National Institute for Health and Care Excellence

Draft for consultation

Type 1 diabetes in adults: diagnosis and management

Economic modelling for continuous glucose monitoring in adults with type 1 diabetes

NICE guideline NG17

Economic model report

November 2021

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funding
<Please insert your statement here

Contents

HE1 Introduction

Given the costs and impact on health-related quality of life associated with hypoglycaemia and long-term complications of type 1 diabetes and unstable HbA1c control, the cost-effectiveness of real-time continuous glucose monitoring (rtCGM) and flash glucose monitoring isCGM) versus conventional self-monitoring of blood glucose (SMBG) was identified by the guideline committee as an area of priority for economic analysis.

The review question addressed in this analysis is:

- In adults with type 1 diabetes, what is the most effective method of glucose monitoring to improve glycaemic control:
  - continuous glucose monitoring
  - flash glucose monitoring
  - conventional self-monitoring of blood glucose (also sometimes called intermittent capillary blood glucose monitoring)?

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

In the economic literature review two cost-utility analyses (CUAs) were identified looking at the cost-effectiveness of glucose monitoring methods to improve glycaemic control in adults with type 1 diabetes in the UK context. Healthcare Improvement Scotland[1] assessed the Freestyle Libre flash glucose monitoring method for both type 1 and type 2 diabetes patients, while Roze et al[2] examined the cost-effectiveness of real-time continuous glucose monitoring among people with type 1 diabetes. Both studies showed that automated glucose monitoring methods are likely to be cost effective compared with SMBG. However, both of these analyses were only based on a single RCT, rather than all the available clinical evidence, and therefore the committee agreed there was value in additional work being undertaken.

Table HE001: Health economic decision problem

Population	Adults (aged 18 years and older) with type 1 diabetes
Intervention	Method of glucose monitoring to improve glycaemic control: • real-time continuous glucose monitoring • flash glucose monitoring
Comparator	Conventional self-monitoring of blood glucose
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, automated glucose monitoring methods 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 blood glucose monitoring methods, taking into account the benefits of lowering HbA1c levels and reducing severe and non-severe hypoglycaemic events. In addition, diabetes-specific and broader psychological benefits were also considered in the model as the technologies have a potential to enhance people's ability to manage their glucose levels and help them regain a sense of personal control over the condition.

HE2.1.1 Population(s)

The primary analysis looked at a cohort of adults representing average individuals with type 1 diabetes in the UK.

HE2.1.2 Interventions

The analysis simulates the following methods of glucose monitoring:

- real-time continuous glucose monitoring
- flash glucose monitoring
- self-monitoring of blood glucose

Analyses of real-time continuous glucose monitoring versus self-monitoring of blood glucose, and flash glucose monitoring versus self-monitoring of blood glucose were conducted. The committee agreed an analysis of real-time versus flash monitoring would not be useful. This was because of the limited clinical data available for this comparison, and because the choice of device often depended on individual characteristics of the person, and therefore the average cost-effectiveness across the population may not be particularly useful.

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[3] against epidemiological and clinical studies of type 1 diabetes. A more detailed description of IQVIA CDM has been published by Palmer et al[4].

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.

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 model 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 model were validated with the committee and, if found appropriate, were used. In a scenario where more reliable or recent UK specific sources were identified, these were used instead. Table HE002 to Table HE010 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, identifying relevant published studies through citation searching of the studies identified through the cost-effectiveness literature review, targeted literature searches, and through studies identified by committee members.

HE2.3.1 Cohort parameters

HE2.3.1.1 Baseline cohort characteristics

Within the IQVIA CDM model the baseline population needs to be defined in terms of patient's demographics, baseline risk factors, and pre-existing complications. These characteristics were sourced from a range of UK specific type 1 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 trial[6], 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 1,000 patients using the IQVIA CDM. Note that for characteristics where the standard deviation was kept at 0, the mean values were kept static when patient cohort was simulated. The simulated patient cohort also does not take into account correlations between risk factors.

Table HE002: Baseline cohort characteristics

Baseline characteristic	Mean	SD	Source/ Comments
Patient demographics			
Age (years)	46.53	12.13	National Diabetes Audit 2019-20[5] Type 1 Diabetes Report: age and duration of diabetes were calculated by obtaining weighted averages since they were reported for categories of patients, rather than as a single mean age.
Duration of Diabetes (years)	21	13.48	
Prop. Male	0.569	n/a	
Baseline risk factors			
HbA1c (%)	9.1	1.7	REPOSE[6] – a cluster randomised trial of 267 adults with type 1 diabetes in the UK recruited from November 2011 to

Baseline characteristic	Mean	SD	Source/ Comments
			December 2012. Conversion to mmol/mol: mean 75.96mmol/mol.
Systolic blood pressure (mmHg)	131.3	16.3	REPOSE[6]
Diastolic blood pressure (mmHg)	80	0	IQVIA CDM default value[7]
Total Cholesterol (mg/dL)	90	16.2	REPOSE[6]; Conversion to mmol/l: mean 2.33mmol/l; SD 0.42mmol/l.
High density cholesterol (mg/dL)	28.8	7.2	REPOSE[6]; Conversion to mmol/l: mean 0.74mmol/l; SD 0.19mmol/l.
Low density cholesterol (mg/dL)	50.4	16.2	REPOSE[6]; Conversion to mmol/l: mean 1.30mmol/l; SD 0.42mmol/l.
Triglyceride (mg/dL)	25.2	18	REPOSE[6]; Conversion to mmol/l: mean 0.28mmol/l; SD 0.20mmol/l.
Body mass index (kg/m^2)	27.2	5	REPOSE[6]
estimated glomerular filtration rate (ml/min/1.72m^2)	78.58	13.24	REPOSE[6] - calculated by obtaining weighted averages since they were reported for categories of patients
Haemoglobin (gr/dl)	14.5	0	IQVIA CDM default value[8]
White blood cell count (10^6/ml)	6.8	0	IQVIA CDM default value[8]
Heart rate (bpm)	72	0	IQVIA CDM default value[8]
Waist to hip ratio	0.93	0	IQVIA CDM default value[8]
Waist circumference	87.84	n/a	IQVIA CDM default value[9]
Urinary Albumin creatinine ratio (mg/mmol)	4.78	10.19	REPOSE[6] - calculated by obtaining weighted averages since they were reported for categories of patients
Serum Creatinine (mg/dL)	1.1	0	IQVIA CDM default value[9]; Conversion to µmol/L: mean 97.24 µmol/l.
Serum Albumin (g/dl)	3.9	0	IQVIA CDM default value[9]; Conversion to g/l: mean 39g/l.
Prop. Smoker	0.192	n/a	REPOSE[6]
Cigarettes/ day	15	n/a	Health Survey for England 2017 & 2018[10] – calculated from the subset of individuals with diabetes
Alcohol consumption (Oz/week)	7.7	n/a	WHO status report on alcohol 2018[11] (converted from l/year to oz/week)
Prop. Physical activity	0.620	n/a	Health Survey for England 2017 & 2018[10] – calculated from the subset of individuals with type 1 diabetes
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	0.942	n/a	National Diabetes Audit 2019-20[5] Type 1 Diabetes Report
Prop. Black	0.023	n/a	
Prop. Asian/ Pacific islander	0.035	n/a	
Baseline CVD complications			
Prop. MI	0.022	n/a	REPOSE[6]
Prop. Angina	0.012	n/a	REPOSE[6]

Baseline characteristic	Mean	SD	Source/ Comments
Prop. Peripheral vascular disease	0	n/a	Assumption
Prop. Stroke	0.003	n/a	REPOSE[6]
Prop. Heart failure	0.006	n/a	REPOSE[6]
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[6]
Prop. Gross proternuria (GPR)	0.045	n/a	REPOSE[6]
Prop. End stage renal disease (ESRD)	0	n/a	Assumption
Baseline retinopathy complications			
Prop. Background retinopathy (BDR)	0.348	n/a	REPOSE[6]
Prop. Proliferative diabetic retinopathy (PDR)	0.093	n/a	REPOSE[6]
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[6]

HE2.3.112 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 to 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).

HE2.3.42 Economics

HE2.3.251 Cost

Default values for costs of chronic and recurrent conditions, and complication costs in the IQVIA CDM model were updated to reflect those of contemporary clinical practice in the UK. Costs for medicines were taken from the NHS Drug Tariff, 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[15]. For the probabilistic analysis values were altered within a range of plus/minus 10%. Note that IQVIA CDM only allows for a single measure of variability across all cost parameters.

Table HE003: Management and complication costs

Input variables	Mean cost per year*	Source/ Comments
Management costs		
Statins	£27.38	Atorvastatin 80 mg tablets x 28 days (unit price: £2.10) - NHS Electronic Drug Tariff June 2021[12]
Aspirin	£16.43	Aspirin 75 mg tablets x 28 days (unit price: £1.26) - NHS Drug Electronic Tariff June 2021[12]
ACE-I/ARB	£22.84	Weighted (by use as reported by Prescription Cost Analysis data March 2021[13]) average costs of: ACE-I/ARB (Source: NHS Electronic Drug Tariff June 2021[12]) Enalapril (10mg x 28; Unit price: £7.04) Lisinopril (10mg tablets x 28; Unit price: £1.08) Perindopril arginine (10mg tablets x 30; Unit price: £10.65) Ramipril (10mg tablets x 30; Unit price: £1.42) Candesartan (8mg tablets x 28; Unit price: £1.54) Eprosartan (600mg tablets x 28; Unit price: £18.16) Losartan (50mg tabletsx 28; Unit price: £1.45) Telmisartan (40mg tablets x 28; Unit price: £2.69)
Screening for micro-albuminuria	£4.25	Cost of ACR/PCR testing from Kerr et al (2012)[14] 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[15]
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		

Input variables	Mean cost per year*	Source/ Comments
MI 1st year	£4,076	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[12], procedure costs from NHS Reference costs, PSSRU Unit Costs of Health & Social Care[15] and the British National Formulary. Assumptions made: 1st year costs were assumed to be cost of first 6 months in event state plus half of 1-year post event state costs. 2nd year costs were assumed to be 1-year post-event state costs. Cost of stroke death within 30 days was assumed to be the cost of a cardiovascular death as reported in CG181. Assumed that one third of angina episodes are stable, and two thirds unstable, based on expert opinion in NG17. This assumption was validated by the committee, with no objections raised. Peripheral arterial disease (PAD) costs from CG181 assumed to be the same as PVD costs.
MI 2nd+ years	£861	
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[16] 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[17] 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[18] 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[17]. **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[12])
Neuropathy 2nd year onwards	£37.10	
Active ulcer	£3,520	Kerr et al (2019)[19] - 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

HE2.3.222 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).

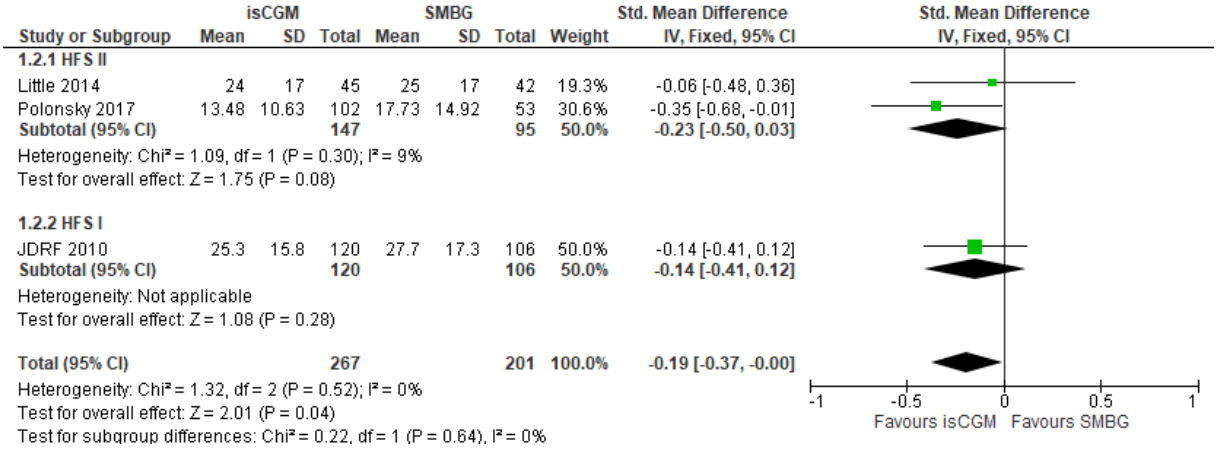
Sources for impact of quality of life by severe and non-severe hypoglycaemic events were identified by looking at primary sources for quality-of-life parameters from our systematic review of economic evidence. The most commonly used sources in the literature were studies by Currie et al[20] and Evans et al[21].

Currie et al[20] sourced information from two surveys conducted in 2000 and 2004 among 1,305 respondents with diabetes. Impact on quality of life was measured using the EQ-5D instrument with the fear of hypoglycaemia measured using the Hypoglycaemia Fear Survey (HFS). Results were based on a multivariate analysis with pooled data used to explore the relationship between frequency of hypoglycaemic events and fear of hypoglycaemia (HFS values). Then the HFS values in conjunction with other independent variables was used to predict the EQ-5D values. Currie et al[20] 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[21] 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[22] was used as it was based on the same data set as Evans et al[21].

A direct utility benefit associated with using a isCGM device is included in the model, with the utility data derived from Matza et al[23], which aimed to quantify the ‘process utility’ associated with isCGM compared with SMBG (i.e. the direct quality of life benefits from using isCGM, based on people’s preferences for using the device, over and above the benefits from improved clinical outcomes such as HbA1c and hypoglycaemic events). In time trade-off interviews, the researchers asked general population participants in the United Kingdom (London and Edinburgh) to value health states that were drafted and refined on the basis of literature, clinician input and a pilot study. The health states had identical descriptions of diabetes and insulin treatment, differing only in glucose monitoring approach. This study showed a small but measurable utility benefit for isCGM. No similar study is available for continuous glucose monitoring. However, the committee were confident that the same ‘process utility’ benefits would occur for rtCGM as for flash, and felt it was reasonable to assume the same benefit to isCGM.

For rtCGM, an additional utility benefit associated with reduced fear of hypoglycaemia (FoH) was also considered, assessed by the Hypoglycaemia Fear Survey (HFS). The HFS was first developed in 1987 for adults with type 1 diabetes and has been significantly revised in the following years to be the HFS-II. Both surveys consist of two subscales: 1) Behaviour (HFS-B) that measures behaviours to prevent low blood glucose; 2) Worry (HFS-W) that measures the hypoglycaemia fear. The utility value was derived only from the worry subscale measured by the HFS and then mapped to the EQ-5D based on a published study[24]. The meta-analysis included three studies identified from the clinical review that compared fear of hypoglycaemia between rtCGM and SMBG based on HFS-I and HFS-II surveys[25,26,27] (see the forest plot below).



Another study that adopted the Swedish version of the HFS survey was excluded since the average response values appeared to be quite different from the other two studies, and it was unclear how this questionnaire differed from the English language version[28]. Since the included studies measured the fear of hypoglycaemia using different versions of HFS questionnaires, standardised mean differences (SMD) were used to transform the results to a uniform scale before combining them in the meta-analysis. SMD expresses the difference in means as a proportion of the standard deviation, so that we can combine measures that were based on different scales measuring the same underlying construct. We then converted the results from meta-analysis back to mean differences based on the HFS-I scale using the pooled standard deviation calculated from the study that used the HFS-I questionnaire. The underlying reason is that the mapping study used HFS-I survey to attach utility values based on the EQ-5D questionnaire, and therefore all the values ultimately needed to be on the HFS-1 scale. It was noted that whilst FoH was an important issue for people with diabetes, there was a potential issue with double counting utility gains when this was included (utility gains associated with hypoglycaemic events may capture some of the FoH as well). Therefore, two versions of the base-case analysis were conducted for the rtCGM – one with the utility gains associated with the reduction in FoH included, and one with them excluded.

No equivalent fear of hypoglycaemia data were available for isCGM, and therefore no equivalent analysis including this benefit was undertaken for isCGM.

Table HE004: Quality of life values

Input variables	Mean utility	Se	Source/ Comment
No complications	0.839	0.0048	Default value in IQVIA CDM which was sourced from Peasgood et al.[29]
Disutility of MI event	-0.055	0.005	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al.[30] Within this systematic review, these relevant parameters were sourced from Clarke et al[31]. QoL post MI was assumed to be baseline utility minus disutility
Utility post MI	0.784	0.007	
Utility CHF	0.6770	0.01	
Disutility of Stroke event	-0.164	0.008	

Input variables	Mean utility	Se	Source/ Comment
Utility post Stroke event	0.675	0.009	of MI from Beaudet et al.[30] A similar calculation was done to obtain QoL post stroke and post amputation.
Disutility amputation event	-0.280	0.011	
Utility post amputation	0.559	0.012	
Utility PVD	0.7240	0.008	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Bagust et al[32]
Utility gross proteinuria	0.7370	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[30]. Within this systematic review, these relevant parameters were sourced from Wasserfallen et al[33]
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[30]. Within this systematic review, these relevant parameters were sourced from Fenwick et al[34]
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[30]. Within this systematic review, these relevant parameters were sourced from Kiberd et al[35]
Utility cataract	0.7690	0.016	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30]. Within this systematic review, these relevant parameters were sourced from Lee et al[36]
Utility proliferative diabetic retinopathy (PDR) laser treatment	0.7150	0.022	Default value in IQVIA CDM which was sourced from a systematic review by Beaudet et al[30].
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[21]. 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
Disutility NSHE nocturnal	-0.008	0.00102	
Disutility SHE daytime	-0.062	0.00433	
Disutility SHE nocturnal	-0.066	0.00485	

Input variables	Mean utility	Se	Source/ Comment
			themselves are just as bad). The descriptions of these health states were derived from a survey of 247 UK patients with diabetes. Hence given that all respondents answered the TTO survey based on the described hypothetical health states, no differences should be assumed between categories of patients. A more important distinction to make is that of results between specific countries, given the differences in the perception of a full health states between countries. Hence given that this analysis is done for a UK population, the UK specific value set was used. Note that the lower CI for NSHE nocturnal was reported as 0.06 which was assumed to be an error, and 0.006 was used when calculating the standard error
Disutility for 1 unit increase in BMI above 25 kg/m^2	-0.0061	n/a	Default value in IQVIA CDM - sourced from Bagust et al[32]
Utility gain of using isCGM (direct utility benefit)	0.03	n/a	Matza et al[23].
Utility gain of using rtCGM (direct utility benefit)	0.03	n/a	Committee assumption
Utility gain related with the reduced fear of hypoglycaemia (rtCGM)	0.02536	n/a	Clinical review

HE2.3.13 Treatments

HE2.3.321 Treatment effects of glucose monitoring devices

Treatment effects for the outcomes listed below were based on the meta-analyses performed as part of the clinical evidence review for this topic (see appendices F and G of the evidence review for the guideline update).

Reduction in HbA1c levels

The reduction in HbA1c levels, calculated as the mean change from baseline are listed in Table HE005. The mean change for SMBG was taken from the economic modelling undertaken for comparing different insulin therapies, using the numbers estimated for detemir twice daily insulin, as that was the primary treatment recommended in the guideline. The committee noted it was unlikely that the cost-effectiveness of different monitoring techniques would change considerably based on differences in the underlying insulin regimen used, as the benefits of rtCGM and isCGM would be expected to accrue for all insulin regimens. Some of the studies included participants using continuous subcutaneous insulin infusion, but the committee agreed it was appropriate to model a population of people starting with multiple daily insulin injections, since this is how most people with type 1 diabetes start treatment, and therefore represents the point at which the initial decision on whether to offer automated blood glucose monitoring needs to be made.

The estimated differences between SMBG and rtCGM and isCGM were then applied to this baseline value for SMBG to estimate changes from baseline in HbA1c for rtCGM and isCGM (no difference was found in HbA1c between isCGM and SMBG). All studies with a follow-up of longer than three months were included as part of this calculation, regardless of the type of insulin being used. Full details of the analyses from which these values were derived are given in appendix F and G of the guideline evidence review.

Table HE005: Reduction in HbA1c levels

Treatments	Change in HbA1c	Se	Source
rtCGM	-0.8344	0.0638	Clinical review
isCGM	-0.4544	0.1174	Clinical review (no difference found in review)
SMBG	-0.4544	0.1174	Insulin guideline NG17: Detemir twice daily

Severe hypoglycaemic events

As for modelling HbA1c values, rates of severe hypoglycaemia for the SMBG arm of the model were taken from the economic modelling undertaken for comparing different insulin therapies, using the numbers estimated for detemir twice daily insulin.

Severe hypoglycaemic event rates for the rtCGM arm were calculated by applying the relative risks obtained from the meta-analysis of severe hypoglycaemic events in the clinical evidence review to the rate of severe hypoglycaemic events in the SMBG arm. To apply the relative risk to annualised rate data, the rates first need to be converted to probabilities at one year, the relative risk applied, and then the number converted back to a rate. The clinical review excludes the Riveline et al[37] study from the meta-analysis of severe hypoglycaemic events rates due to differences in the inclusion criteria for that study (in particular, it recruited a population of people with poorly controlled diabetes at baseline). A sensitivity analysis was also conducted including that study as part of the meta-analysis (see the section on sensitivity analyses below).

Severe hypoglycaemic event rates for the isCGM arm were based on Bolinder et al[38]., the only study included in the clinical review that reported data on hypoglycaemia for isCGM versus SMBG in people with type 1 diabetes. The study reported the number of events when glucose fell below various threshold values. As a proxy for severe hypoglycaemia, an outcome of sensor glucose values <2.2mmol/L (40 mg/dL) per 24-hour period was used. The number of times per day that glucose fell below this threshold reduced for both study groups but the extent of reduction was greater for the isCGM group, representing a statistically significant ($p<0.0001$) 55% reduction in the number of events when participants' glucose levels fell in this hypoglycaemic range compared with the SMBG group.

Severe hypoglycaemic event rates (per 100 patient years) used in the base-case analysis are listed in table HE006.

Table HE006: Severe hypoglycaemic event rates

Treatments	Event rate (per 100 patient years)
rtCGM	18.55
isCGM	13.5765
SMBG	30.17

Non-severe hypoglycaemic events

As for modelling HbA1c and severe hypoglycaemia, rates of non-severe hypoglycaemia for the SMBG arm of the model were taken from the economic modelling undertaken for comparing different inulin therapies, using the numbers estimated for detemir twice daily insulin.

Non-severe hypoglycaemic events for rtCGM were mostly reported as mean differences in number of events (usually defined as sensor glucose values <3.9mmol/L [70 mg/dL]). Therefore, to estimate a percentage reduction in events, a meta-analysis was conducted for the SMBG arms of the rtCGM trials, to estimate a baseline rate of hypoglycaemic events, and the reduction in numbers of events with rtCGM was then applied to estimate a percentage reduction in events (estimated at 21.5%).

Non-severe hypoglycaemic event rates for the isCGM arm were based on Bolinder et al[38]., the only study included in the clinical review that reported data on hypoglycaemia for isCGM versus SMBG in people with type 1 diabetes. The study reported number of events when glucose fell below various threshold values. As a proxy for non-severe hypoglycaemia, an outcome of sensor glucose values <3.9mmol/L (70 mg/dL) was used. The number of times per day that glucose fell below this threshold reduced for both study groups but the extent of reduction was greater for the isCGM group, representing a statistically significant (p<0.0001) 25.8% reduction in the number of events when participants' glucose levels fell in this hypoglycaemic range compared with the SMBG group.

Non-severe hypoglycaemic event rates (per 100 patient years) used in the base-case analysis are listed in table HE007.

Table HE007: Non-severe hypoglycaemic event rates

Treatments	Event rate (per 100 patient years)
rtCGM	2053.902
isCGM	1941.688
SMBG	2616.83

Nocturnal hypoglycaemic events

The clinical evidence review found no strong evidence to suggest the proportion of nocturnal hypoglycaemic events differs based on the type of monitoring used. Thus, if a device reduces the amount of hypoglycaemic events, it is likely to reduce both daytime and nocturnal events by approximately the same proportion, and therefore a single proportion of nocturnal events was applied across all the treatment arms. This proportion (13.96%) was taken from the economic modelling undertaken for comparing different insulin therapies, using the numbers estimated for detemir twice daily insulin.

HE2.3.322 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 glucose monitoring methods with regard to the discontinuation of treatments, no treatment failure was assumed in this analysis.

HE2.3.373 Treatment costs

Monitoring device costs

We derived the cost for isCGM from NHS England's national arrangements[39], which outline the cost to the NHS of isCGM glucose monitoring. The cost of each sensor is £35 and each lasts two weeks. The annual cost is therefore 26 x £35 = £910.

For rtCGM, our base case assumes an annual cost of £2,000. This is the ceiling price listed in the NHS England and NHS Improvement funding document (September 2020)[40]. This ceiling price is only directly applicable for pregnant women, but the committee agreed that it was a reasonable proxy for the prices that may be paid for rtCGM for non-pregnant population as well, assuming rtCGM was widely rolled out for people with type 1 diabetes. This cost is also similar to the costs estimated when individual rtCGM devices are considered (for example, Roze et al[2]. estimated an annual cost of £1,850 for rt-CGM).

Table HE008: Annual costs of monitoring approaches

Treatments	Cost
isCGM	£910
rtCGM	£2000

SMBG costs

In the absence of a glucose monitoring device, SMBG is the sole method used to determine blood glucose levels. When a device is used, some self-monitoring will still be required. The model estimates SMBG costs by multiplying the daily frequency of self-monitoring by the unit cost of strips and lancets (£0.26 combined). We obtained this cost from the average of all the strips and lancets reported as first-line diabetic equipment in the NHS Electronic Drug Tariff[12].

We identified data regarding frequency of SMBG among people with type 1 diabetes from previous literature, shown in Table HE011. The committee advised that although the following numbers reflect the average frequency in SMBG use among T1DM people, there might be some variations since some tend to use SMBG more often than others. We account for the uncertainty in SMBG use in the sensitivity analyses described below.

Table HE009: SMBG resource use

Parameter name	Value (95% CI)	Source
Daily self-monitoring		
SMBG	4.6	Roze et al[2].
isCGM	0.46	Healthcare Improvement Scotland[1]
rtCGM	0.15	Roze et al[2].

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 HE012 lists the input parameters used for proportions of patients who were managed for various chronic and recurrent conditions.

Table HE010: 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	
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 TA 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 Sensitivity analyses

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

HE2.4.1 Deterministic sensitivity analyses

A number of deterministic sensitivity analyses were performed to test for the robustness of our base case results, and they were conducted under the base case scenario for both rtCGM (with utility gains from reduced fear of hypoglycaemia) and isCGM. These scenarios were:

1. **Diabetes duration:**

Duration of diabetes was 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.

2. **Time horizon:**
   Reducing the time horizon on the analysis from lifetime (80 years) to 1 year, 10 years and 25 years.

3. **HbA1c progression approach:**
   In the base analyses, it was assumed that the difference in HbA1c levels between rtCGM/isCGM and SMBG arms remained constant over time. In sensitivity analyses, the UKPDS progression approach was adopted, assuming that the difference in HbA1c between study arms reduced over time.

4. **Higher daily usage of SMBG**
   A higher frequency of SMBG (10 times per day) was assumed for both the SMBG arm (10 times per day) and rtCGM/isCGM arms (3 times per day) to represent a subgroup of people who use a substantial amount of SMBG, even when using other monitoring devices (for example, people who continue to test at meal times).

5. **Higher severe hypoglycaemic event rate in the rtCGM arm by including Riveline et al. 2020**
   After including the Riveline et al. 2020, the meta-analysis gives a higher estimate of severe hypoglycaemic events in the rtCGM arm, at a level of 25.36 per 100 patient years.

6. **Higher cost of rtCGM at £3,000 per year**
   The annual cost of rtCGM was increased to £3,000 per year following the suggestion from the committee. This represents an upper bound on the potential cost of rtCGM, assuming the full prices in the NHS supply chain catalogue are paid, with no discounts, for individuals requiring the full technology (i.e. people requiring a receiver device as they do not have a smartphone that can fulfil this function).

HE2.4.2 Probabilistic sensitivity analyses

The IQVIA CDM allows for a probabilistic analysis to account for the uncertainty surrounding the model input parameters listed above. The probability distributions around each parameter are set by default in the IQVIA CDM, as explained in the document available in the IQVIA CDM website. When the probabilistic version of the model is run, values are randomly selected simultaneously for each model input parameter from its respective probability distribution. These values are then used to calculate the respective costs and QALYs. This was repeated 1,000 times (1,000 bootstraps) for the base case, and then mean costs and QALYs calculated across those samples.

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

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

Note that the deterministic version of IQVIA CDM also has an element of stochastic variability in it due to a baseline cohort of 1,000 patients being simulated to run the economic analysis on.

HE3 Results

HE3.1 Base-case cost–utility results

There are two versions for the base case analyses: scenario 1 does not include the additional utility benefit associated with reduced fear of hypoglycaemia (FoH), while scenario 2 does include this benefit. The committee noted that because isCGM was already found to be clearly cost-effective without the inclusion of this additional benefit, it was unnecessary to run a version of the model including this benefit for isCGM (given the lack of data on fear of hypoglycaemia with isCGM monitoring).

The base case results in scenario 1 (Table HE011) showed that isCGM was a cost-effective treatment compared with SMBG under a threshold of £20,000 per QALY, while rtCGM only appeared cost effective at the £30,000 threshold. In scenario 2 rtCGM was cost-effective compared with SMBG at a threshold of £20,000 per QALY.

Table HE012: Base-case deterministic cost–utility results (without utility benefits associated with reduced FoH)

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs SMBG)
SMBG	52,979	11.641			
rtCGM	75,668	12.569	22,688	0.928	24,436
isCGM	61,156	12.446	8,177	0.805	10,157

Table HE013: Base-case deterministic cost–utility results (with utility benefits associated with reduced FoH)

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs SMBG)
SMBG	52,979	11.641			
rtCGM	75,668	13.028	22,688	1.388	16,351

HE3.2 Deterministic sensitivity analyses

Results of the sensitivity analyses performed are shown in Tables HE014 and HE015. isCGM remained cost-effective at a threshold of £20,000 per QALY except when changing the HbA1c progression method. rtCGM (based on the analysis including fear of hypoglycaemia) was mostly cost-effective at £20,000 per QALY except when reducing the time horizon to one year, changing the HbA1c progression approach and increasing the price of rtCGM to £3,000 per year. However, the ICERs of rtCGM in these scenarios were still below the £30,000 per QALY threshold. The committee agreed the analysis with reducing benefit of CGM over time was not particularly concerning, as unlike with a drug there was no clinical reason to expect the benefits of rtCGM would reduce over time, provided a person continued to make use of the device.

Table HE016: Summary findings of sensitivity analyses (rtCGM vs. SMBG)

Sensitivity analyses	Costs		QALYs		ICER (vs SMBG)
	rtCGM	SMBG	rtCGM	SMBG	
New onset diabetes	123,658	101,985	15.79	14.14	13,103

Sensitivity analyses	Costs		QALYs		ICER (vs SMBG)
	rtCGM	SMBG	rtCGM	SMBG	
Time horizon 1 year	2,303	823	0.75	0.69	22,968
Time horizon 10 year	22,771	10,760	6.14	5.56	20,834
Time horizon 25 year	54,761	34,861	11.07	9.97	18,091
HbA1c progression UKPDS approach	84,729	52,979	12.73	11.64	29,152
Higher SMBG use	80,653	62,179	13.03	11.64	13,249
Higher SHE rate in rtCGM	76,114	52,979	12.95	11.64	17,630
Higher annual cost for rtCGM	93,769	52,979	13.03	11.64	29,396

Table HE017: Summary findings of deterministic sensitivity analyses (isCGM vs. SMBG)

Sensitivity analyses	Costs		QALYs		ICER (vs SMBG)
	isCGM	SMBG	isCGM	SMBG	
New onset diabetes	111,860	101,985	15.11	14.14	10,159
Time horizon 1 year	1,263	823	0.73	0.69	10,162
Time horizon 10 year	14,466	10,760	5.93	5.56	10,159
Time horizon 25 year	41,736	34,861	10.65	9.97	10,156
HbA1c progression UKPDS approach	67,075	52,979	12.28	11.64	22,014
Higher SMBG use	65,484	62,180	12.45	11.64	4,104

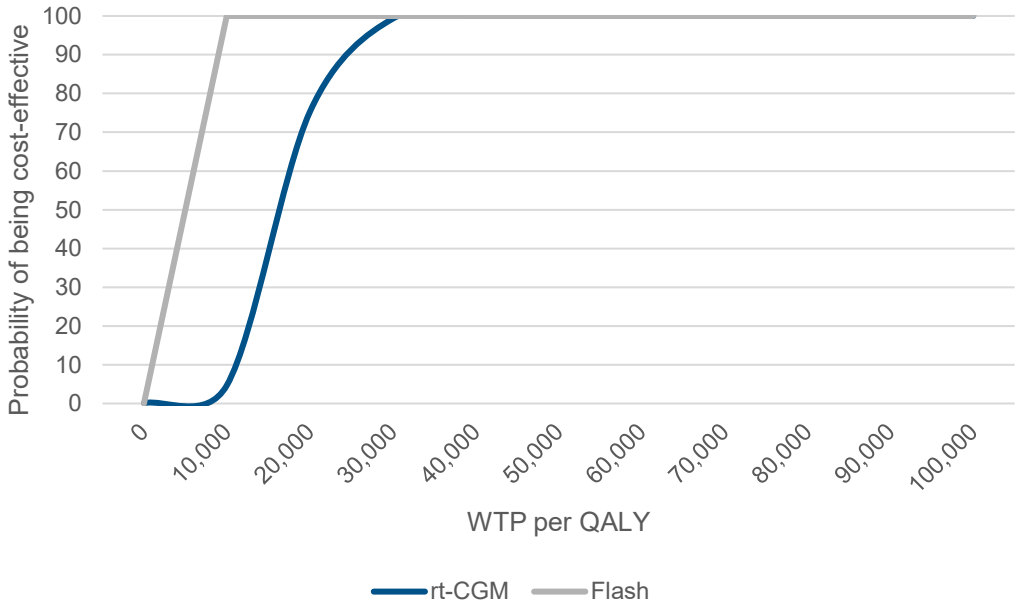
HE3.3 Probabilistic sensitivity analysis

Probabilistic sensitivity results were reported below in tables HE018, and the cost-effectiveness acceptability curves (CEAC) are shown in figure HE001. Both rtCGM and isCGM were cost-effective in probabilistic sensitivity analyses. If the threshold exceeded £30,000 per QALY, both devices appeared to be cost-effective compared with the SMBG. With a lower threshold value at £20,000 per QALY, isCGM remained consistently cost-effective while the probability of rtCGM being cost-effective was around 75%.

Table HE019: Summary findings of probabilistic sensitivity analyses

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs SMBG)
SMBG	59,177	11.035			
rtCGM	80,584	12.306	21,406	1.271	16,846
isCGM	66,868	11.792	7,691	1.186	10,155

Figure HE002: Cost-effectiveness acceptability curve in probabilistic sensitivity analyses



HE3.4 Discussion

HE3.4.1 Principal findings

In the base analysis where the utility gains associated with reduced FoH were not considered, isCGM was cost effective compared with SMBG at a threshold of £20,000 per QALY, while rtCGM was only cost-effective at a threshold of £30,000 per QALY. When incorporating utility gains from reduced fear of hypoglycaemia for the rtCGM arm, it also became cost-effective compared with SMBG at a threshold of £20,000 per QALY. The cost-effectiveness results were mostly robust across different scenarios except when limiting the time horizon to one year, changing the HbA1c progression approach and increasing the rtCGM price to £3,000 per year. However, under a threshold of £30,000 per QALY, both devices are cost-effective across all scenarios.

HE3.4.2 Weaknesses of the analysis

As common with economic analysis of this nature, there was uncertainty around the model input parameters. Therefore, a number of deterministic and probabilistic sensitivity analyses were conducted along with two versions of base case scenarios. Flash remained cost-effective across all scenarios, while rtCGM was likely to be cost-effective in the majority of the cases.

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 sensitivity analysis among newly diagnosed diabetes people where in an ideal situation all associated baseline risk factors would have changed through associated covariances once the baseline risk factor specific to this subgroup was changed.

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.

HE3.4.3 Comparison with other CUAs

The literature review of economic evidence identified 2 CUAs in the context of the UK, one for isCGM and one for rtCGM. There were a number of differences between our study and previous literature. Healthcare Improvement Scotland[1] used a simple two-stage model structure that consisted of alive and death. The study only accounted for hypoglycaemic events and did not consider HbA1c levels as the health outcome. Roze et al[2] also used CORE diabetes model, but their clinical estimates were withdrawn from a single trial. Despite these differences in modelling and data source, our results were consistent with both studies that showed rtCGM and isCGM devices are cost effective compared with SMBG for people with type 1 diabetes.

HE3.5 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. A number of deterministic and probabilistic sensitivity analyses were considered to account for uncertainty surrounding the model inputs.

isCGM was cost-effective compared with SMBG at a threshold of £20,000 per QALY, while rtCGM was only cost-effective when incorporating utility gains from reduced fear of hypoglycaemia in the economic models. Results remained robust across the majority of sensitivity analyses, except when reducing the time horizon to one year, changing the HbA1c progression approach and increasing the rtCGM price to £3,000 per year. However, at a threshold of £30,000 per QALY, both types of devices are cost-effective across all scenarios.

HE4 References

1. Healthcare Improvement Scotland. "What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy? What it an evidence note?". SHTG Advice on health technologies: In response to an enquiry from the Scottish Diabetes Group (SDG). 2018.
2. Roze, S., et al. "Long-term cost-effectiveness of dexcom G6 real-time continuous glucose monitoring versus self-monitoring of blood glucose in patients with type 1 diabetes in the U.K." *Diabetes care* 2020; 43(10): 2411-2417.
3. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. *Value Health* 2014;17(6):714-724.
4. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and costeffectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Current Medical Research and Opinion*. 2004;20(sup1):S5-S26.
5. NHS Digital. National Diabetes Audit (NDA) 2019-20 Type 1 Diabetes report – Supporting Information. Published online 12th August 2021. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/national-diabetes-audit-2019-20-type-1-diabetes.
6. Heller S, White D, Lee E, et al. A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial. *Health Technology Assessment*. 2017; 21(20):1-278.
7. The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med* 2009; 362:1575-1585.
8. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM.UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia* 2013; 56(9):1925-33.
9. Aaron R. Folsom et al. Prediction of Coronary Heart Disease in Middle-Aged Adults With Diabetes. *Diabetes Care* 2003; 26(10): 2777–2784.
10. NHS Digital. Health Survey for England 2017 & 2018. Published online 4th December 2018 & 3rd December 2019. https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england
11. World Health Organisation. Global status report on alcohol and health 2018. Published online 2018. https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf?ua=1&ua=1
12. National Health Service. Electronic Drug Tariff. Published 2021. Accessed June 22, 2021. https://www.drugtariff.nhsbsa.nhs.uk/#/00157519-FA/FA00157076/
13. National Health Service. Prescription Cost Analysis (PCA) data March 2021. Published online 2021. https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data
14. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant*. 2012;27(suppl_3):iii73-iii80.
15. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2020. Published online 2020. https://www.pssru.ac.uk/project-pages/unit-costs/
16. Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weitgasser R, Lahtela J, Jensen MM, Östenson C-G. Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work-time loss, and wellbeing in insulin-treated patients with diabetes in seven European countries. *J Medical Economics*. 2013;16(12):1453-1461.

17. Hammer M, Lammert M, Mejías SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. *Journal of Med Economics*. 2009;12(4):281-290.
18. Heller SR, Frier BM, Hersløv ML, Gundgaard J, Gough SCL. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. *Diabet Med*. 2016;33(4):471-477.
19. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. *Diabet Medicine*. 2019;36(8):995-1002.
20. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Curr Med Res Opin*. 2006;22(8):1523-1534.
21. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health Quality of Life Outcomes*. 2013;11(1):90.
22. Lauridsen JT, Lønborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. *Quality Life Research*. 2014;23(9):2645-2650.
23. Matza, L. S., Stewart, K. D., Davies, E. W., Hellmund, R., Polonsky, W. H., & Kerr, D.. Health State Utilities Associated with Glucose Monitoring Devices. *Value in Health*. 2017;20(3):507-511.
24. Currie, C. J., Morgan, C. L., Poole, C. D., Sharplin, P., Lammert, M., & McEwan, P.. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Current Medical Research and Opinion*. 2006;22(8):1523-1534.
25. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Lawrence JM, Laffel L, Wysocki T, Xing D, Huang ES, Ives B, Kollman C, Lee J, Ruedy KJ, Tamborlane WV. Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. *Diabetes Care*. 2010 Oct;33(10):2175-7.
26. Little SA, Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, Chadwick TJ, Barendse S, Stocken DD, Brennand C, Marshall SM, Wood R, Speight J, Kerr D, Flanagan D, Heller SR, Evans ML, Shaw JA. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care*. 2014 Aug;37(8):2114-22.
27. Polonsky WH, Hessler D, Ruedy KJ, Beck RW; DIAMOND Study Group. The Impact of Continuous Glucose Monitoring on Markers of Quality of Life in Adults With Type 1 Diabetes: Further Findings From the DIAMOND Randomized Clinical Trial. *Diabetes Care*. 2017 Jun;40(6):736-741.
28. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, Schwarz E, Ólafsdóttir AF, Frid A, Wedel H, Ahlén E, Nyström T, Hellman J. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. *JAMA*. 2017 Jan 24;317(4):379-387. doi: 10.1001/jama.2016.19976.
29. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The impact of diabetes-related complications on preference-based measures of health-related quality of life in adults with type I diabetes. *Medical Decision Making*. 2016;36(8):1020-1033.
30. Beaudet A, Clegg J, Thuresson P-O, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value in Health*. 2014;17(4):462-470.
31. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Medical Decision Making*. 2002;22(4):340-349.
32. Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. *Health Economics*. 2005;14(3):217-230.
33. Wasserfallen J-B, Halabi G, Saudan P, et al. Quality of life on chronic dialysis:

comparison between haemodialysis and peritoneal dialysis. *Nephrology Dialysis Transplant*. 2004;19(6):1594-1599.
34. Fenwick EK, Xie J, Ratcliffe J, et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Investigative Ophthalmology & Visual Science*. 2012;53(2):677-684.
35. Kiberd BA, Jindal KK. Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation. *BMJ*. 1995;311(7020):1595-1599.
36. Lee WJ, Song K-H, Noh JH, Choi YJ, Jo M-W. Health-related quality of life using the EuroQol 5D questionnaire in Korean patients with type 2 diabetes. *Journal of Korean Medical Science*. 2012;27(3):255-260.
37. Riveline, J.P., et al. Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: a 1-year multicenter study.; *Diabetes care*. 2012;35 (5); 965-71.
38. Bolinder, J. et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial.; *Lancet* (London, England); 2016;388(10057);2254-2263
39. NHS England. Flash glucose monitoring: national arrangements for funding of relevant diabetes patients. 2019. Available from: www.england.nhs.uk/publication/flash-glucose-monitoring-national-arrangements-for-funding-of-relevant-diabetes-patients
40. NHS England and NHS Improvement. Type 2 Diabetes Prevention Programme and Type 1 diabetes glucose monitoring: Continuous glucose monitors – pregnancy. 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2020/10/C0770-dpp-and-cgm-letter.pdf.