Comb 25 5x3ml cartridges[a]	17.50	15	100	0.011 67	1,197	
	Insuman Comb 25 SoloStar 5X3ml pre-filled disposable devices[a]	19.80	15	100	0.013 20	13,325	
Glargine U100	Lantus 5x3ml cartridges[a]	37.77	15	100	0.025 18	107,241	0.02518
	Lantus solo star 5x3ml pre-filled disposable devices[a]	37.77	15	100	0.025 18	480,341	
Glargine U300	Toujeo Solo Star 3x1.5ml pre-filled disposable devices[a]	32.14	4.5	300	0.023 81	107,762	0.02381
	Toujeo Double Star 3x3ml pre-filled disposable devices[a]	64.27	9	300	0.023 80	14,598	
Absaglar	5x3ml cartridges[b]	35.28	15	100	0.023 52	8,326	0.02352
	5x3ml pre-filled disposable pens[b]	35.28	15	100	0.023 52	92,773	
Semglee	5x3ml pre-filled disposable injection[b]	29.99	15	100	0.019 99	11,104	0.01999
Degludec U100	Tresiba Penfill: 5x3ml cartridges[a]	46.60	15	100	0.031 07	42,455	0.03107
	Trexiba FlexTouch: 5x3ml pre-filled disposable device[a]	46.60	15	100	0.031 07	161,601	
Detemir	Levemir Penfill: 5x3ml cartridges[a]	42.00	15	100	0.028 00	119,503	0.02802
	Levemir FlexPen: 5x3ml pre-filled disposable device[a]	42.00	15	100	0.028 00	227,186	
	Levemir InnoLet 5X 3ml pens[a]	44.85	15	100	0.029 90	3,745	
Bolus insulin							
	Humalog® 100 units/mL KwikPen® 5x3ml cartridges[b]	28.31	15	100	0.018 87	121,588	0.01965
	Humalog® 100 units/mL KwikPen® Junior 5x3ml[b]	29.46	15	100	0.019 64	80	
	Humalog KwikPen 100units/ml inj 3ml pre-filled pens[b]	29.46	15	100	0.019 64	109,515	
	Humalog® 200 units/mL KwikPen® 5X3ml pre-filled pens[b]	58.92	15	200	0.019 64	19,456	
	Insulin Lispro biosimilar (Insulin lispro Sanofi solo star) 5x3ml cartridges[b]	21.23	15	100	0.014 15	498	
	Insulin Lispro biosimilar (Insulin lispro Sanofi) 5x3ml pre-filled pens[b]	22.10	15	100	0.014 73	1,108	
	Insulin Lispro biosimilar (Lyumjev) 5x3ml cartridges[b]	28.31	15	100	0.018 87	39	

Type of insulin	Product	Unit price (£)	Ml	units /ml	price/ unit	Quantity	Weighted average price/unit
	Insulin Lispro biosimilar (Lyumjev) 5x3ml pre-filled pens[b]	29.46	15	100	0.019 64	58	
	Lyumjev®▼ 200 units/mL KwikPen® 5x3ml[b]	58.92	15	200	0.019 64	0	
	Fiasp Flextouch 100units/ml 5x3ml pre-filled pens[b]	30.60	15	100	0.020 40	35,870	
	Fiasp Penfill 100units/ml 5x3ml cartridges[b]	28.31	15	100	0.018 87	24,839	
	Novorapid penfil 100 units/ml 3x5ml cartrdiges[b]	28.31	15	100	0.018 87	417,395	
	Novorapid FlexPen 100units/ml 5x3ml pre-filled pens[b]	30.60	15	100	0.020 40	557,025	
	NovoRapid FlexTouch100units/ml 5x3ml pre-filled pens[b]	32.13	15	100	0.021 42	25,848	
	Apidra® SoloStar 100units/ml 5x3ml pre-filled disposable devices[b]	28.30	15	100	0.018 87	5,416	
	Apidra 100units/ml 5x3ml cartridges[b]	28.30	15	100	0.018 87	44,721	

(a) Sourced from NHS Electronic Drug Tariff March 2021[35]
(b) Sourced from BNF March 2021[35] *(NHS indicative prices)*

Daily basal and bolus insulin dose was calculated by performing NMAs using information reported in trials from the systematic review of clinical evidence. 16 trials reported data on daily basal dose, and 12 trials reporting daily bolus dose. The networks diagrams of studies reporting basal and bolus doses are shown in figure HE001 and HE002 respectively.

Figure HE001: Network diagram for basal dose

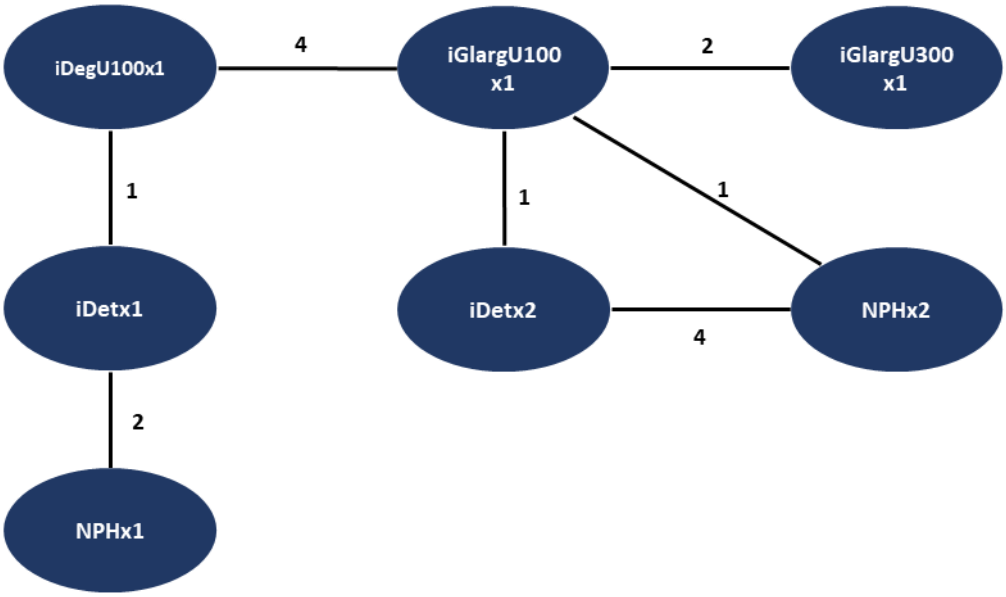
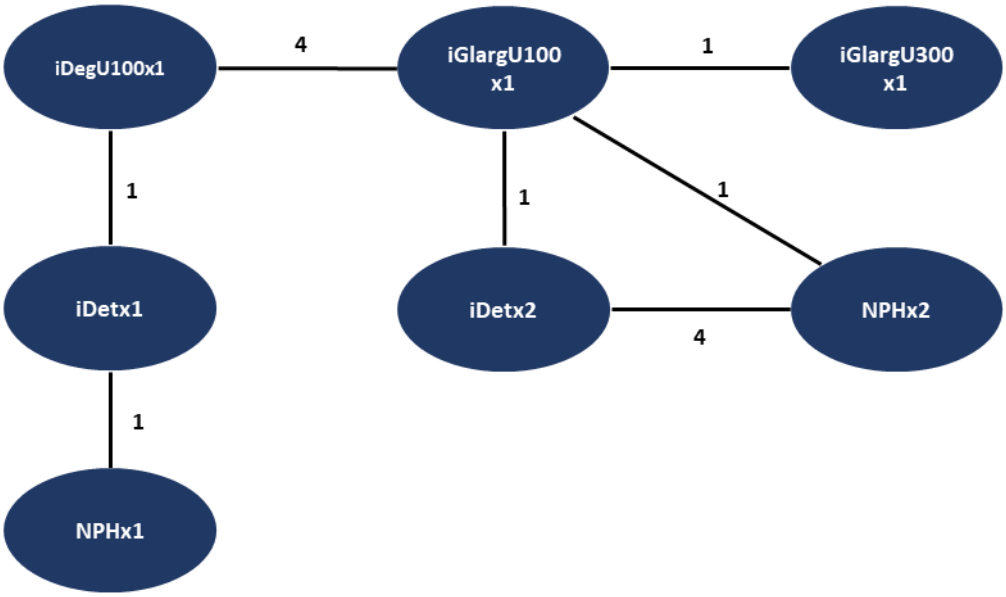


Figure HE002: Network diagram for bolus dose



A random effects model was selected to perform the network meta-analysis for both basal and bolus dose due to heterogeneity caused by insulin regimens differing in both injection frequency and dose concentration. The model fit statistics are for both NMAs are shown in table HE014.

Table HE014: Model fit statistics

Outcomes	Number of studies	FE/RE	Total residual deviance	DIC	Standard deviation of random effects distribution (95%CI)	Preferred model
Basal dose	16 trials	**FE**	44.96	135.836	n/a	RE
		RE	32.19	135.82	2.676	
Bolus dose	14 trials	**FE**	39.54	130.646	n/a	RE
		RE	29.48	125.29	2.691	

The absolute daily dose in each insulin regimen was calculated by performing a random effects meta-analysis on all the individual study arms reporting data on detemir twice daily (chosen as the primary treatment recommended in NG17), and then applying the mean differences estimated from the NMA to that baseline absolute value for detemir twice daily.

Both the relative effects of each insulin regimen compared to detemir twice daily, and the absolute daily basal and bolus dose are shown in table HE015 and HE016 respectively. Given that the priority was on obtaining the absolute daily dose for each insulin regimen and not the relative effect nor the best performing insulin regimen in terms of daily dose, the rankograms and caterpillar plots have not been presented. As would be expected, insulins where a lower basal dose is given tend to have a higher bolus dose, due to the person needing approximately the same amount of insulin overall.

Table HE015: Daily basal dose

Insulin regimen	Mean difference (vs Det x2)[a]	Daily dose (units) [a]
Detemir twice daily	n/a	34.55
Detemir once daily	-8.20 (-13.64, -2.60)	26.34
NPH once daily	-6.05 (-13.68, 1.26)	28.49
NPH twice daily	-0.74 (-4.002, 2.57)	33.81
Glargine U100 once daily	-10.13 (-14.99, -5.04)	24.44
Glargine U300 once daily	-5.22 (-11.92, 1.91)	29.35
Degludec U100 once daily	-9.99 (-15.44, -4.11)	24.58

(a) Median of the posterior distribution from the NMA

Table HE016: Daily bolus dose

Insulin regimen	Mean difference (vs Det x2)[a]	Daily dose (units) [a]
Detemir twice daily	n/a	28.8
Detemir once daily	8.25 (2.62, 13.81)	37.05
NPH once daily	8.647 (-3.07, 20.32)	37.44
NPH twice daily	-2.213 (-5.46, 1.01)	26.59
Glargine U100 once daily	2.45 (-2.57, 7.57)	31.25
Glargine U300 once daily	6.34 (-2.09, 14.81)	35.13
Degludec U100 once daily	2.56 (-3.45, 8.34)	31.35

(a) Median of the posterior distribution from the NMA

Annual basal and bolus costs were calculated by calculating using information weighted average price/ unit (table HE013) and daily dose (tables HE014, HE015) and adding the cost

of basal injections (cost of bolus injections were assumed to be the same across regimens). The cost per needle was assumed to £0.05 per injection as recommended by the committee based on information from a document on the guidance for CCGs[54]. The annual treatment cost of each insulin regimen is shown in table HE017.

Table HE017: Daily bolus dose

Inulin regimen	Basal injection frequency	Annual Basal cost (£)	Annual Bolus cost (£)	Annual needle cost (£)	Annual cost (£)
Detemir twice daily	2	353	207	36.50	596
Detemir once daily	1	269	266	18.25	553
NPH once daily	1	149	269	18.25	436
NPH twice daily	2	177	191	36.50	404
Glargine U100 once daily	1	225	224	18.25	467
Glargine U300 once daily	1	255	252	18.25	525
Degludec U100 once daily	1	279	225	18.25	522
Glargine U100 twice daily	2	234	218	36.50	488

HE2.3.4 Clinical

The clinical module with the IQVIA CDM contains data that describes the natural history of diseases. Default parameters for the type 1 diabetes were used in this module. The clinical parameters and the clinical progression parameters (transitional probabilities) used in the default version for type 1 diabetes patients 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 HE018 lists the input parameters used for proportions of patients who were managed for various chronic and recurrent conditions.

Table HE018: Other management parameters

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
Proportion on statins for primary prevention	0.474	
Proportion on ACE-inhibitors for primary prevention	0.213	

Input parameter	Mean	Source/ comments
Proportion on aspirin for secondary prevention	0.887	Sourced from Kotseva et al
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 submission
Others		
Sensitivity of eye screening	80%	Sourced from Lopes-Bastida 2007
Specificity of eye screening	97%	
Sensitivity of gross proteinuria screening	85%	
Sensitivity of micro albuminuria screening	75%	Sourced from Cortes-Sanabria 2006
Specificity of micro albuminuria screening	97%	

HE2.4 Subgroup analyses

The following subgroup were looked at in addition to the base case to evaluate the possibility of the treatment decision changing in various subgroups. Only the specific baseline parameter was adjusted for these relevant subgroups, as there was no evidence on other input parameters (such as treatment effects) differing by subgroup, nor information on the covariances between baseline factors.

- Ethnicity:
  Black, Asian and White/other population were looked at separately with baseline proportion with respective ethnicities set to 1. Note that white/other includes mixed, other, not stated and not known groups.
- Diabetes duration:
  Duration of diabetes set to 0 to mimic a type 1 diabetes population at initial diagnosis. Information with regard to age, gender, ethnicity and proportion of smokers in a type 1 diabetes population at initial diagnosis was obtained from the National diabetes audit[31].
- Baseline HbA1c:
  Populations with low (6.6% (sd: 1.3%)) and high baseline (11.6% (sd: 1.3%)) HbA1c were looked at separately.
- Age:
  A younger (age: 32 (sd: 10)) and older (age: 62 (sd: 10)) population were looked at separately.

HE2.5 Sensitivity analyses

HE2.5.1 Deterministic sensitivity analyses

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

1. **Time horizon:**
   Reducing the time horizon on the analysis from lifetime to one year.

2. **Basal/bolus dose:**
   We assumed a flat daily basal and bolus dose of 24 units in each insulin regimen (meaning all insulins are assumed to need the same dose, rather than using the different doses estimated for each insulin from the RCTs in the clinical review). This resulted in changes to the treatment costs as shown in table HE019.

Table HE019: Treatment costs in sensitivity analysis 2

Inulin regimen	Annual cost (£)
Detemir twice daily	454
Detemir once daily	436
NPH once daily	316
NPH twice daily	334
Glargine U100 once daily	411
Glargine U300 once daily	399
Degludec U100 once daily	463

3. **Discount rate:**
   Discount rate for life years, QALYs and costs reduced from 3.5% to 1.5%.

4. **Baseline quality of life**
   A scenario where the baseline utility was lower than that of the DAFNE population following concerns from the committee that the QoL of the DAFNE population might be higher than that of the average type 1 diabetes patient in the UK. The lower baseline utility was assumed to be 0.785 (se: 0.007) which was sourced from the UKPDS population[48]. The committee noted this alternative was also imperfect (being based on a type 2 diabetes population) and therefore agreed the DAFNE number was more appropriate for the base-case analysis.

5. **Price of Glargine equal to biosimilars:**
   The price of a 5x3ml pack of Glargine U100 was reduced to the price of its cheapest biosimilar, Semglee (reduced from £37.77 to £29.99[35])

6. **Threshold analysis on price of Glargine:**
   A threshold analysis where the price of a 5x3ml pack of Glargine was reduced until it became the most cost-effective treatment strategy.

7. **Proportional of nocturnal hypoglycaemic events**
   The proportion of nocturnal hypoglycaemic events reported in table HE012 was doubled across insulin regimens to mimic a scenario where patients experienced a larger proportion of nocturnal hypoglycaemic events.

HE2.5.2 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:

- Insulin treatment costs
- Proportion of nocturnal hypoglycaemic events
- 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 Clinical outcomes

Per person cumulative severe and non-severe hypoglycaemic events for insulin regimens in the base case analysis for treatment effect scenarios 1,2, and 3 are shown in figures HE003 – HE005. In scenarios 1 (figure HE003) and 2 (figure HE004) the detemir twice daily regimen has the lowest rates of severe and non-severe hypoglycaemic events, which is line with the results of the NMA. It is also worth noting that in scenario 2, severe hypoglycaemic events are lower in glargine U100 and glargine U300 when compared to scenario 1. As expected, in scenario 3 (figure HE005) the per person cumulative severe and non-severe hypoglycaemic event were similar across insulin regimens, with small differences occurring due to the stochastic variances, and small difference in life expectancy due to differences in HbA1c values.

Figure HE003: Cumulative events per person (scenario 1)

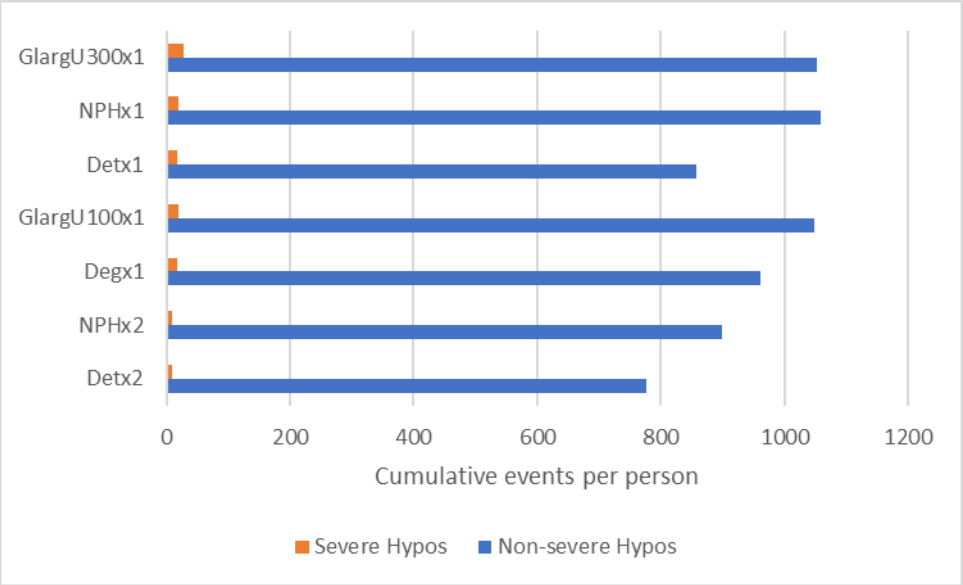


Figure HE004: Cumulative events per person (scenario 2)

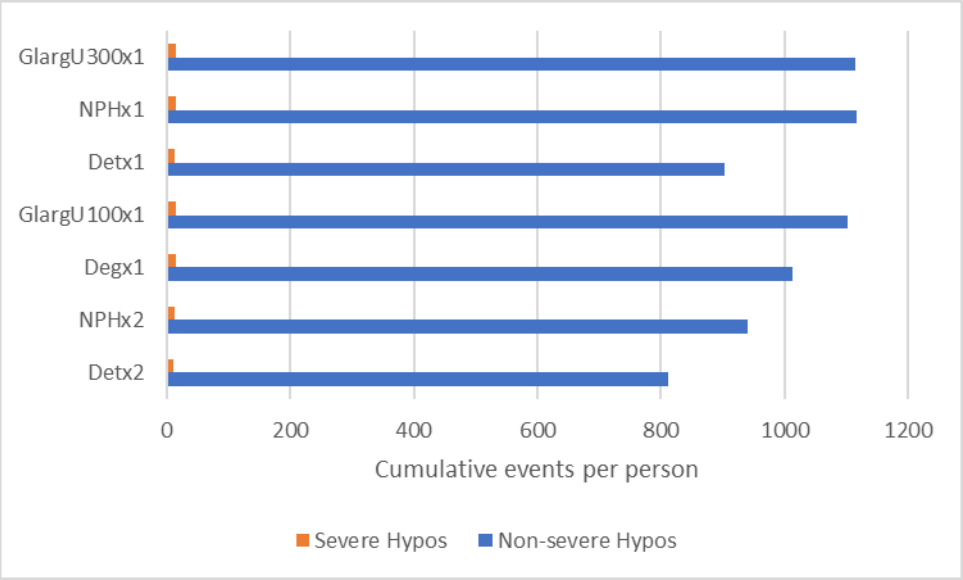
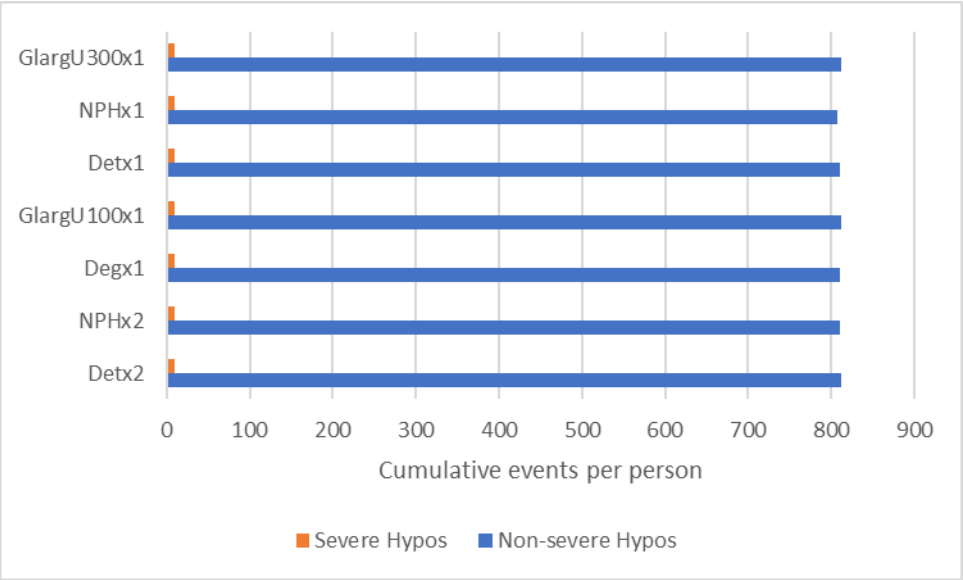


Figure HE005: Cumulative events per person (scenario 3)



HE3.2 Base-case cost–utility results

In scenario 1 our base case results (table HE020) showed that at a threshold of £20,000 per QALY, detemir twice daily was the most cost-effective treatment strategy, while amongst once daily insulin regimens glargine U100 once daily was the most cost-effective treatment strategy. At a threshold of £30,000 per QALY detemir twice daily remained the most cost-effective treatment strategy. However, at the £30,000 threshold degludec U100 once daily replace glargine U100 once daily as the most cost-effective treatment strategy. Note that in the tables below, glargine U100 refers to the original/ branded glargine and not its biosimilars. The impact of price reductions by biosimilars is discussed later on in the deterministic sensitivity analysis.

Table HE020: Base-case deterministic cost–utility results (scenario 1)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.54	55,429	175,271	290,621	1	1
NPHx2	17.40	11.40	53,444	174,516	288,496	2	2
GlargU100x1	17.42	11.11	54,934	167,346	278,486	3	4
Degx1	17.41	11.17	56,650	166,790	278,510	4	3
Detx1	17.41	11.16	57,151	165,949	277,499	5	5
NPHx1	17.35	10.89	57,886	159,994	268,934	6	6
GlargU300x1	17.43	10.77	58,295	157,025	264,685	7	7

(a) Ranked in descending order according to net monetary benefit

In scenario 2 the base case results (table HE021) showed that detemir twice daily was the most cost-effective treatment strategy, whilst glargine U100 replaced NPH twice daily as the

second most cost-effective treatment strategy. The treatment decision did not change at a threshold of £30,000 per QALY.

Table HE021: Base-case deterministic cost–utility results (scenario 2)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.47	55,795	173,685	288,425	1	1
GlargU100x1	17.42	11.30	53,836	172,144	285,134	2	2
NPHx2	17.40	11.30	54,028	171,972	284,972	3	3
Detx1	17.41	11.34	56,056	170,744	284,144	4	4
Degx1	17.41	11.29	55,920	169,960	282,900	5	5
GlargU300x1	17.43	11.22	55,589	168,791	280,981	6	6
NPHx1	17.35	11.09	56,722	165,098	276,008	7	7

(a) Ranked in descending order according to net monetary benefit

In scenario 3 (table HE022) where no differences in hypoglycaemic events were assumed between insulin regimens, glargine U100 once daily was the most cost-effective treatment strategy at the £20,000 per QALY threshold, with the treatment decision not changing at the £30,000 threshold.

Table HE022: Base-case deterministic cost–utility results (scenario 3)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	52,592	179,248	295,168	1	1
GlargU300x1	17.43	11.54	54,271	176,429	291,779	2	2
NPHx2	17.40	11.48	53,226	176,354	291,144	3	3
Degx1	17.41	11.53	54,896	175,684	290,974	4	4
Detx2	17.43	11.54	55,429	175,271	290,621	5	5
Detx1	17.41	11.48	55,399	174,241	289,061	6	6
NPHx1	17.35	11.41	55,410	172,810	286,920	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3 Subgroup analysis

Results of the subgroup analysis performed are shown below. The most cost-effective treatment strategies in the majority of subgroups were the same as in the base case results. Exceptions to this rule were the subgroup analysis of an older population and a population with lower baseline levels of HbA1c.

In older populations (table HE038), the lower life expectancy of the patients meant that older patients experienced the long-term benefits of insulin regimens, especially reductions in HbA1c levels, for a shorter time frame. This coupled with the lower treatment costs of the NPH twice daily regimen resulted in the NPH twice daily regimen performing better, being the most cost-effective treatment strategy in scenario 1 at a willingness-to-pay of £20,000 per QALY. The most cost-effective treatment strategy remained the same as the base case in scenarios 2 and 3 (table HE039, HE040).

Similarly, in populations with lower levels of HbA1c levels (table HE041-43) the NPH twice daily regimen performed better, due to a combination of reductions in HbA1c levels having

less of an impact at lower baseline levels of HbA1c, and the lower treatment costs of the NPH twice daily regimen. This resulted in the NPH twice daily regiment being the most cost-effective treatment strategy in scenario 1 (tableHE41) at the £20,000 threshold. The most cost-effective treatment strategy did not change in scenarios 2 and 3.

In a population of people at diagnosis of type 1 diabetes (table HE034) the treatment decision did change in scenario 3 due to Glargine U300 once daily having a marginally higher net monetary at the £20,000 threshold. This was largely due to the stochastic variability involved when simulating the baseline cohort, rather than representing a structurally different result.

HE3.3.1 Deterministic results for a White (including other non-Black and non-Asian) population

Table HE023: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.41	11.52	55,290	175,190	290,430	1	1
NPHx2	17.38	11.39	53,242	174,458	288,308	2	2
GlargU100x1	17.42	11.12	54,625	167,675	278,825	3	3
Degx1	17.38	11.15	56,287	166,673	278,153	4	4
Detx1	17.37	11.13	57,044	165,576	276,886	5	5
NPHx1	17.34	10.89	57,499	160,261	269,141	6	6
GlargU300x1	17.42	10.76	57,880	157,380	265,010	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE024: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.41	11.46	55,655	173,605	288,235	1	1
GlargU100x1	17.42	11.30	53,528	172,452	285,442	2	2
NPHx2	17.38	11.29	53,748	171,972	284,832	3	3
Detx1	17.37	11.32	55,949	170,351	283,501	4	4
Degx1	17.38	11.27	55,557	169,843	282,543	5	5
GlargU300x1	17.42	11.22	55,174	169,166	281,336	6	6
NPHx1	17.34	11.08	56,282	165,398	276,238	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE025: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	52,284	179,576	295,506	1	1
GlargU300x1	17.42	11.53	53,858	176,782	292,102	2	2
NPHx2	17.38	11.47	52,873	176,447	291,107	3	3
Degx1	17.38	11.51	54,535	175,565	290,615	4	4
Detx2	17.41	11.52	55,290	175,190	290,430	5	5

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx1	17.37	11.46	55,294	173,866	288,446	6	6
NPHx1	17.34	11.40	54,854	173,226	287,266	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.2 Deterministic results for a Black population

Table HE026: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.76	11.82	56,411	180,009	298,219	1	1
NPHx2	17.75	11.69	54,883	178,977	295,907	2	2
GlargU100x1	17.78	11.41	56,237	171,863	285,913	3	3
Degx1	17.76	11.46	58,008	171,152	285,732	4	4
Detx1	17.76	11.44	58,972	169,908	284,348	5	5
NPHx1	17.71	11.18	59,383	164,297	276,137	6	6
GlargU300x1	17.77	11.05	59,198	161,742	272,212	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE027: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.76	11.76	56,784	178,376	295,956	1	1
GlargU100x1	17.78	11.59	55,118	176,722	292,642	2	2
NPHx2	17.75	11.59	55,479	176,381	292,311	3	3
Detx1	17.76	11.63	57,856	174,784	291,104	4	4
Degx1	17.76	11.58	57,229	174,411	290,231	5	5
GlargU300x1	17.77	11.51	56,439	173,761	288,861	6	6
NPHx1	17.71	11.38	58,193	169,487	283,327	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE028: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.78	11.89	53,849	183,991	302,911	1	1
GlargU300x1	17.77	11.83	55,097	181,523	299,833	2	2
NPHx2	17.75	11.78	54,660	180,860	298,620	3	3
Degx1	17.76	11.82	56,093	180,347	298,567	4	4
Detx2	17.76	11.82	56,411	180,009	298,219	5	5
Detx1	17.76	11.78	57,185	178,355	296,125	6	6
NPHx1	17.71	11.71	56,855	177,365	294,475	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.3 Deterministic results for an Asian population

Table HE029: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.60	11.64	57,784	174,996	291,386	1	1
NPHx2	17.55	11.49	56,288	173,472	288,352	2	2
GlargU100x1	17.61	11.22	57,529	166,891	279,101	3	3
Degx1	17.59	11.27	59,332	166,128	278,858	4	4
Detx1	17.57	11.25	60,144	164,796	277,266	5	5
NPHx1	17.54	11.00	60,357	159,703	269,733	6	6
GlargU300x1	17.62	10.87	60,487	156,993	265,733	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE030: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.60	11.58	58,154	173,386	289,156	1	1
GlargU100x1	17.61	11.41	56,420	171,720	285,790	2	2
NPHx2	17.55	11.39	56,877	170,903	284,793	3	3
Detx1	17.57	11.43	59,039	169,621	283,951	4	4
Degx1	17.59	11.40	58,594	169,326	283,286	5	5
GlargU300x1	17.62	11.33	57,752	168,908	282,238	6	6
NPHx1	17.54	11.20	59,178	164,842	276,852	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE031: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.61	11.70	55,166	178,914	295,954	1	1
GlargU300x1	17.62	11.65	56,422	176,598	293,108	2	2
NPHx2	17.55	11.57	56,067	175,313	291,003	3	4
Degx1	17.59	11.63	57,560	175,120	291,460	4	3
Detx2	17.60	11.64	57,784	174,996	291,386	5	5
Detx1	17.57	11.58	58,375	173,165	288,935	6	6
NPHx1	17.54	11.53	57,853	172,647	287,897	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.4 Deterministic results for a population at diagnosis of type 1 diabetes (diabetes duration = 0)

Table HE032: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	18.36	12.19	71,102	172,678	294,568	1	1
NPHx2	18.32	12.04	69,976	170,744	291,104	2	2
GlargU100x1	18.36	11.74	70,951	163,909	281,339	3	3
Degx1	18.32	11.79	73,341	162,419	280,299	4	4
Detx1	18.31	11.77	74,447	160,933	278,623	5	5
NPHx1	18.25	11.50	75,529	154,411	269,381	6	6
GlargU300x1	18.37	11.38	74,333	153,287	267,097	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE033: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	18.36	12.12	71,487	170,993	292,233	1	1
GlargU100x1	18.36	11.94	69,798	168,942	288,312	2	2
NPHx2	18.32	11.93	70,590	168,070	287,400	3	3
Detx1	18.31	11.96	73,300	165,940	285,560	4	4
Degx1	18.32	11.92	72,574	165,766	284,936	5	5
GlargU300x1	18.37	11.86	71,487	165,693	284,283	6	6
NPHx1	18.25	11.70	74,306	159,754	276,784	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE034: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU300x1	17.62	11.65	56,422	176,598	293,108	1	5
GlargU100x1	18.36	12.25	68,490	176,430	298,890	2	1
Detx2	18.36	12.19	71,102	172,678	294,568	3	2
NPHx2	18.32	12.12	69,746	172,674	293,884	4	3
Degx1	18.32	12.16	71,500	171,760	293,390	5	4
Detx1	18.31	12.11	72,609	169,631	290,751	6	6
NPHx1	18.25	12.04	72,928	167,872	288,272	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.5 Deterministic results for a young population (mean age = 32)

Table HE035: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	20.92	13.76	85,503	189,717	327,327	1	1
NPHx2	20.86	13.58	83,899	187,741	323,561	2	2
GlargU100x1	20.93	13.27	85,114	180,206	312,866	3	3
Degx1	20.89	13.32	87,637	178,683	311,843	4	4
Detx1	20.88	13.30	88,835	177,065	310,015	5	5
NPHx1	20.83	13.00	89,808	170,252	300,282	6	6
GlargU300x1	20.92	12.85	88,831	168,149	296,639	7	7

(a) Ranked in descending order according to net monetary benefit at

Table HE036: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	20.92	13.69	85,938	187,822	324,702	1	1
GlargU100x1	20.93	13.49	83,807	185,893	320,743	2	2
NPHx2	20.86	13.47	84,594	184,706	319,356	3	3
Detx1	20.88	13.51	87,532	182,748	317,888	4	4
Degx1	20.89	13.46	86,767	182,453	317,063	5	5
GlargU300x1	20.92	13.39	85,612	182,168	316,058	6	6
NPHx1	20.83	13.24	88,421	176,319	308,689	7	7

(a) Ranked in descending order according to net monetary benefit at

Table HE037: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	20.93	13.84	82,326	194,374	332,724	1	1
GlargU300x1	20.92	13.76	84,043	191,237	328,877	2	2
NPHx2	20.86	13.68	83,638	189,922	326,702	3	4
Detx2	20.92	13.76	85,503	189,717	327,327	4	3
Degx1	20.89	13.74	85,550	189,270	326,680	5	5
Detx1	20.88	13.68	86,751	186,929	323,769	6	6
NPHx1	20.83	13.62	86,861	185,499	321,679	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.6 Deterministic results for an older population (mean age = 62)

Table HE038: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
NPHx2	12.76	8.43	28,323	140,297	224,607	1	2
Detx2	12.76	8.51	30,183	140,077	225,207	2	1
GlargU100x1	12.78	8.21	30,037	134,243	216,383	3	4
Degx1	12.76	8.25	30,879	134,061	216,531	4	3
Detx1	12.75	8.24	31,398	133,302	215,652	5	5
NPHx1	12.71	8.04	31,212	129,568	209,958	6	6
GlargU300x1	12.76	7.95	32,194	126,706	206,156	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE039: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	12.76	8.47	30,457	138,883	223,553	1	1
NPHx2	12.76	8.36	28,760	138,400	221,980	2	2
GlargU100x1	12.78	8.35	29,217	137,803	221,313	3	3
Detx1	12.75	8.37	30,580	136,880	220,610	4	4
Degx1	12.76	8.34	30,333	136,447	219,837	5	5
GlargU300x1	12.76	8.28	30,170	135,510	218,350	6	6
NPHx1	12.71	8.19	30,340	133,380	215,240	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE040: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	12.78	8.57	28,286	143,134	228,844	1	1
NPHx2	12.76	8.49	28,159	141,681	226,601	2	2
GlargU300x1	12.76	8.52	29,188	141,192	226,382	3	3
Degx1	12.76	8.51	29,569	140,711	225,851	4	4
Detx2	12.76	8.51	30,183	140,077	225,207	5	5
Detx1	12.75	8.48	30,089	139,491	224,281	6	6
NPHx1	12.71	8.43	29,361	139,159	223,419	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.7 Deterministic results for a population with lower levels of baseline HbA1c (mean HbA1c = 6.6%)

Table HE041: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
NPHx2	17.97	12.26	32,634	212,506	335,076	1	2
Detx2	17.99	12.38	35,728	211,852	335,642	2	1
Degx1	17.97	12.01	36,048	204,132	324,222	3	3
GlargU100x1	17.98	11.94	35,268	203,552	322,962	4	5
Detx1	17.98	12.00	36,906	203,094	323,094	5	4
NPHx1	17.95	11.76	35,818	199,302	316,862	6	6
GlargU300x1	17.98	11.59	38,421	193,279	309,129	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE042: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.99	12.32	36,106	210,214	333,374	1	1
NPHx2	17.97	12.16	33,236	209,884	331,444	2	2
GlargU100x1	17.98	12.13	34,138	208,482	329,792	3	4
Detx1	17.98	12.19	35,777	208,003	329,893	4	3
Degx1	17.97	12.14	35,296	207,404	328,754	5	5
GlargU300x1	17.98	12.05	35,630	205,450	325,990	6	6
NPHx1	17.95	11.96	34,615	204,565	324,155	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE043: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.98	12.43	32,857	215,823	340,163	1	1
NPHx2	17.97	12.34	32,408	214,392	337,792	2	2
Degx1	17.97	12.38	34,242	213,298	337,068	3	3
GlargU300x1	17.98	12.38	34,273	213,287	337,067	4	4
NPHx1	17.95	12.29	33,261	212,539	335,439	5	6
Detx2	17.99	12.38	35,728	211,852	335,642	6	5
Detx1	17.98	12.34	35,099	211,641	335,011	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.3.8 Deterministic results for a population with higher levels of baseline HbA1c (mean HbA1c = 11.6%)

Table HE044: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	16.31	10.40	97,385	110,655	214,675	1	1
NPHx2	16.27	10.28	96,079	109,461	212,231	2	2
GlargU100x1	16.32	10.01	97,305	102,895	202,995	3	3
Degx1	16.29	10.06	99,088	102,072	202,652	4	4
Detx1	16.27	10.04	99,781	100,979	201,359	5	5
NPHx1	16.22	9.81	100,383	95,717	193,767	6	6
GlargU300x1	16.32	9.69	99,995	93,705	190,555	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE045: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	16.31	10.35	97,729	109,171	212,621	1	1
GlargU100x1	16.32	10.18	96,274	107,386	209,216	2	2
NPHx2	16.27	10.18	96,628	107,052	208,892	3	3
Detx1	16.27	10.21	98,753	105,447	207,547	4	4
Degx1	16.29	10.17	98,401	105,059	206,789	5	5
GlargU300x1	16.32	10.11	97,451	104,789	205,909	6	6
NPHx1	16.22	9.99	99,289	100,511	200,411	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE046: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	16.32	10.46	95,104	114,096	218,696	1	1
GlargU300x1	16.32	10.41	96,212	111,968	216,058	2	2
NPHx2	16.27	10.35	95,873	111,187	214,717	3	3
Detx2	16.31	10.40	97,385	110,655	214,675	4	4
Degx1	16.29	10.39	97,440	110,440	214,380	5	5
Detx1	16.27	10.35	98,135	108,765	212,215	6	6
NPHx1	16.22	10.29	98,058	107,762	210,672	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.4 Deterministic sensitivity analysis

Results of the sensitivity analysis performed are shown in tables HE047 – HE067, with results staying consistent with the base case in the majority of sensitivity analysis. Exceptions to this rule was when reducing the time horizon to one year and reducing the price of glargine U100 to account for the impact of biosimilars. When reducing the time

horizon to one year, NPH twice daily ranked higher across all three scenarios, being the most cost-effective treatment option in scenarios 1 and 2 (table HE047, HE048). This was due to a combination of NPHs lower prices, and a one-year model not taking into account the long-term benefits from a reduction in HbA1c levels.

Our sensitivity analysis on the price of glargine U100 showed that price of a 5x3ml pack of a biosimilar for glargine U100 would have to be at least 39% cheaper than the current branded glargine U100 price for it to be cost-effective in scenario 2 at a WTP of £20,000 per QALY (table HE063). At present the cheapest biosimilar for Glargine U100, Semglee, is around 20.6% cheaper. In scenario 1 (table HE062), the differences in hypoglycaemic event rates between glargine U100 once daily and detemir twice daily were too large for a reduction in the price of glargine to impact the treatment decision.

HE3.4.1 Sensitivity analysis 1 (time horizon = 1 year)

Table HE047: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
NPHx2	0.96	0.68	808	12,832	19,652	1	1
Detx2	0.96	0.69	981	12,759	19,629	2	2
Degx1	0.96	0.67	1,005	12,375	19,065	3	3
Detx1	0.96	0.67	1,035	12,325	19,005	4	4
GlargU100x1	0.96	0.66	983	12,297	18,937	5	5
NPHx1	0.96	0.66	962	12,178	18,748	6	6
GlargU300x1	0.96	0.65	1,131	11,769	18,219	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE048: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
NPHx2	0.96	0.68	839	12,701	19,471	1	2
Detx2	0.96	0.68	1,001	12,679	19,519	2	1
Detx1	0.96	0.68	975	12,585	19,365	3	3
GlargU100x1	0.96	0.67	924	12,556	19,296	4	4
Degx1	0.96	0.68	965	12,535	19,285	5	5
NPHx1	0.96	0.67	898	12,462	19,142	6	6
GlargU300x1	0.96	0.67	984	12,416	19,116	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE049: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	0.96	0.69	857	12,943	19,843	1	1
NPHx2	0.96	0.69	796	12,924	19,784	2	2
NPHx1	0.96	0.69	827	12,873	19,723	3	4
Degx1	0.96	0.69	910	12,850	19,730	4	3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU300x1	0.96	0.69	913	12,827	19,697	5	5
Detx1	0.96	0.69	940	12,780	19,640	6	6
Detx2	0.96	0.69	981	12,759	19,629	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.4.2 Sensitivity analysis 2 (basal and bolus dose = 24 units per day)

Table HE050: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.54	52,901	177,799	293,149	1	1
NPHx2	17.40	11.40	52,200	175,760	289,740	2	2
GlargU100x1	17.42	11.11	53,937	168,343	279,483	3	5
Detx1	17.41	11.16	55,071	168,029	279,579	4	3
Degx1	17.41	11.17	55,600	167,840	279,560	5	4
NPHx1	17.35	10.89	55,759	162,121	271,061	6	6
GlargU300x1	17.43	10.77	56,051	159,269	266,929	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE051: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.47	53,267	176,213	290,953	1	1
NPHx2	17.40	11.30	52,784	173,216	286,216	2	3
GlargU100x1	17.42	11.30	52,840	173,140	286,130	3	4
Detx1	17.41	11.34	53,976	172,824	286,224	4	2
GlargU300x1	17.43	11.22	53,345	171,035	283,225	5	6
Degx1	17.41	11.29	54,871	171,009	283,949	6	5
NPHx1	17.35	11.09	54,594	167,226	278,136	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE052: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	51,595	180,245	296,165	1	1
GlargU300x1	17.43	11.54	52,028	178,672	294,022	2	2
Detx2	17.43	11.54	52,901	177,799	293,149	3	3
NPHx2	17.40	11.48	51,982	177,598	292,388	4	4
Degx1	17.41	11.53	53,846	176,734	292,024	5	5
Detx1	17.41	11.48	53,318	176,322	291,142	6	6
NPHx1	17.35	11.41	53,283	174,937	289,047	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.4.3 Sensitivity analysis 3 (discount rate = 1.5%)

Table HE053: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	23.31	15.31	84,447	221,753	374,853	1	1
NPHx2	23.25	15.11	81,952	220,328	371,468	2	2
GlargU100x1	23.30	14.74	83,638	211,142	358,532	3	3
Degx1	23.28	14.81	86,206	210,034	358,154	4	4
Detx1	23.27	14.79	86,911	208,869	356,759	5	5
NPHx1	23.17	14.43	88,232	200,308	344,578	6	6
GlargU300x1	23.31	14.27	88,270	197,170	339,890	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE054: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	23.31	15.23	84,939	219,621	371,901	1	1
GlargU100x1	23.30	14.99	82,161	217,599	367,479	2	2
NPHx2	23.25	14.98	82,737	216,903	366,723	3	3
Detx1	23.27	15.04	85,439	215,301	365,671	4	4
Degx1	23.28	14.98	85,225	214,295	364,055	5	5
GlargU300x1	23.31	14.88	84,630	213,030	361,860	6	6
NPHx1	23.17	14.69	86,668	207,152	354,062	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE055: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	23.30	15.38	80,487	227,173	381,003	1	1
GlargU300x1	23.31	15.31	82,858	223,282	376,352	2	2
NPHx2	23.25	15.22	81,659	222,781	375,001	3	3
Degx1	23.28	15.29	83,848	222,012	374,942	4	4
Detx2	23.31	15.31	84,447	221,753	374,853	5	5
Detx1	23.27	15.23	84,554	220,026	372,316	6	6
NPHx1	23.17	15.12	84,906	217,534	368,754	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.4.4 Sensitivity analysis 4 (baseline QoI = 0.785)

Table HE056: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.41	55,429	172,731	286,811	1	1
NPHx2	17.40	11.28	53,444	172,096	284,866	2	2
GlargU100x1	17.42	10.99	54,934	164,806	274,676	3	4
Degx1	17.41	11.05	56,650	164,330	274,820	4	3
Detx1	17.41	11.03	57,151	163,509	273,839	5	5
NPHx1	17.35	10.78	57,886	157,694	265,484	6	6
GlargU300x1	17.43	10.64	58,295	154,485	260,875	7	7

(b) Ranked in descending order according to net monetary benefit

Table HE057: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.35	55,795	171,145	284,615	1	1
GlargU100x1	17.42	11.17	53,836	169,584	281,294	2	3
NPHx2	17.40	11.18	54,028	169,552	281,342	3	2
Detx1	17.41	11.22	56,056	168,284	280,454	4	4
Degx1	17.41	11.17	55,920	167,500	279,210	5	5
GlargU300x1	17.43	11.09	55,589	166,271	277,201	6	6
NPHx1	17.35	10.98	56,722	162,778	272,528	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE058: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.47	52,592	176,708	291,358	1	1
NPHx2	17.40	11.36	53,226	173,934	287,514	2	3
GlargU300x1	17.43	11.41	54,271	173,889	287,969	3	2
Degx1	17.41	11.41	54,896	173,224	287,284	4	4
Detx2	17.43	11.41	55,429	172,731	286,811	5	5
Detx1	17.41	11.36	55,399	171,801	285,401	6	6
NPHx1	17.35	11.30	55,410	170,510	283,470	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.4.5 Sensitivity analysis 5 (price of Glargine U100 = price of Semglee)

Table HE059: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.54	55,429	175,271	290,621	1	1
NPHx2	17.40	11.40	53,444	174,516	288,496	2	2
GlargU100x1	17.42	11.11	54,108	168,172	279,312	3	3
Degx1	17.41	11.17	56,650	166,790	278,510	4	4
Detx1	17.41	11.16	57,151	165,949	277,499	5	5
NPHx1	17.35	10.89	57,886	159,994	268,934	6	6
GlargU300x1	17.43	10.77	58,295	157,025	264,685	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE060: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.47	55,795	173,685	288,425	1	1
GlargU100x1	17.42	11.30	53,011	172,969	285,959	2	2
NPHx2	17.40	11.30	54,028	171,972	284,972	3	3
Detx1	17.41	11.34	56,056	170,744	284,144	4	4
Degx1	17.41	11.29	55,920	169,960	282,900	5	5
GlargU300x1	17.43	11.22	55,589	168,791	280,981	6	6
NPHx1	17.35	11.09	56,722	165,098	276,008	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE061: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	51,767	180,073	295,993	1	1
GlargU300x1	17.43	11.54	54,271	176,429	291,779	2	2
NPHx2	17.40	11.48	53,226	176,354	291,144	3	3
Degx1	17.41	11.53	54,896	175,684	290,974	4	4
Detx2	17.43	11.54	55,429	175,271	290,621	5	5
Detx1	17.41	11.48	55,399	174,241	289,061	6	6
NPHx1	17.35	11.41	55,410	172,810	286,920	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.4.6 Sensitivity analysis 6 (threshold analysis on price of Glargine U100 - reduced by 39%)

Table HE062: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.54	55,429	175,271	290,621	1	1
NPHx2	17.40	11.40	53,444	174,516	288,496	2	2
GlargU100x1	17.42	11.11	53,372	168,908	280,048	3	3
Degx1	17.41	11.17	56,650	166,790	278,510	4	4
Detx1	17.41	11.16	57,151	165,949	277,499	5	5
NPHx1	17.35	10.89	57,886	159,994	268,934	6	6
GlargU300x1	17.43	10.77	58,295	157,025	264,685	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE063: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.30	52,275	173,705	286,695	1	2
Detx2	17.43	11.47	55,795	173,685	288,425	2	1
NPHx2	17.40	11.30	54,028	171,972	284,972	3	3
Detx1	17.41	11.34	56,056	170,744	284,144	4	4
Degx1	17.41	11.29	55,920	169,960	282,900	5	5
GlargU300x1	17.43	11.22	55,589	168,791	280,981	6	6
NPHx1	17.35	11.09	56,722	165,098	276,008	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE064: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	51,030	180,810	296,730	1	1
GlargU300x1	17.43	11.54	54,271	176,429	291,779	2	2
NPHx2	17.40	11.48	53,226	176,354	291,144	3	3
Degx1	17.41	11.53	54,896	175,684	290,974	4	4
Detx2	17.43	11.54	55,429	175,271	290,621	5	5
Detx1	17.41	11.48	55,399	174,241	289,061	6	6
NPHx1	17.35	11.41	55,410	172,810	286,920	7	7

Ranked in descending order according to net monetary benefit

HE3.4.7 Sensitivity analysis 7 (doubling the proportion of nocturnal hypoglycaemic events)

Table HE065: Scenario 1

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.48	55,429	174,131	288,911	1	1
NPHx2	17.40	11.32	53,444	172,936	286,126	2	2
GlargU100x1	17.42	11.11	54,934	167,206	278,276	3	3
Degx1	17.41	11.12	56,650	165,810	277,040	4	4
Detx1	17.41	11.07	57,151	164,209	274,889	5	5
NPHx1	17.35	10.79	57,886	157,914	265,814	6	6
GlargU300x1	17.43	10.70	58,295	155,625	262,585	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE066: Scenario 2

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	17.43	11.42	55,795	172,545	286,715	1	1
GlargU100x1	17.42	11.29	53,836	172,024	284,954	2	2
NPHx2	17.40	11.22	54,028	170,372	282,572	3	3
Detx1	17.41	11.25	56,056	169,024	281,564	4	4
Degx1	17.41	11.25	55,920	168,980	281,430	5	5
GlargU300x1	17.43	11.15	55,589	167,491	279,031	6	6
NPHx1	17.35	10.99	56,722	163,058	272,948	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE067: Scenario 3

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	17.42	11.59	52,592	179,188	295,078	1	1
GlargU300x1	17.43	11.48	54,271	175,269	290,039	2	2
NPHx2	17.40	11.40	53,226	174,854	288,894	3	5
Degx1	17.41	11.49	54,896	174,804	289,654	4	3
Detx2	17.43	11.48	55,429	174,131	288,911	5	4
Detx1	17.41	11.40	55,399	172,621	286,631	6	6
NPHx1	17.35	11.32	55,410	171,010	284,220	7	7

(a) Ranked in descending order according to net monetary benefit

HE3.5 Probabilistic sensitivity analysis

Probabilistic results for scenarios 1-3 are reported below in tables HE068, HE069 and HE070 with the treatment order not differing from the deterministic results. For the 2 highest ranking treatments in each scenario the cost-effectiveness acceptability curves are shown in figures

HE006-HE008. Additionally the CEACs comparing the 2 highest ranking once daily regimens in scenario 1 is shown in figure HE009. The highest ranking once daily regimen in scenarios 2 and 3 (glargine U100 once daily) was a part of the top 2 ranking treatments overall.

Table HE068: Base-case probabilistic cost–utility results (scenario 1)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	16.08	10.77	61,820	153,480	261,130	1	1
NPHx2	16.04	10.63	60,117	152,503	258,813	2	2
GlargU100x1	16.08	10.38	61,573	145,947	249,707	3	3
Degx1	16.05	10.42	62,953	145,467	249,677	4	4
Detx1	16.05	10.41	63,851	144,329	248,419	5	5
NPHx1	16.00	10.18	64,183	139,397	241,187	6	6
GlargU300x1	16.07	10.05	64,407	136,553	237,033	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE069: Base-case probabilistic cost–utility results (scenario 2)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
Detx2	16.08	10.71	62,159	152,021	259,111	1	1
GlargU100x1	16.08	10.55	60,555	150,385	255,855	2	2
NPHx2	16.04	10.54	60,659	150,141	255,541	3	3
Detx1	16.05	10.58	62,835	148,765	254,565	4	4
Degx1	16.05	10.53	62,275	148,405	253,745	5	5
GlargU300x1	16.07	10.47	61,897	147,483	252,173	6	6
NPHx1	16.00	10.36	63,101	144,119	247,729	7	7

(a) Ranked in descending order according to net monetary benefit

Table HE070: Base-case probabilistic cost–utility results (scenario 3)

Insulin regimen	Discounted			Net monetary benefit		Ranking[a]	
	Life Years	QALYs	Costs (£)	£20K/QALY	£30K/QALY	£20K/QALY	£30K/QALY
GlargU100x1	16.08	10.82	59,401	156,979	265,169	1	1
GlargU300x1	16.07	10.76	60,675	154,545	262,155	2	2
NPHx2	16.04	10.71	59,914	154,206	261,266	3	3
Degx1	16.05	10.75	61,327	153,713	261,233	4	4
Detx2	16.08	10.77	61,820	153,480	261,130	5	5
Detx1	16.05	10.71	62,224	152,016	259,136	6	6
NPHx1	16.00	10.66	61,885	151,275	257,855	7	7

(a) Ranked in descending order according to net monetary benefit

Figure HE006: Cost-effectiveness acceptability curve to top 2 ranking treatments (scenario 1)

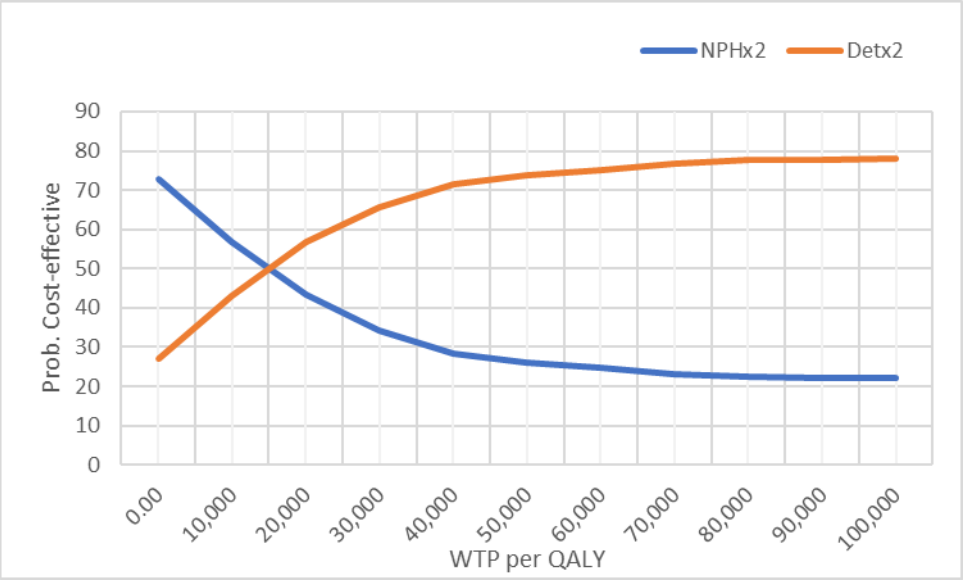


Figure HE007: Cost-effectiveness acceptability curve to top 2 ranking treatments (scenario 2)

Figure HE008: Cost-effectiveness acceptability curve to top 2 ranking treatments (scenario 3)

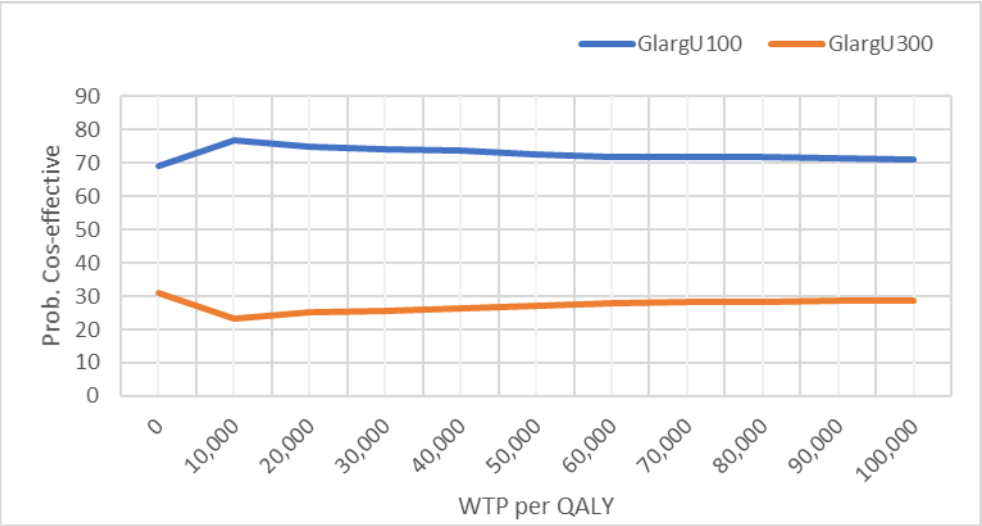
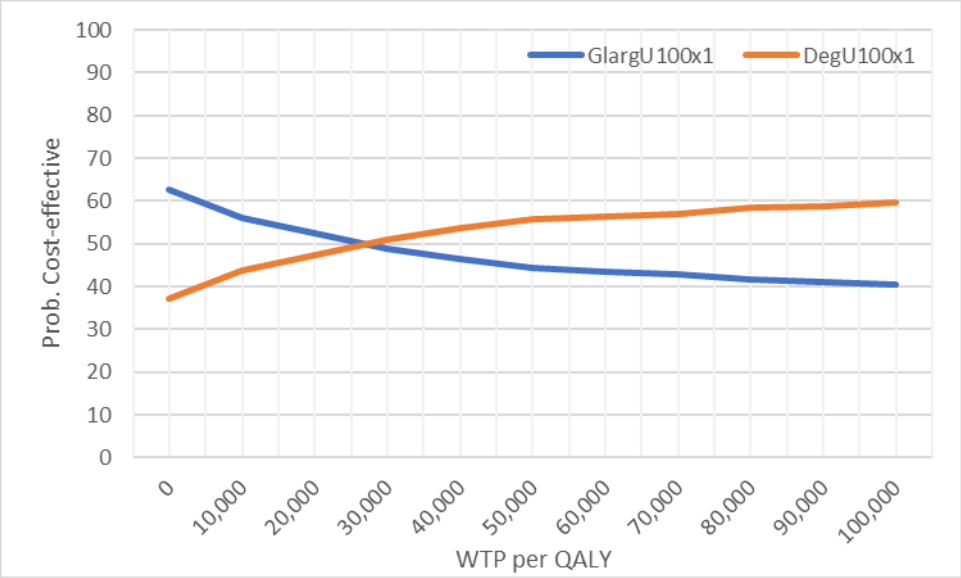


Figure HE009: Cost-effectiveness acceptability curve to top 2 ranking once daily insulin regimens (scenario 1)



HE3.6 Discussion

HE3.6.1 Principal findings

In scenario 1 where all the results from the NMA of severe and all hypoglycaemic events was incorporated into our economic analysis, detemir twice daily was the most cost-effective treatment option in both the deterministic and probabilistic results. This held across all sensitivity analysis, except when limiting the time horizon to one year (where the cheapest treatment option of NPH twice daily was the most cost-effective). In scenario 1, glargine U100 once daily was the most cost-effective once daily insulin regimen at a WTP of £20,000. Degludec U100 was the most cost-effective once daily insulin regimen at a WTP of £30,000, except in a scenario where the price of glargine U100 was reduced to that of its cheapest biosimilar (Semglee). Treatment decisions in the base case for scenario 1 broadly held across most subgroups barring an older population and a population with lower baseline levels of HbA1c where NPH twice daily was the most cost-effective at a WTP of £20,000 per QALY. The preference for NPH twice daily was due to a combination of its cheaper price, the

shorter life expectancy in older people which resulted in them not experience the long-term benefits due to reduced HbA1c levels offered by other insulin regimens for as long a period of time, and the effects of reductions in HbA1c by other insulin regimens being dampened in populations with lower baseline levels of HbA1c.

In scenario 2 where results of all hypoglycaemic events from the NMA were combined with proportions of severe hypoglycaemic events in RCTs, detemir twice daily remained the most cost-effective treatment option in both the deterministic and probabilistic analysis. Glargine U100 once daily was the second most cost-effective across all regimens, and the most cost-effective amongst once daily regimens. Glargine ranked higher in scenario 2 due to differences in severe hypoglycaemic events between glargine U100 once daily and other regiments being smaller when compared to scenario 1 (because the NMA for all hypoglycaemic events found a smaller benefit for detemir versus glargine than the NMA for severe hypoglycaemic events). The results in the base case held across sensitivity analysis except when limiting the time horizon to one year and in a scenario where the price of glargine U100 was reduced by 39% which resulted in glargine U100 being the most cost-effective treatment strategy at a WTP of £20,000 per QALY. The most cost-effective treatment option in scenario 2 did not change in specific subgroups.

Scenario 3, where no differences in hypoglycaemic events were assumed across insulin regimens, reported results favouring regimens which resulted in the largest decrease in HbA1c levels.

This economic analysis is directly applicable to an adult type 1 diabetes population in the UK. Generalisability of its results to a population or setting not include in the guideline scope would be inappropriate.

HE3.6.2 Weaknesses of the analysis

As common with economic analysis of this nature, there was uncertainty around the model input parameters. However, the treatment decision remained the same across both the probabilistic and deterministic results. Further evaluations were done across three scenarios in the base case analysis and across a number of deterministic sensitivity analysis to account for this.

There was significant uncertainty around the estimates of all and severe hypoglycaemic events from the NMAs conducted. To account for this, three scenarios were used in our base case to account for hypoglycaemic events. Detemir twice daily was the most cost-effective treatment option in both scenarios 1 and 2, whilst as expected the regimen with the largest reduction in HbA1c levels was the most cost-effective in scenario 3 where no differences in hypoglycaemic events were assumed.

In our analysis the baseline factors were sourced from various UK specific sources. However, the lack of a single data source to obtain all baseline risk factors meant that covariances between baseline risk factors could not be accounted for. This particularly hampered our subgroup analysis where in an ideal situation all associated baseline risk factors would have changed through associated covariances once the baseline risk factor specific to the subgroup was changed.

Our subgroup analysis was also limited by a lack of information on how treatment effects differed between subgroups. This outlined the need for further research if recommendations are to be made for specific subgroups.

When sourcing data of model input parameters, an attempt was made to include data applicable to a type 1 diabetes population where appropriate. However, in some cases data from type 2 populations had to be used due to a lack of reliable type 1 data sources. This included the data sources from impact on quality of life from long-term diabetes related complications. These data sources were however checked with committee who advised that

the impact on quality of life from long-term diabetes related complications are unlikely to change between type 1 and type 2 patients. The economic analysis also does not incorporate the impact on quality of life from flexible dosing regimens, and patient disutility due to multiple injections. The only available data source for this information had not reported results by type of diabetes, and the committee believed the impact on quality of life from multiple injections and flexible dosing regimens are likely to differ between type 1 and type 2 patients due to the younger average age of type 1 patients.

HE3.6.3 Comparison with other CUAs

The literature review of economic evidence identified 27 CUAs, 10 of which were based in the UK. Of these only the CUA developed for NG17 by Dawoud et al[14] is directly comparable to our analysis as it is the only CUA to consider all available insulin therapies stratified by dosing frequency over a lifetime time horizon. There were a number of important differences between our analysis and Dawoud et al. Firstly Dawoud et al only accounted for severe hypoglycaemic events and did not consider differences in non-severe hypoglycaemic events between insulin regimens. Secondly Dawoud et al did not consider the impact on nocturnal hypoglycaemic events, especially with regard to its impact on quality of life. Thirdly Dawoud et al assumed a flat daily dose of 24 units per insulin regimen, whereas differences in daily doses insulin regimens have been accounted for in our analysis.

Despite the differences in highlighted above, Dawoud et al reported that detemir twice daily was the most cost-effective treatment strategy which mimics our base case findings in scenarios 1 and 2. However Dawoud et al ranks the glargine once daily insulin regimen second in terms of cost-effectiveness which is in line with our base case results from scenario 2 but differs from scenario 1 where NPH twice daily ranks second. These differences are due to the results of the NMA of severe hypoglycaemic events, which reported higher severe hypoglycaemic event rates for glargine U100 once daily. These higher rates were primarily driven by data from Pieber et al[55] which was not included in Dawoud et al.

Of the other CUAs based in the UK, 4 were industry funded studies based on a time horizon of one year and only accounted for differences in hypoglycaemic events between insulins. Of these, three studies[3,11,12] compared degludec vs glargine, reporting results favouring degludec while Pollock et al[2] compared detemir vs NPH, with results favouring detemir. The results of the studies comparing degludec vs glargine were in line with the scenario 1 treatment decisions in sensitivity analysis 1 where the time horizon was limited to one year. However, results from Pollock et al reported a contrasting treatment decision to our analysis when limited to one year, with Pollock et al sourcing clinical effectiveness data from a meta-analysis published in 2010 and only including non-severe hypoglycaemic events.

Of the 5 long-term CUAs based in the UK, Warren et al[17] compared Glargine vs NPH, conducting an analysis across 9 years but only accounting for hypoglycaemic events. The CUA by Evans et al[13] which reported results favouring degludec when compared to “other basal insulin” was based on clinical data by a single case series analysis of 35 type 1 diabetes patients. Two long-term CUAs[18,26] based on the CORE model comparing Detemir vs NPH (dosing frequency not reported) reported results favouring detemir. The remaining long-term CUA based in the UK[27] compared glargine vs NPH, with results favouring glargine. However, there was a lack of clarity on whether the NPH arm included was a once or twice daily regimen.

HE3.7 Conclusions

Our economic analysis was based on information from the systematic review of current clinical evidence and a range of other model input parameters including costs and quality of life which were sourced following input from the committee. Three scenarios were considered

in the base case, to account for uncertainty surround the treatment effects on severe and all hypoglycaemic events.

When incorporating information from all the NMAs performed (scenario 1) the two twice daily regimens, detemir twice daily and NPH twice daily, ranked first and second in terms of cost-effectiveness. Amongst the once daily regimens glargine U100 once daily was the most cost-effective option at a WTP of £20,000 per QALY, with this changing to degludec U100 once daily at a WTP of £30,000 per QALY. Results remained robust across sensitivity analysis, except when reducing the time horizon to one year. Treatment decisions only differed in the elderly and in a population with low levels of baseline HbA1c at a WTP of £20,000. However, the subgroup analysis had severe limitation and highlighted the need for further research.

When excluding the results from the NMA of severe hypoglycaemic events (scenario 2) due to the large levels of uncertainty surrounding point estimates, detemir twice daily was still the most cost-effective treatment strategy. However, glargine U100 once daily ranked second in this scenario. A sensitivity analysis showed that a 39% price reduction in a 5x3ml pack of glargine U100 resulted in it being the most cost-effective treatment option.

Results from scenario 3 showed that regimens with the highest point estimates for reduction in HbA1c levels were more cost-effective. This was expected as in scenario 3 no difference in hypoglycaemic event rates between insulin regimens were assumed.

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