NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Background:
Following the scoping workshop on 23 February 2021, stakeholders were informed that NICE was considering transferring the assessment from diagnostic guidance (DG) process, to a multiple technology assessment (MTA) process. This was then confirmed, therefore the assessment was transferred on to the MTA pathway and will publish as technology appraisal guidance rather than diagnostics guidance.

The assessment was paused in July 2021 to allow real world data to be collected by NHS England and NHS Improvement on the use of hybrid closed loop systems for people with type 1 diabetes in the NHS to be included in the assessment. During this time the recommendations on glucose monitoring in the NICE guideline on Type 1 diabetes in adults: diagnosis and management (NG17) were revised, the final scope and protocol were updated to reflect this.

Contents:

6 Company submission summaries from:

a. Camdiab Ltd
b. Dexcom International Ltd
c. Medtronic Ltd
d. Tandem Diabetes Care Inc

(Air Liquide Healthcare – not providing a submission)

7 NHS England - Hybrid Closed Loop Systems pilot data:

- Adult centres
- Paediatric centres
- Enablers and barriers affecting adoption of diabetic technologies

8 Patient and professional groups submissions from:

- Diabetes UK
- JDRF

9 Expert personal perspectives from:

Experts appointed via the MTA expert nomination process:

- Julie Brake – clinical expert, nominated by Insulet International Ltd
- Joanne Richardson - patient expert, nominated by National Children and Young People's Diabetes Network

Experts appointed by the Diagnostics Assessment Programme
(Originally appointed as specialist committee members, before the topic was re-routed as a Multiple Technology Appraisal):

- Nicola Birchmore - clinical expert
- Alison Finney - patient expert
- Jeff Foot - patient expert
- Peter Hindmarsh - clinical expert
- Sufyan Hussain - clinical expert
- Fiona Regan - clinical expert
- Philip Weston - clinical expert

10 Updated Assessment Report (15 November 2022) prepared by Warwick Evidence, Warwick Medical School, University of Warwick

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

Evidence overview: Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

This overview summarises the main issues the diagnostics advisory committee needs to consider. It should be read together with the final scope and the updated external assessment report (15 November 2022).

1 Aims and scope

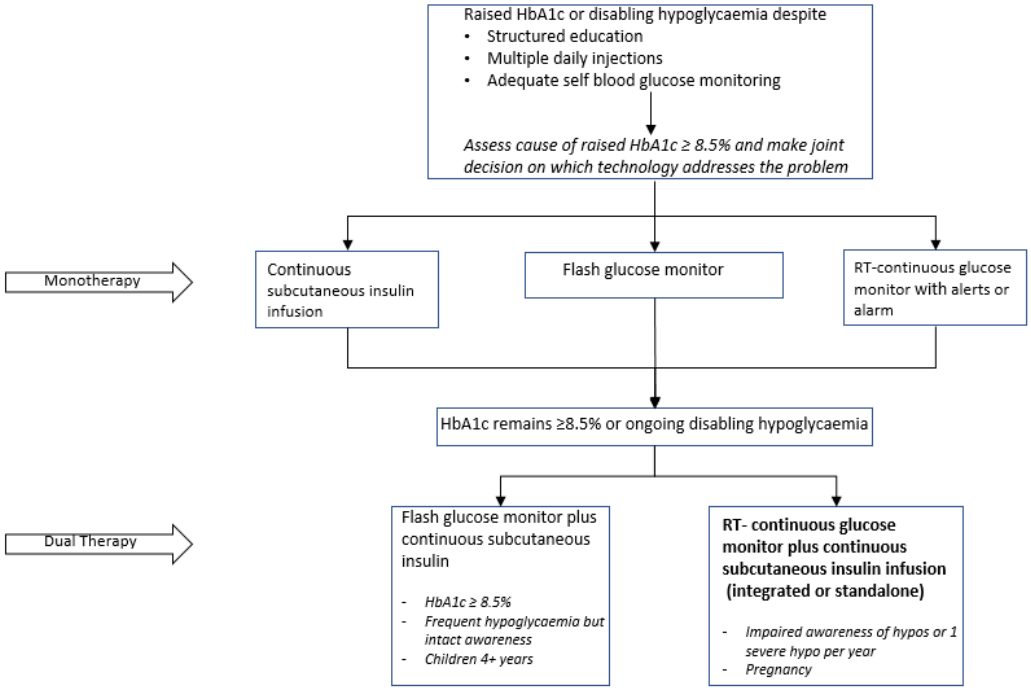
The purpose of this assessment is to evaluate the clinical and cost effectiveness of using hybrid closed loop systems for managing glucose levels in type 1 diabetes.

In type 1 diabetes, a person's blood glucose level becomes too high (hyperglycaemia) because there is no, or very little, production of insulin by the pancreas. The goal of treatment in type 1 diabetes is to keep blood glucose within a healthy range by providing the body with supplemental insulin. If the level of circulating insulin becomes too high, blood glucose levels can become too low leading to hypoglycaemia (also known as a hypo).

The management of type 1 diabetes has several components and typically involves lifestyle adjustments, regular measuring of blood glucose levels, use of multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII) and periodic assessment of blood glucose control. Long-term monitoring of blood glucose control can be done by measuring glycated haemoglobin (HbA1c levels), which is the average plasma glucose over the preceding 3 months. NICE guidelines on diabetes (type 1 and type 2) in children and young people, type 1 diabetes in adults and diabetes in pregnancy recommend that people with type 1 diabetes should aim for a target HbA1c level of 48 millimoles per mole (6.5%) or lower to minimise the risk of long term complications from diabetes.

Time in range is a measure of glycaemic control which shows the percentage of time a person spends within a target glucose range. It is obtained from continuous glucose monitor data and gives an idea of changes in glucose patterns within a day and between days. The international consensus on time in range recommends a time in range of at least 70% in a glucose range of 3.9 to 10 millimoles per litre for people with type 1 diabetes. Time below range (percentage of time between 3.0 to 3.9 mmol/litre) is associated with increased risk of severe hypoglycaemia, while time above range (percentage of time between 10 to 13.9 mmol/litre) may indicate a risk of ketoacidosis. Blood glucose monitoring can be done by self monitoring (capillary blood testing), or by real time continuous (rtCGM) or intermittently scanned continuous glucose monitors (isCGM). The Diabetes UK position statement on the appropriate use of technology in type 1 diabetes is shown in figure 1.

Figure 1 Technology care pathway for type 1 diabetes



Adapted from Type 1 diabetes technology pathway: consensus statement for the use of technology in Type 1 diabetes Choudhary et al. 2019.

Integrated sensor augmented pump (SAP) systems combine rtCGM with continuous subcutaneous insulin infusion (CSII). This assessment is an update of NICE diagnostics guidance 21 (DG21). This guidance assessed 2 integrated SAP systems and recommended the MiniMed Paradigm Veo system as an option for managing blood glucose levels in people with type 1 diabetes if they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion. The Vibe and G4 PLATINUM CGM system was not recommended for routine adoption by the NHS as further evidence was needed to show the clinical effectiveness. The SAP systems assessed in DG21 are no longer available to the NHS and they have been replaced by successor systems with enhanced features.

Hybrid closed loop (HCL) systems use a mathematical algorithm to automatically drive insulin delivery in response to continuously monitored interstitial fluid glucose levels. They use a combination of real-time glucose monitoring from a CGM device and a control algorithm to direct insulin delivery through a CSII pump. Basal insulin is delivered automatically whereas bolus doses at mealtimes are manually delivered by the user. Some of these systems are built by combining interoperable devices from different manufacturers.

Decision question

Does the use of hybrid closed loop systems for managing glucose levels in type 1 diabetes represent a clinically and cost-effective use of NHS resources?

Populations

People with type 1 diabetes who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion or real time continuous glucose monitoring or intermittently scanned glucose monitoring. These difficulties may include:

- not maintaining HbA1c levels of 6.5% or below or
- not maintaining at least 70% time in range of 3.9 -10 mmol/litre or
- ongoing disabling hypoglycaemia

If evidence permits the following subpopulations should be included:

- Women with type 1 diabetes who are pregnant and those planning pregnancy (not including gestational diabetes). Please note that in this assessment this subpopulation is not required to fulfil the criteria of prior use of at least 1 technology.
- Children with type 1 diabetes. If possible, evidence should be analysed based on the following age groups:
  - 5 years and under
  - 6 to 11 years
  - 12 to 19 years
- People with extreme fear of hypoglycaemia
- People with diabetes related complications that are at risk of deterioration

Interventions

Hybrid closed loop systems

Comparators

For the economic modelling the comparators will be:

- Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated)
- Intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion

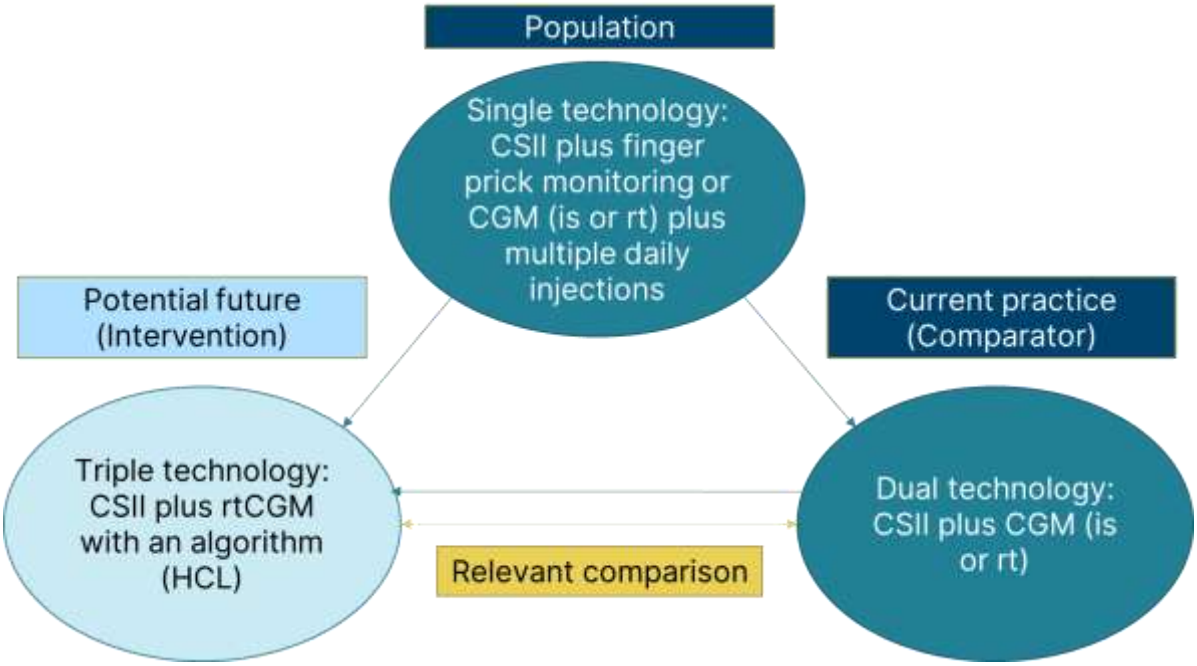
Where evidence permits scenarios assessing the following comparators should be presented for women with type 1 diabetes who are pregnant or those planning pregnancy:

- Real time continuous glucose monitoring with multiple daily insulin injections
- Intermittently scanned glucose monitoring with multiple daily insulin injections
- Self blood glucose monitoring with continuous subcutaneous insulin infusion

Healthcare setting

The healthcare setting for the interventions is self-use supervised by primary or secondary care. Figure 2 shows how the population, intervention and comparator fit into the care pathway. Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope for Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes.

Figure 2 Overview of population and technologies in the current care pathway



2 Clinical effectiveness evidence

The EAG did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. Find the full systematic review results from page 66 of the external assessment report.

Overview of included studies

Randomised controlled trials

There were 12 randomised controlled trials (RCTs) (11 publications). Most were multinational trials with participants recruited from centres in various countries including Australia, Austria, France, Germany, Israel, Luxembourg, New Zealand, Slovenia, UK and USA. The interventions varied across the different RCTs and some used systems consisting of interoperable devices from different manufacturers. Thabit et al. 2015 reported the results of 2 RCTs (1 in adults and 1 in children and adolescents). The study by Collyns et al. 2021 reported 3 separate sets of results from 1 RCT (children, adolescents and adults). Table 1 shows the population characteristics of the RCTs. Find more details of the included RCTs, including details of HCL systems used and comparators, in appendix 2 (page 287) of the external assessment report.

The EAG said that the inclusion criteria used in the RCTs were relatively narrow and most participants had reasonably good glycaemic control at entry. The EAG said that overall, studies were heterogeneous in terms of RCT design (parallel groups or cross over design with wash-out phase between different treatments), population, participants age, gender, numbers of participants and other demographics including run-in times, duration of observation periods, and number and types of previous treatments. The EAG also said that the studies did not consistently describe comparators.

Table 1 Population characteristics of the included RCTs

Study	Recruiting centres	Age description (years)	Description of comparator	Number of participants
Benhamou et al. 2022 (NCT04042207)	France	Adults (48.2 [±13·4])	SAP PLGS	63
Boughton et al. 2019 (NCT04025762)	UK (n=3 centres), Austria (n=1 centre) (diabetes outpatient clinics)	Elderly (68 [62 to 70])	CSII plus rtCGM	37
Collyns et al. 2021 (NCT04073576)	New Zealand (2 centres)	Children (7-13)	LGS/PLGS	19
Collyns et al. 2021	New Zealand (2 centres)	Adolescents (14-21)	LGS/PLGS	14
Collyns et al. 2021	New Zealand (2 centres)	adults (22-80)	LGS/PLGS	26
Kariyawasam et al. 2022 (NCT03671915)	France (2 centres), Belgium (1 centre), paediatric endocrinology departments	Young (6-12)	CSII plus rtCGM	22
McAuley et al. 2022 (ACTRN12619000515190)	Australia (2 centres)	Elderly (67 [± 5])	LGS/PLGS	30
Stewart et al. 2018 (ISRCTN83316328)	England (3 antenatal clinics)	Pregnant (32.8 [±5])	CSII plus rtCGM	16

Thabit et al. 2015 (NCT01961622) (Adults)	UK, Germany, Austria	Adults (40 [±9·4])	CSII plus rtCGM	33
Thabit et al. 2015 (NCT01778348) (Children and adolescents)	UK, 3 centres	Children and adolescents (6 to 18)	CSII plus rtCGM	25
Tauschmann et al. 2018 (NCT02523131)	UK, US	Children and young adults 22 (13 to 26)	CSII plus rtCGM	86
von dem Berge et al. 2022 (NCT03815487)	Germany (1 centre)	Pre-school and school children (2 to 14)	LGS/PLGS	38
Ware et al. 2022a (NCT03784027)	Austria (3), Germany (1), Luxembourg (1), and UK (2)	Very young children (1 to 7)	CSII plus rtCGM	74
Ware et al. 2022b (NCT02925299)	UK, USA (paediatric diabetes centres, 7 UK and USA)	Children and adolescents (6 to 18)	CSII plus CGM	135

LGS/PLGS = low glucose suspend/predictive low glucose suspend

RCTs in which HCL treatment was received for 4 or more weeks (range of 4 to 26 weeks) were included if the comparator was relevant to the decision problem. Comparators were SAP systems classified as continuous subcutaneous insulin infusion (CSII) plus continuous glucose monitoring (CGM) and low glucose suspend or predictive low glucose suspend (LGS/PLGS) systems. Where reported, CGMs used in the studies were rtCGMs. The LGS/PLGS systems are earlier versions of automated insulin delivery systems that use continuous glucose sensor data to allow immediate real-time manual adjustment of insulin therapy. The systems produce alerts if the glucose levels become too high or too low, if levels are rapidly changing, or if the system predicts that levels will be too high or too low in the near future. LGS systems can automatically suspend insulin delivery if there is no response to a low-glucose warning. PLGS systems automatically suspend insulin if the system predicts that the person is heading towards hypoglycaemia. Other insulin adjustments are made manually by the user. LGS and PLGS systems are no longer available in the NHS.

Table 3 in the external assessment report summarises the baseline characteristics and the main outcome measures reported in the RCTs (pages 73 to 79).

Quality assessment of RCTs

The EAG used the revised Cochrane risk of bias tool for randomised trials to critically appraise the 12 RCTs. In this assessment the EAG treated the 2 RCTs included in Thabit et al. 2015 as 1 study. The EAG said that 5 of the RCTs had some concerns about their risk of bias and 3 had a high risk of bias (Benhamou et al. 2021, von dem Berge et al. 2022 and Collyns et al. 2021). High risk of bias was most common in relation to the randomisation process and deviations from intended interventions. In terms of randomisation 1 RCT (Collyns et al. 2021) had a high risk of bias and 4 had some concerns. In terms of deviations from intended interventions 1 RCT had a high risk of bias (Benhamou et al. 2022) and 6 had some concerns. Three RCTs also had

some concerns of the risk of bias relating to selection of the reported results. All 12 RCTs had a low risk of bias in relation to both missing outcome data and outcomes measurement. Full details of the quality assessment of the RCTs are on pages 109 to 110 of the external assessment report.

Observational studies

Nine observational studies were identified that provided outcomes indicating glycaemic performance in people with type 1 diabetes mellitus (T1DM), using HCL or AHCL (advanced HCL) systems. Two of the observational studies were NHSE pilot studies, 1 in adults and 1 in children and young people (CYP). The adult study included 570 adults with T1DM (with complete follow-up data) from 31 diabetes centres across England that started HCL therapy. The CYP study included 251 children and young people (under 19 years), with T1DM for at least a year and had 2 HbA1c measures prior to the start of HCL. Most observational studies used similar inclusion criteria to those used in the RCTs. The EAG said that the NHSE pilot studies were broader in recruitment and included adult participants that had poorer glycaemic control in terms of HbA1c and hyperglycaemia at baseline than the other observational studies.

The observational studies included more participants than the RCTs. For the NHSE pilot data, the adult study accumulated over 200 person years of HCL observations and the CYP study around 100 person years.

Details of the population characteristics of the 9 observational studies are in table 4 on page 90 in the external assessment report. Outcome results reported in the observational studies are shown in table 5, pages 92 to 97.

No quality assessment was done on the observational studies.

Quality assessment of NHS England evidence

The EAG said that the NHSE pilot studies were non-randomised studies with no control group and with a before-after study design. It said that the before-and-after study design limited the scientific value of the evidence because

there was a greater risk of bias due to lack of randomisation, lack of a true control, and selection bias. In addition, the findings of the two pilots are interim results and therefore may not give the full results.

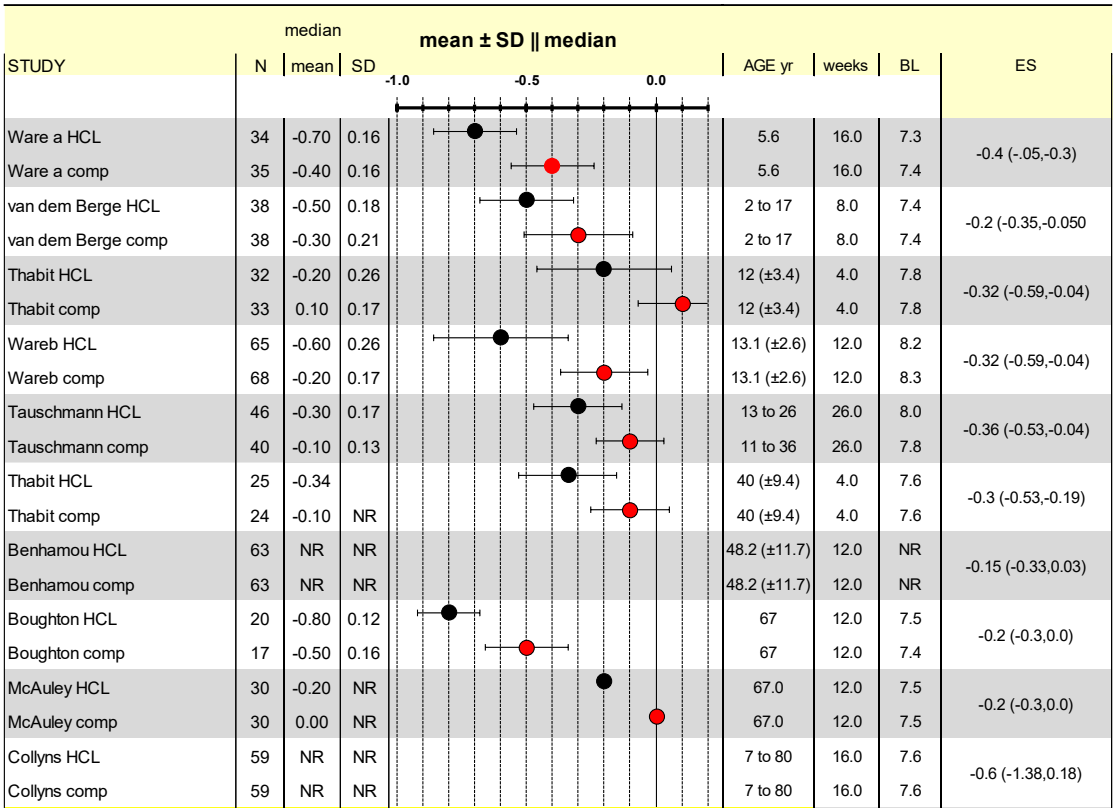
Intermediate outcomes: RCTs

All RCT studies reported results for change in percentage HbA1c, change in percentage time in range indicating satisfactory glycaemic control (3.9 to 10 or 3.5 to 7.8 mmol/litre, percentage time above range (more than 10 mmol/litre), and percentage time below range (less than 3.9, 3.5, 3.3, 3.0 or 2.8 mmol/litre depending on the study). The following outcome sections for the RCTs include descriptive comparisons with the NHSE pilot study data where relevant. Because LGS/PLGS systems are no longer available to purchase in the UK, results comparing the clinical effectiveness of CSII plus CGM with LGS/PLGS are not discussed in the following sections.

Change in HbA1c percentage

A reduction of HbA1c over time indicates improved glycaemic control. A negative mean difference or net effect size estimate (ES) comparing HCL with the comparator indicates superior glycaemic control with HCL. The study by Kariyawasam et al. was not included because it only reported baseline data so change in HbA1c could not be estimated and the net effect was not reported. Stewart et al. was not included because it only reported end of study medians (no baseline) so change could not be estimated. Figure 3 shows the change from baseline in percentage HbA1c for each arm over the treatment period for the different RCTs.

Figure 3 Change (mean ± sd or median) in percentage HbA1c over treatment period in RCTs



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Ware a HCL	34	-0.70	0.16	5.6	16.0	7.3	-0.4 (-.05,-0.3)
Ware a comp	35	-0.40	0.16	5.6	16.0	7.4	
van dem Berge HCL	38	-0.50	0.18	2 to 17	8.0	7.4	-0.2 (-0.35,-0.050
van dem Berge comp	38	-0.30	0.21	2 to 17	8.0	7.4	
Thabit HCL	32	-0.20	0.26	12 (±3.4)	4.0	7.8	-0.32 (-0.59,-0.04)
Thabit comp	33	0.10	0.17	12 (±3.4)	4.0	7.8	
Wareb HCL	65	-0.60	0.26	13.1 (±2.6)	12.0	8.2	-0.32 (-0.59,-0.04)
Wareb comp	68	-0.20	0.17	13.1 (±2.6)	12.0	8.3	
Tauschmann HCL	46	-0.30	0.17	13 to 26	26.0	8.0	-0.36 (-0.53,-0.04)
Tauschmann comp	40	-0.10	0.13	11 to 36	26.0	7.8	
Thabit HCL	25	-0.34		40 (±9.4)	4.0	7.6	-0.3 (-0.53,-0.19)
Thabit comp	24	-0.10	NR	40 (±9.4)	4.0	7.6	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-0.15 (-0.33,0.03)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.80	0.12	67	12.0	7.5	-0.2 (-0.3,0.0)
Boughton comp	17	-0.50	0.16	67	12.0	7.4	
McAuley HCL	30	-0.20	NR	67.0	12.0	7.5	-0.2 (-0.3,0.0)
McAuley comp	30	0.00	NR	67.0	12.0	7.5	
Collyns HCL	59	NR	NR	7 to 80	16.0	7.6	-0.6 (-1.38,0.18)
Collyns comp	59	NR	NR	7 to 80	16.0	7.6	

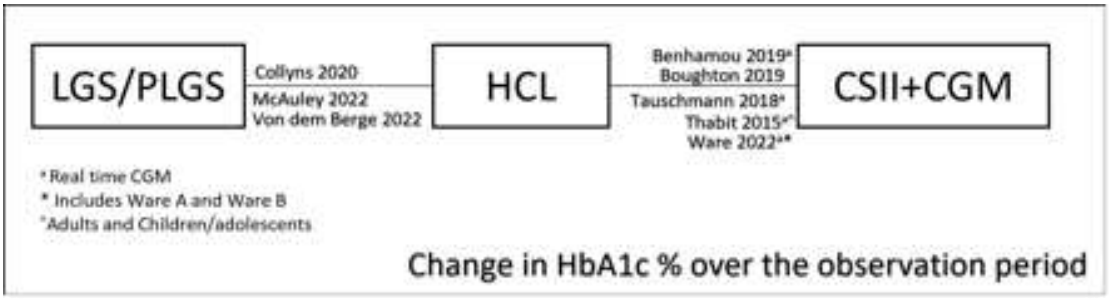
Weeks = treatment period; BL = baseline value; comp = comparator; HCL = hybrid closed loop; N = number of participants; yr = years; ES = net effect size mean difference 95% CI [HCL vs. comparator]; medians have no error bars. For Collyns et al. ES was only reported for all 3 age groups combined.

The EAG said that the range of mean baseline percentage HbA1c in the RCTs was narrow (7.4 to 8.3). In all studies, the reduction in percentage HbA1c was greater for HCL than the comparator. Change in percentage HbA1c over the treatment period in HCL was modest (range -0.2 to -0.8). Net effect sizes ranged from -0.15 to -0.6. Relative to the NHS real world pilot study baseline is lower in these studies (NHS baseline = 9.4 % HbA1c) and the net ES smaller (NHS ES = -1.5). In the NHS pilot study treatment with HCL brings the mean % HbA1c to 7.9 approaching a level comparable with the upper range values seen in RCTs after HCL use.

Change in HbA1c percentage: Network meta-analysis

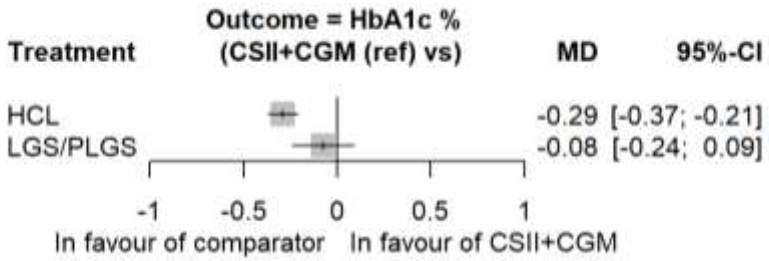
The EAG did a frequentist random effects network meta-analysis (NMA) of the change in HbA1c percentage estimates. The NMA included 10 estimates. The reference treatment class was continuous subcutaneous insulin infusion (CSII) plus continuous glucose monitoring (CGM), where estimates more than 0 favoured CSII plus CGM. Figure 4 shows the network map for the change in HbA1c percentage over the observation period from the included studies.

Figure 4 Network map of the outcome Change in HbA1c %



Compared with CSII plus CGM, the NMA showed that the HCL arm of the RCTs had an improvement in HbA1c percentage, that is HCL decreased the percentage HbA1c by 0.29 (95% CI: -0.37 to -0.21). The NMA results are shown in figure 5.

Figure 5 Results of the NMA of the outcome Change in HbA1c % over observation period

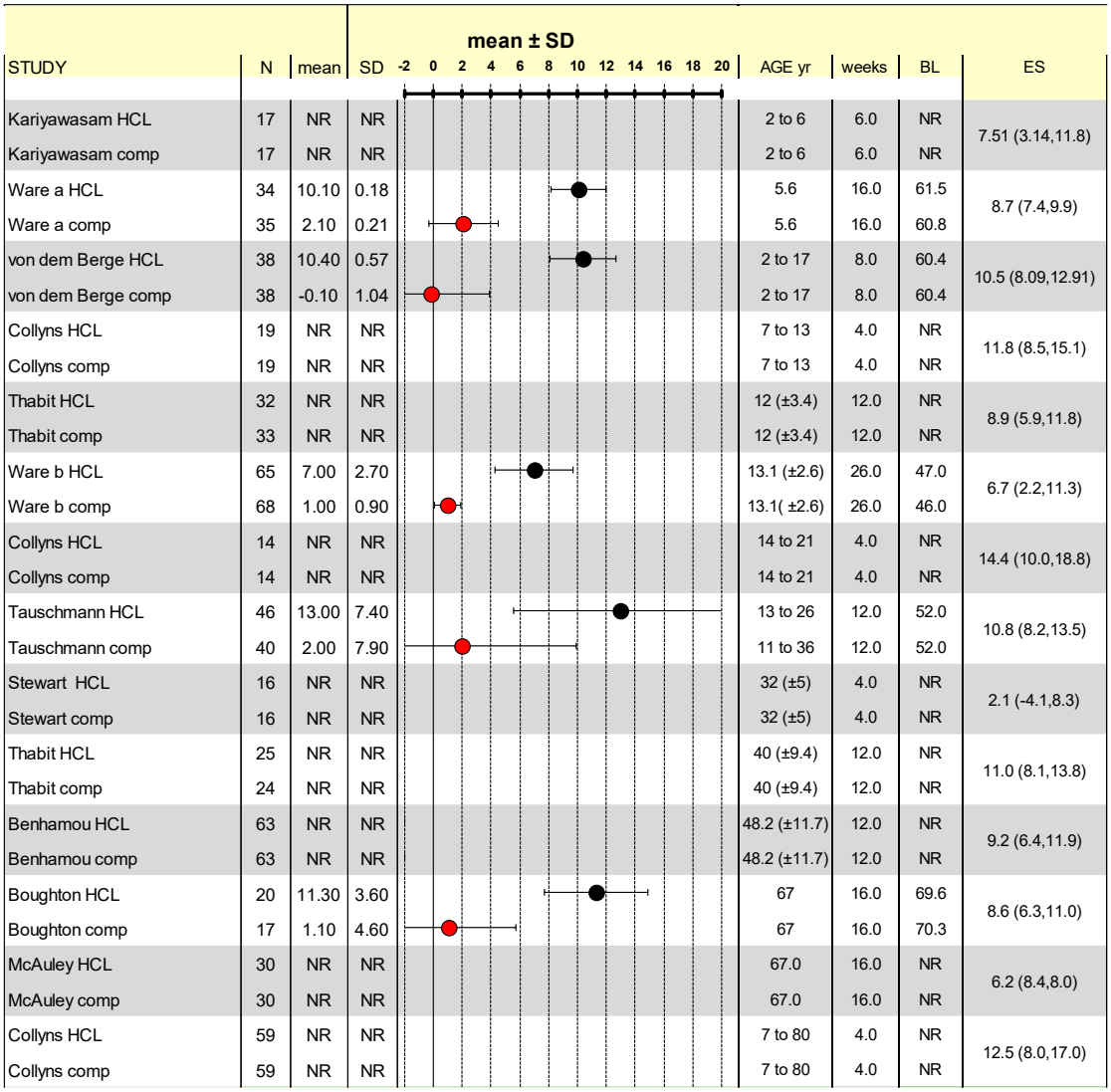


Percentage time in range (between 3.9 to 10 mmol/litre)

All RCTs reported results for percentage time in range between 3.9 to 10 mmol/litre except for the study by Stewart et al. which included a pregnant population and reported time in range 3.5 to 7.8 mmol/litre. For this outcome, better glycaemic control is indicated by more time in range.

In all the RCTs the increase in percentage time in range was greater in the HCL arm than the comparator arm. The EAG said that in all cases, this was a statistically significant ($p<0.05$) difference. The lowest mean baseline percentage time in range was 46 to 47%, in all other studies it was over 50%. In the NHS Pilot study, baseline was 34.2% allowing considerable scope for improvement with HCL treatment which was 28.5% (unadjusted; 95% CI: 25.6 to 13.5). The change from baseline in the HCL arm of RCTs with adults of similar age range as those in the adult NHS Pilot ranged from 10% to 15%. The EAG said that the size of improvement in percentage time in range appears to be greater the lower the baseline level.

Figure 6 Change from baseline in percentage time in range 3.9 to 10 mmol/litre forest plot



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	7.51 (3.14,11.8)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	10.10	0.18	5.6	16.0	61.5	8.7 (7.4,9.9)
Ware a comp	35	2.10	0.21	5.6	16.0	60.8	
von dem Berge HCL	38	10.40	0.57	2 to 17	8.0	60.4	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04	2 to 17	8.0	60.4	
Collyns HCL	19	NR	NR	7 to 13	4.0	NR	11.8 (8.5,15.1)
Collyns comp	19	NR	NR	7 to 13	4.0	NR	
Thabit HCL	32	NR	NR	12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR	12 (±3.4)	12.0	NR	
Ware b HCL	65	7.00	2.70	13.1 (±2.6)	26.0	47.0	6.7 (2.2,11.3)
Ware b comp	68	1.00	0.90	13.1(±2.6)	26.0	46.0	
Collyns HCL	14	NR	NR	14 to 21	4.0	NR	14.4 (10.0,18.8)
Collyns comp	14	NR	NR	14 to 21	4.0	NR	
Tauschmann HCL	46	13.00	7.40	13 to 26	12.0	52.0	10.8 (8.2,13.5)
Tauschmann comp	40	2.00	7.90	11 to 36	12.0	52.0	
Stewart HCL	16	NR	NR	32 (±5)	4.0	NR	2.1 (-4.1,8.3)
Stewart comp	16	NR	NR	32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR	40 (±9.4)	12.0	NR	11.0 (8.1,13.8)
Thabit comp	24	NR	NR	40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	9.2 (6.4,11.9)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	11.30	3.60	67	16.0	69.6	8.6 (6.3,11.0)
Boughton comp	17	1.10	4.60	67	16.0	70.3	
McAuley HCL	30	NR	NR	67.0	16.0	NR	6.2 (8.4,8.0)
McAuley comp	30	NR	NR	67.0	16.0	NR	
Collyns HCL	59	NR	NR	7 to 80	4.0	NR	12.5 (8.0,17.0)
Collyns comp	59	NR	NR	7 to 80	4.0	NR	

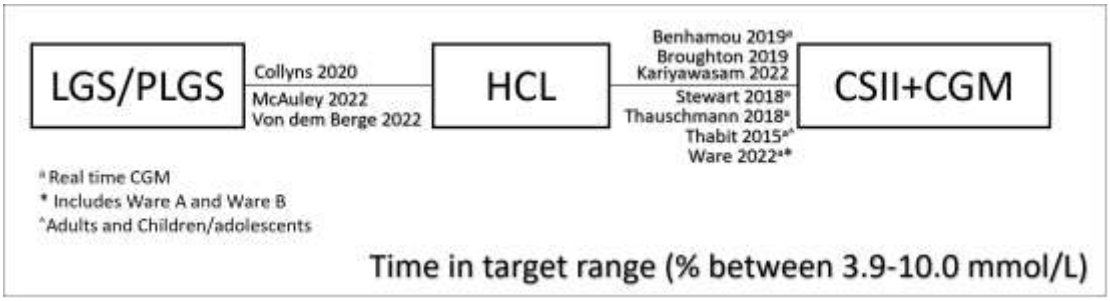
Weeks = treatment period; BL = baseline value ; comp = comparator; HCL = hybrid closed loop; N = number of participants; yr = years; ES = net effect size mean difference 95% CI [HCL vs. comparator]; medians have no error bars. NB. The population in Stewart et al., was pregnant women and the time in range refers to 3.5 to 7.8 mmol/litre rather than 3.9 to 10 mmol/litre. Collyns et

al. has 3 entries corresponding to 2 age groups (7 to 13 and 14 to 21) and all age groups combined (7 to 80).

Percentage time in range (between 3.9 to 10 mmol/litre) NMA

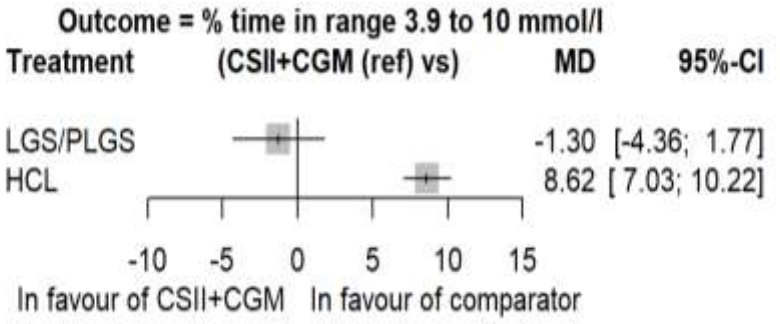
The EAG did a frequentist random effects NMA of the percentage time in range between 3.9 to 10 mmol/litre. The NMA included 12as shown in the network map (figure 7).

Figure 7 Network map of time in target range 3.9 to 10 mmol/litre



The reference treatment class was CSII plus CGM, where estimates of less than 0 favoured CSII plus CGM. Compared with the CSII plus CGM treatment classification, HCL significantly increased the percentage time in range (between 3.9 to 10.0 mmol/litre), with a mean difference (MD) of 8.62 (7.03 to 10.22). The forest plot of the NMA is shown in figure 8.

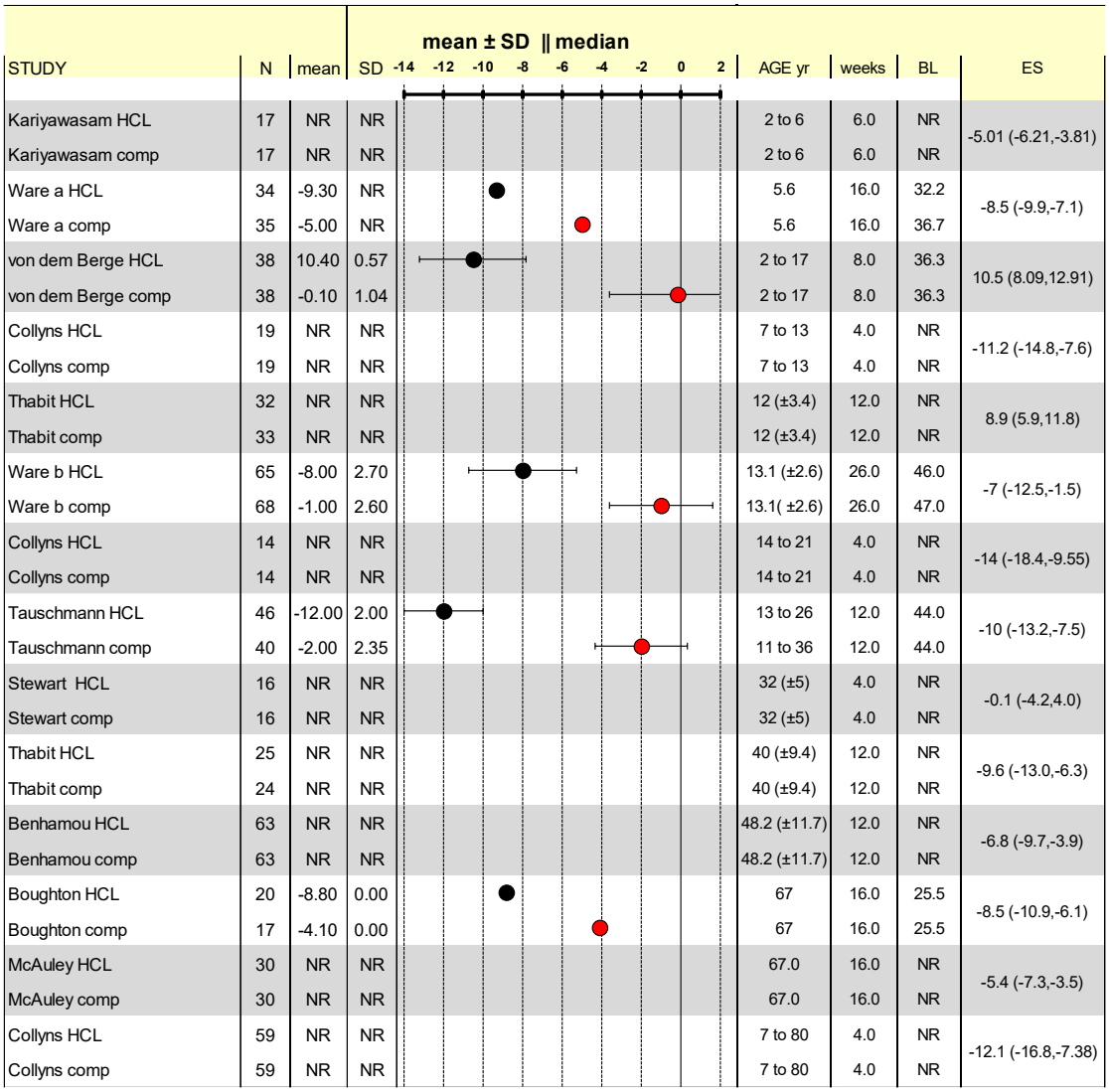
Figure 8 NMA results for time in target range between 3.9 to 10 mmol/litre



Percentage time above range (over 10 mmol/litre)

For this outcome, increased percentage time in range indicates a tendency to hyperglycaemia and poor glycaemic control. For example, a negative mean difference (intervention minus comparator) indicates that more time was spent in the range more than 10 mmol/litre in the comparator group and therefore the intervention provided better glycaemic control. In all studies HCL reduced the percentage time above range more than in the comparator arms. The EAG said that the difference between arms (net effect size) was statistically significant in all cases ($p < 0.05$). Figure 9 shows the change from baseline in percentage time above range (over 10.0 mmol/litre) reported in the RCTs.

Figure 9 Percentage time above range (over 10 mmol/litre) forest plot



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-5.01 (-6.21,-3.81)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	-9.30	NR	5.6	16.0	32.2	-8.5 (-9.9,-7.1)
Ware a comp	35	-5.00	NR	5.6	16.0	36.7	
von dem Berge HCL	38	10.40	0.57	2 to 17	8.0	36.3	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04	2 to 17	8.0	36.3	
Collyns HCL	19	NR	NR	7 to 13	4.0	NR	-11.2 (-14.8,-7.6)
Collyns comp	19	NR	NR	7 to 13	4.0	NR	
Thabit HCL	32	NR	NR	12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR	12 (±3.4)	12.0	NR	
Ware b HCL	65	-8.00	2.70	13.1 (±2.6)	26.0	46.0	-7 (-12.5,-1.5)
Ware b comp	68	-1.00	2.60	13.1(±2.6)	26.0	47.0	
Collyns HCL	14	NR	NR	14 to 21	4.0	NR	-14 (-18.4,-9.55)
Collyns comp	14	NR	NR	14 to 21	4.0	NR	
Tauschmann HCL	46	-12.00	2.00	13 to 26	12.0	44.0	-10 (-13.2,-7.5)
Tauschmann comp	40	-2.00	2.35	11 to 36	12.0	44.0	
Stewart HCL	16	NR	NR	32 (±5)	4.0	NR	-0.1 (-4.2,4.0)
Stewart comp	16	NR	NR	32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR	40 (±9.4)	12.0	NR	-9.6 (-13.0,-6.3)
Thabit comp	24	NR	NR	40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-6.8 (-9.7,-3.9)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-8.80	0.00	67	16.0	25.5	-8.5 (-10.9,-6.1)
Boughton comp	17	-4.10	0.00	67	16.0	25.5	
McAuley HCL	30	NR	NR	67.0	16.0	NR	-5.4 (-7.3,-3.5)
McAuley comp	30	NR	NR	67.0	16.0	NR	
Collyns HCL	59	NR	NR	7 to 80	4.0	NR	-12.1 (-16.8,-7.38)
Collyns comp	59	NR	NR	7 to 80	4.0	NR	

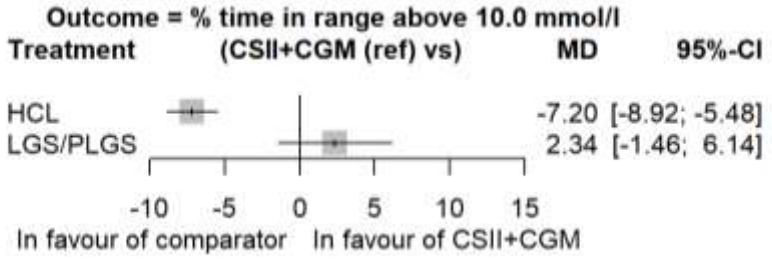
N = number of participants contributing data; yr = years; weeks = treatment duration; BL = mean baseline value ; ES = net effect size comparing reduction in % in range in HCL arm relative to control arm, n.b. the ES values reported were usually statistically adjusted. Benhamou and Thabit and only reported net ES. Ware and Boughton studies reported median values. Median values have no error bars.

Percentage time above range (over 10 mmol/litre) NMA

The NMA included the same 12 estimates as those in the time in range (between 3.9 to 10 mmol/litre) NMA (see network map in figure 7). The

reference treatment class was CSII plus CGM, where estimates over 0 favoured CSII plus CGM. Compared with CSII plus CGM, HCL significantly decreased time above range (percentage above 10.0 mmol/litre), with a mean difference (MD) of -7.2% (95% CI -8.92 to -5.48). The NHS Pilot study reported an unadjusted reduction in time above range of 14 mmol/litre or over (rather than 10 mmol/litre) of 22.2 %.

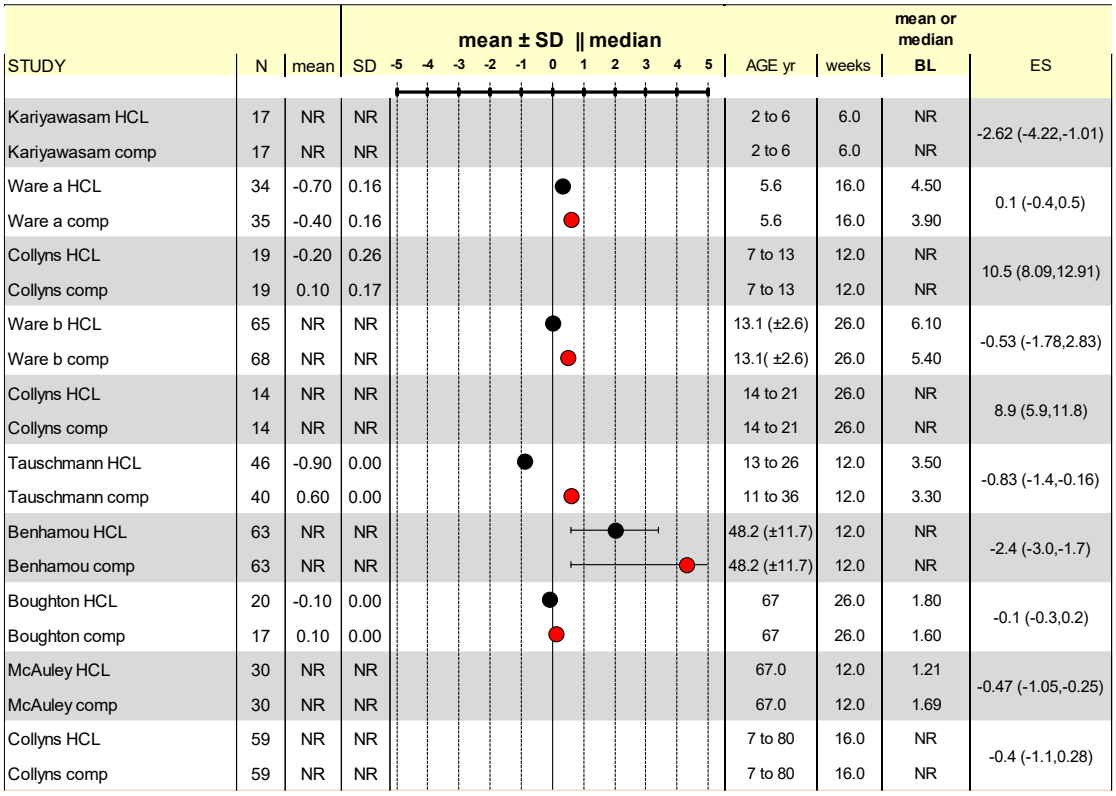
Figure 10 NMA results for time in target range (% more than 10 mmol/litre)



Percentage time below range (less than 3.9 mmol/litre)

For this outcome, a positive mean difference (intervention minus comparator) indicates that more time was spent in the range less than 3.9 mmol/litre in the intervention group and so there was a higher risk of hypoglycaemia for the intervention group compared with the comparator. The EAG said that because of skewed data, results were mostly reported as medians with IQRs, with only a few studies reporting mean (plus or minus sd). Figure 11 shows the percentage time below range (less than 3.9 mmol/litre) reported in the RCTs. The mean or median percentage time below range at baseline was small (6% or less), the ES was also small occasionally reaching statistical significance. The NHS Pilot study did not report this outcome.

Figure 11 Percentage time below range less than 3.9 mmol/litre forest plot

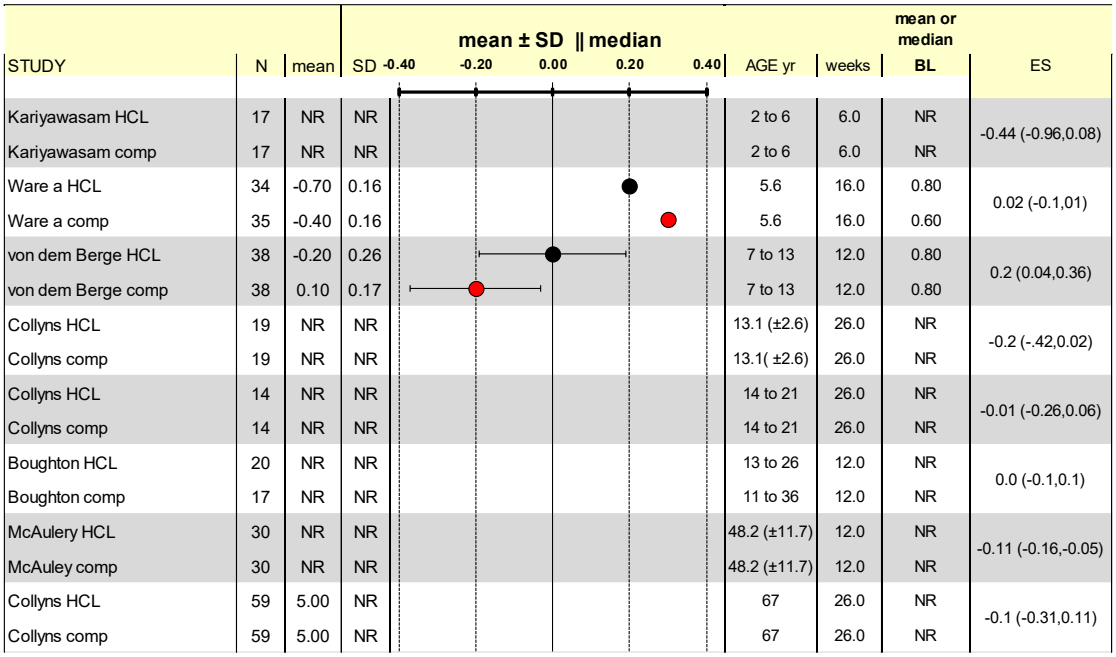


STUDY	N	mean	SD	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-2.62 (-4.22,-1.01)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16	5.6	16.0	4.50	0.1 (-0.4,0.5)
Ware a comp	35	-0.40	0.16	5.6	16.0	3.90	
Collyns HCL	19	-0.20	0.26	7 to 13	12.0	NR	10.5 (8.09,12.91)
Collyns comp	19	0.10	0.17	7 to 13	12.0	NR	
Ware b HCL	65	NR	NR	13.1 (±2.6)	26.0	6.10	-0.53 (-1.78,2.83)
Ware b comp	68	NR	NR	13.1(±2.6)	26.0	5.40	
Collyns HCL	14	NR	NR	14 to 21	26.0	NR	8.9 (5.9,11.8)
Collyns comp	14	NR	NR	14 to 21	26.0	NR	
Tauschmann HCL	46	-0.90	0.00	13 to 26	12.0	3.50	-0.83 (-1.4,-0.16)
Tauschmann comp	40	0.60	0.00	11 to 36	12.0	3.30	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-2.4 (-3.0,-1.7)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.10	0.00	67	26.0	1.80	-0.1 (-0.3,0.2)
Boughton comp	17	0.10	0.00	67	26.0	1.60	
McAuley HCL	30	NR	NR	67.0	12.0	1.21	-0.47 (-1.05,-0.25)
McAuley comp	30	NR	NR	67.0	12.0	1.69	
Collyns HCL	59	NR	NR	7 to 80	16.0	NR	-0.4 (-1.1,0.28)
Collyns comp	59	NR	NR	7 to 80	16.0	NR	

N = number of participants contributing data; yr = years; weeks = treatment duration; BL = mean baseline value ; ES = net effect size comparing reduction in % in range in HCL arm relative to control arm, n.b. the ES values reported were usually statistically adjusted

Some of the RCTs also reported percentage time below range less than 3.0 mmol/litre. The mean or median percentage time below range was less than 1.5% in both arms (see table 3, in the external assessment report) and ES values (HCL compared with comparator) reported were very small. These are shown in figure 12. This outcome was reported in the NHS Pilot study. The percentage times below range were reported as: baseline 0.36%; follow up 0.34%; providing a difference for HCL of -0.02 (95%CI : -0.01 to 0.2).

Figure 12 Percentage time below range less than 3.0 mmol/litre forest plot



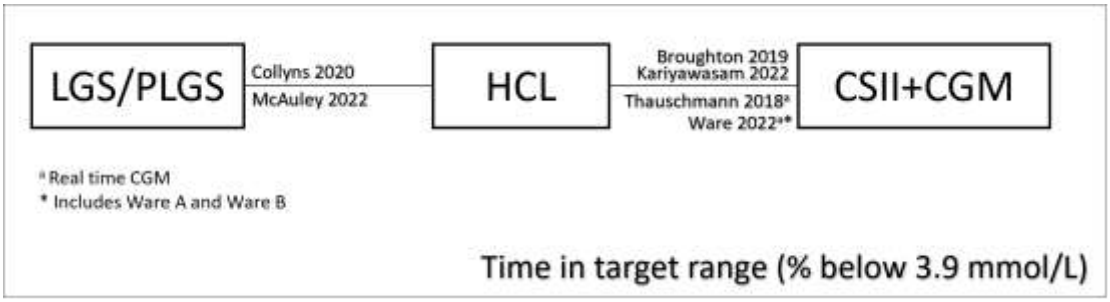
STUDY	N	mean	SD	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-0.44 (-0.96,0.08)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16	5.6	16.0	0.80	0.02 (-0.1,01)
Ware a comp	35	-0.40	0.16	5.6	16.0	0.60	
von dem Berge HCL	38	-0.20	0.26	7 to 13	12.0	0.80	0.2 (0.04,0.36)
von dem Berge comp	38	0.10	0.17	7 to 13	12.0	0.80	
Collyns HCL	19	NR	NR	13.1 (±2.6)	26.0	NR	-0.2 (-.42,0.02)
Collyns comp	19	NR	NR	13.1(±2.6)	26.0	NR	
Collyns HCL	14	NR	NR	14 to 21	26.0	NR	-0.01 (-0.26,0.06)
Collyns comp	14	NR	NR	14 to 21	26.0	NR	
Boughton HCL	20	NR	NR	13 to 26	12.0	NR	0.0 (-0.1,0.1)
Boughton comp	17	NR	NR	11 to 36	12.0	NR	
McAulery HCL	30	NR	NR	48.2 (±11.7)	12.0	NR	-0.11 (-0.16,-0.05)
McAuley comp	30	NR	NR	48.2 (±11.7)	12.0	NR	
Collyns HCL	59	5.00	NR	67	26.0	NR	-0.1 (-0.31,0.11)
Collyns comp	59	5.00	NR	67	26.0	NR	

N = number of participants contributing data; yr = years; weeks = treatment duration; BL = mean baseline value ; ES = net effect size comparing reduction in % in range in HCL arm relative to control arm, n.b. the ES values reported were usually statistically adjusted

Percentage time below range (less than 3.9 mmol/litre) NMA

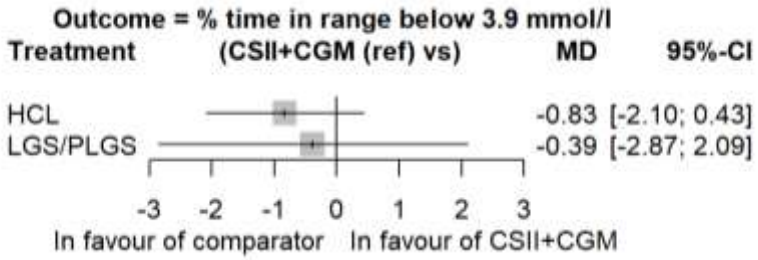
The NMA included 7 estimates from 7 studies as shown in the network map (figure 13). The reference treatment class was CSII plus CGM, where estimates more than 0 favoured CSII plus CGM.

Figure 13 Network map of time below range less than 3.9 mmol/litre



Although there was a mean difference of less than 0 (that is, favouring HCL) The EAG said there was no statistically significant difference between HCL and CSII plus CGM. The NMA forest plot is shown in figure 14.

Figure 14 NMA results for time below range less than 3.9 mmol/litre



Subgroup analyses

The EAG did a subgroup analysis where studies were categorised based on mean or median age of participants at baseline. Participants less than 18 years were classed as children and young adults, participants 18 years and over were classed as adults. The NMA results in the subgroups were similar to those in the whole population. The change in HbA1c percentage for HCL was -0.31 (-0.43, -0.20) in the children and young adults subgroup and -0.24 (-0.32, -0.15) in the adult subgroup. Find full details and results of the subgroup analyses on pages 104 to 105 of the external assessment report.

Intermediate outcomes: Observational studies

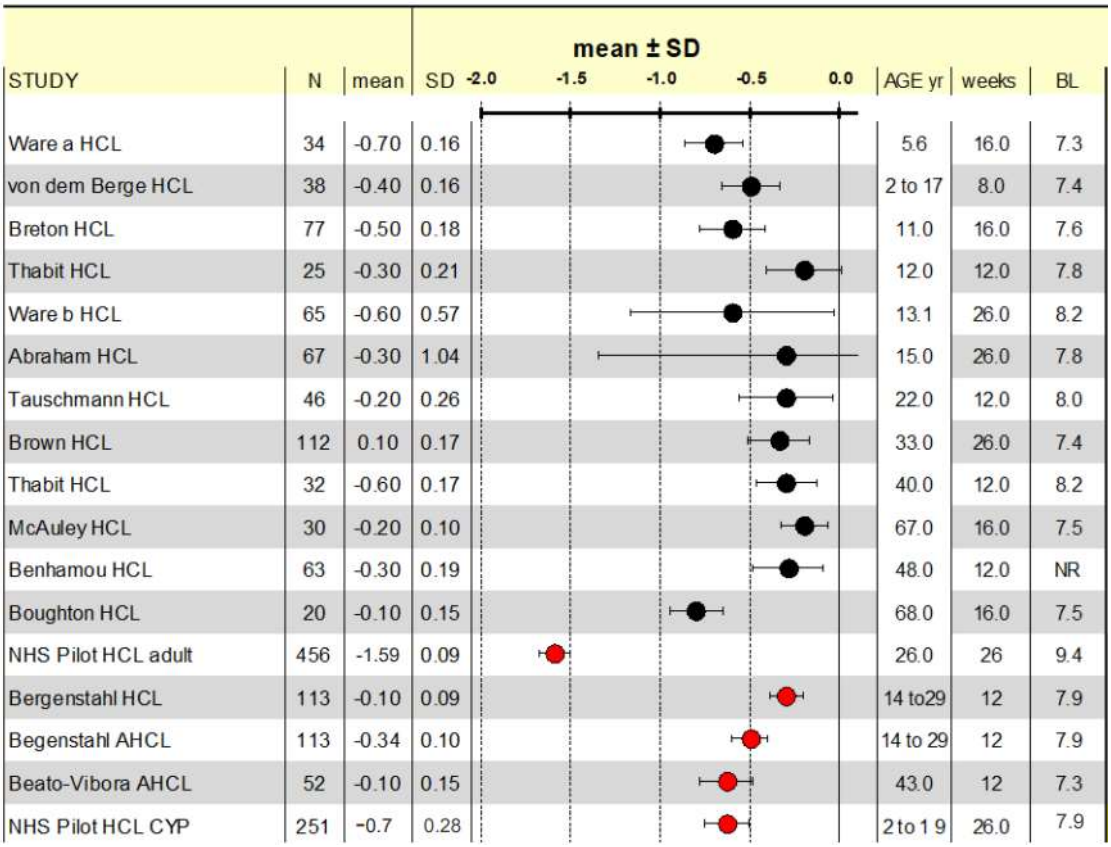
The EAG said that the outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of

glycaemic performance such as HbA1c percentage, percentage time in range (3.9 to 10 mmol/litre), and percentage time above range (over 10mmol/litre) all improved on transfer to HCL (or to AHCL) without any strong evidence that hypoglycaemia became more of a problem. However, the EAG said that changes in hypoglycaemia were mostly underpowered in these studies.

Change in HbA1c percentage

HbA1c percentage improved on transfer to HCL (or to an advanced HCL). The range of change was narrow across RCTs and single arm studies. The improvement in HbA1c percentage level was much greater in the NHSE adult pilot study, however the EAG said that in this study, the baseline level was considerably above that in all other studies (around 9.4%) and so there was greater scope for improvement. In the NHS Pilot with children and young people (CYP) baseline HbA1c was lower (around 7.8%) and benefit more modest (-0.70%). Figure 15 shows the change in HbA1c percentage from baseline in study participants receiving HCL intervention.

Figure 15 Change in HbA1c % from baseline in study participants receiving HCL intervention



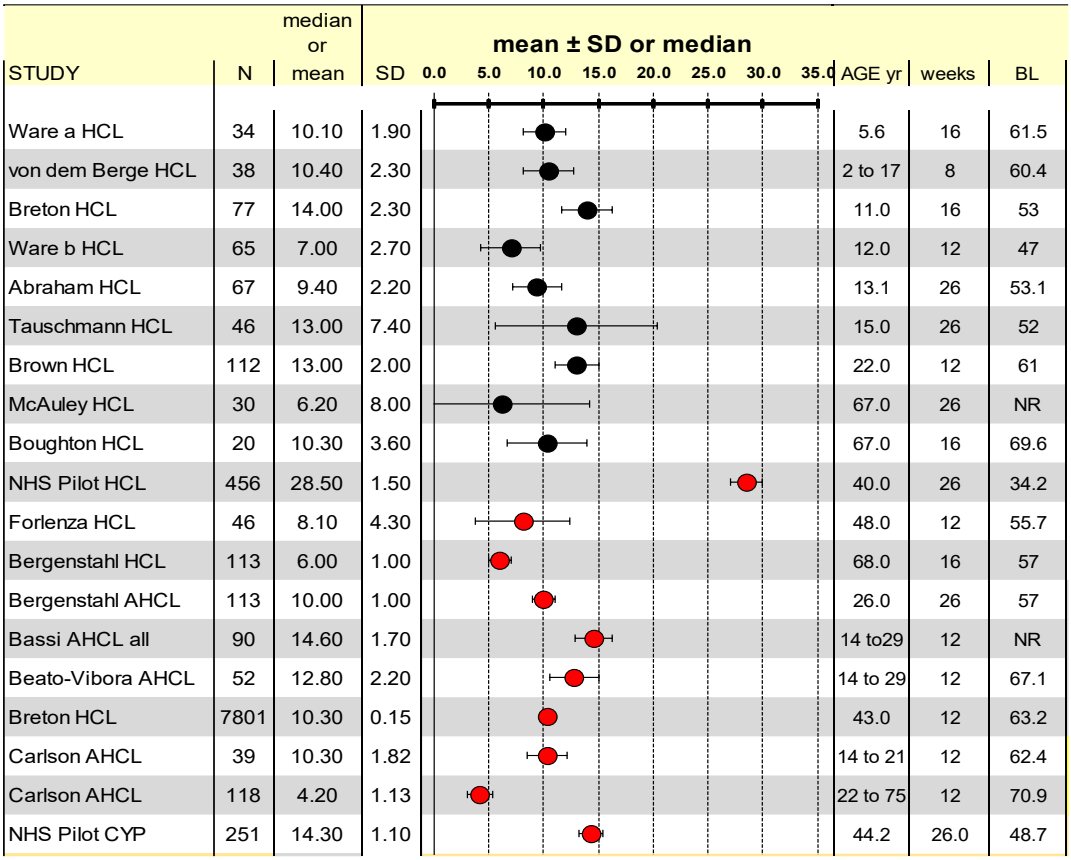
STUDY	N	mean	SD	AGE yr	weeks	BL
Ware a HCL	34	-0.70	0.16	5.6	16.0	7.3
von dem Berge HCL	38	-0.40	0.16	2 to 17	8.0	7.4
Breton HCL	77	-0.50	0.18	11.0	16.0	7.6
Thabit HCL	25	-0.30	0.21	12.0	12.0	7.8
Ware b HCL	65	-0.60	0.57	13.1	26.0	8.2
Abraham HCL	67	-0.30	1.04	15.0	26.0	7.8
Tauschmann HCL	46	-0.20	0.26	22.0	12.0	8.0
Brown HCL	112	0.10	0.17	33.0	26.0	7.4
Thabit HCL	32	-0.60	0.17	40.0	12.0	8.2
McAuley HCL	30	-0.20	0.10	67.0	16.0	7.5
Benhamou HCL	63	-0.30	0.19	48.0	12.0	NR
Boughton HCL	20	-0.10	0.15	68.0	16.0	7.5
NHS Pilot HCL adult	456	-1.59	0.09	26.0	26	9.4
Bergenstahl HCL	113	-0.10	0.09	14 to29	12	7.9
Begenstahl AHCL	113	-0.34	0.10	14 to 29	12	7.9
Beato-Vibora AHCL	52	-0.10	0.15	43.0	12	7.3
NHS Pilot HCL CYP	251	-0.7	0.28	2 to 1 9	26.0	7.9

Percentage time in range (between 3.9 to 10 mmol/litre)

Most studies had a baseline time in range (3.9 to 10 mmol/litre) above 50%. In the NHSE adult pilot adult study, the baseline time in range was 34.2%. The EAG said that this likely reflects the broad inclusion of patients and indicates that along with the higher HbA1c baseline, that people in this study had poor glycaemic control before receiving the HCL intervention. Similarly, in the NHSE CYP pilot study, the baseline time in range was relatively poor at 48.7%. In the NHSE adult pilot, the benefit from HCL was larger (28.5%) than the other studies with a mean value at the end of follow up of 62.7%. The EAG said that this end of follow up value was similar to the values from the other observational studies. In the NHSE CYP pilot, the end of study time in range was also similar at 63%. Figure 16 shows a forest plot of percentage

time in range (between 3.9 and 10 mmol/litre) in study participants from both RCTs and observational studies that had HCL intervention.

Figure 16 Change from baseline of percentage time in range (3.9 to 10 mmol/litre)



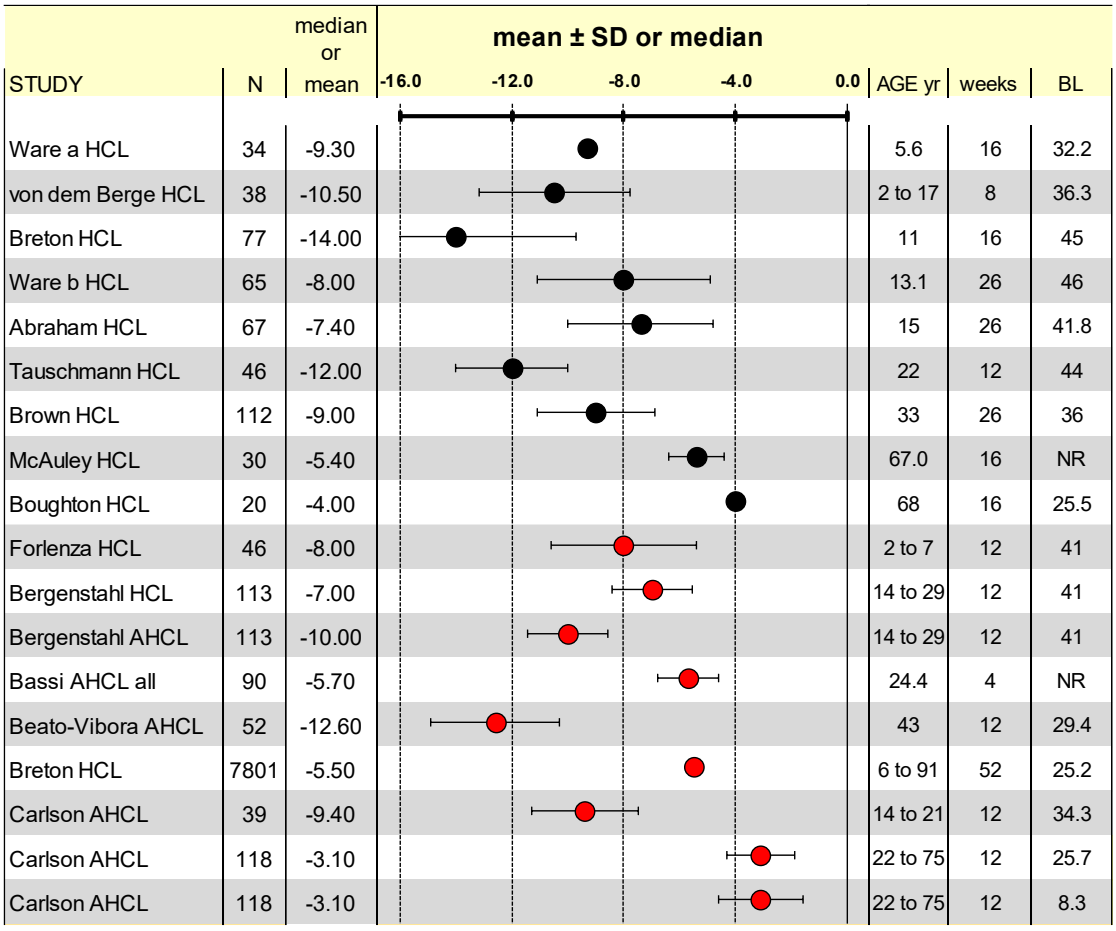
STUDY	N	median or mean	SD	AGE yr	weeks	BL
Ware a HCL	34	10.10	1.90	5.6	16	61.5
von dem Berge HCL	38	10.40	2.30	2 to 17	8	60.4
Breton HCL	77	14.00	2.30	11.0	16	53
Ware b HCL	65	7.00	2.70	12.0	12	47
Abraham HCL	67	9.40	2.20	13.1	26	53.1
Tauschmann HCL	46	13.00	7.40	15.0	26	52
Brown HCL	112	13.00	2.00	22.0	12	61
McAuley HCL	30	6.20	8.00	67.0	26	NR
Boughton HCL	20	10.30	3.60	67.0	16	69.6
NHS Pilot HCL	456	28.50	1.50	40.0	26	34.2
Forlenza HCL	46	8.10	4.30	48.0	12	55.7
Bergenstahl HCL	113	6.00	1.00	68.0	16	57
Bergenstahl AHCL	113	10.00	1.00	26.0	26	57
Bassi AHCL all	90	14.60	1.70	14 to29	12	NR
Beato-Vibora AHCL	52	12.80	2.20	14 to 29	12	67.1
Breton HCL	7801	10.30	0.15	43.0	12	63.2
Carlson AHCL	39	10.30	1.82	14 to 21	12	62.4
Carlson AHCL	118	4.20	1.13	22 to 75	12	70.9
NHS Pilot CYP	251	14.30	1.10	44.2	26.0	48.7

Percentage time above range (over 10 mmol/litre)

All studies reported an improvement from baseline, ranging from 3.0% to 14% reduction in percentage time above range. The NHSE adult pilot study did not report this outcome but did report unadjusted (uncorrected) percentage time above range (above 14 mmol/litre). At baseline the percentage time above 14 mmol/litre was 37.4% and a further 26.6% of time was in the range between 10 and 14 mmol/litre, indicating that at baseline the NHSE Pilot study participants had a large percentage of time in the hyperglycaemic state

(around 64% of time). Transfer to HCL resulted in large reduction of 22.6% time above the 14 mmol/litre range. The benefit of HCL in the range 10 to 14 mmol/litre was more modest (a reduction in time above range of 4%). The EAG said that these results suggest that HCL improved hyperglycaemia considerably in the upper range but that a substantial proportion remained slightly above the 10 mmol/litre cut off. Figure 17 shows a forest plot of the change from baseline in the percentage time above range (above 10 mmol/litre).

Figure 17 Change from baseline of percentage time above range (above 10 mmol/litre)



STUDY	N	median or mean	AGE yr	weeks	BL
Ware a HCL	34	-9.30	5.6	16	32.2
von dem Berge HCL	38	-10.50	2 to 17	8	36.3
Breton HCL	77	-14.00	11	16	45
Ware b HCL	65	-8.00	13.1	26	46
Abraham HCL	67	-7.40	15	26	41.8
Tauschmann HCL	46	-12.00	22	12	44
Brown HCL	112	-9.00	33	26	36
McAuley HCL	30	-5.40	67.0	16	NR
Boughton HCL	20	-4.00	68	16	25.5
Forlenza HCL	46	-8.00	2 to 7	12	41
Bergenstahl HCL	113	-7.00	14 to 29	12	41
Bergenstahl AHCL	113	-10.00	14 to 29	12	41
Bassi AHCL all	90	-5.70	24.4	4	NR
Beato-Vibora AHCL	52	-12.60	43	12	29.4
Breton HCL	7801	-5.50	6 to 91	52	25.2
Carlson AHCL	39	-9.40	14 to 21	12	34.3
Carlson AHCL	118	-3.10	22 to 75	12	25.7
Carlson AHCL	118	-3.10	22 to 75	12	8.3

Percentage time below range (less than 3.9 mmol/litre)

The change in percentage time below range (less than 3.9 mmol/litre and less than 3.0 mmol/litre) was reported in most observational studies. Both

percentage time below 3.9 mmol/litre at baseline (range from 2.1% in the NHS Pilot adult study to 3.4%) and after HCL intervention were small, with a resulting mean improvement of around 1% or less. The NHS pilot adult study reported a change of -0.5% and an associated p value of less than 0.001. The NHSE CYP pilot study also reported a statistically significant improvement. Only 1 other study (Carlson et al., adult patients) reported a statistically significant improvement (p less than 0.05).

Figure 18 shows the mean (95% CI) change from baseline in percentage time below 3.9 mmol/litre; confidence intervals were wide. Some of the single arm studies reported other outcomes indicative of hypoglycaemic status, most commonly percentage time below range less than 3.0 mmol/litre. The results are shown in figure 19.

Figure 18 Mean (95% CI) change from baseline in percentage time below range less than 3.9 mmol/litre

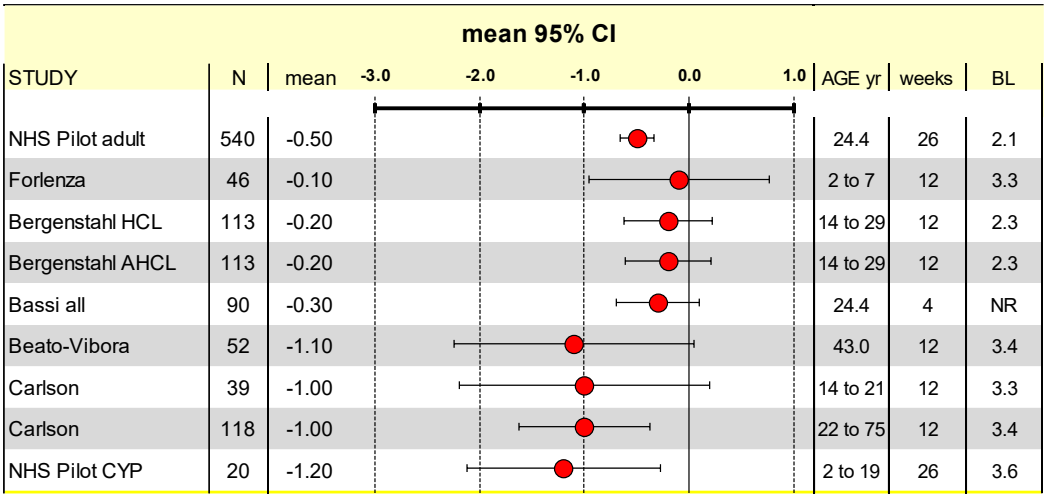
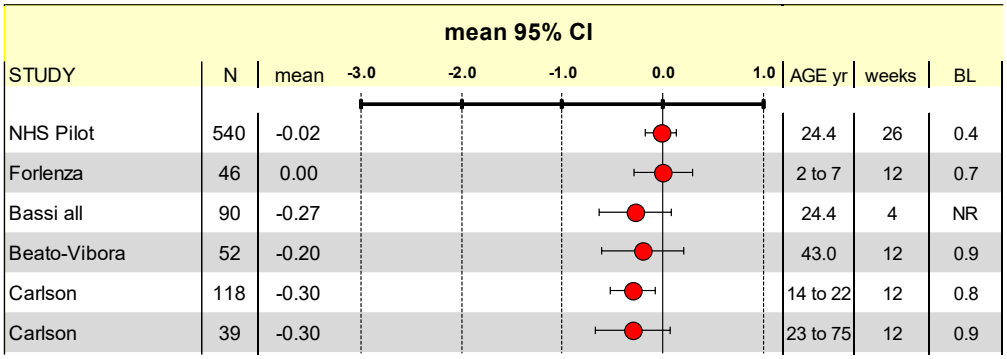


Figure 19 Mean (95% CI) change from baseline in percentage time below range less than 3.0 mmol/L



Clinical outcomes

The EAG said that the studies did not consistently report any additional outcomes, however some of the RCTs did report on adverse events.

Adverse events

The EAG said that the RCTs reported a low number of adverse events for both treatment groups. Although some reports of hypoglycaemia were identified in the included studies, the EAG did not identify any clear trends and differences between HCL and the comparator. In the study by Benhamou et al. 2022, one severe hypoglycaemia event and one ketoacidosis event were reported in 2 different participants. The ketoacidosis occurred while the patient was under closed loop. The severe hypoglycaemia occurred while the patient had temporarily switched to open loop treatment.

Patient reported outcomes

The EAG said that there were several studies that used various tools and different survey approaches to report technology satisfaction. Only 1 study (Benhamou et al. 2022), comparing an open loop to a closed loop system, found that user satisfaction had increased significantly after the closed loop period. Other studies did not observe any significant changes.

The FLAIR study, reported mean scores on the glucose monitoring satisfaction survey at screening, at the end of the period using the HCL system and at the end of the period using the advanced HCL system. Emotional burden and behavioural burden satisfaction subscales were significantly improved with the advanced HCL system.

The study by Tauschmann et al. 2018 used the Paediatric Quality of Life Inventory (PedsQL) questionnaire. This was given to participants and guardians of participants under 17 years, before and after the intervention period. The use of the closed-loop system was not associated with any additional burden.

McAuley et al. 2022 used the hypoglycaemia fear survey score and reported no significant difference between HCL and sensor augmented pump (SAP) groups.

The study by Wheeler et al. 2022 reported patient reported outcomes from the Collyns et al. 2021 study. It compared technology satisfaction and sleep quality between advanced HCL and SAP plus predictive low-glucose management (PLGM). Overall treatment satisfaction was significantly higher for the advanced HCL group compared to the SAP plus PLGM group. There was no significant difference in anticipated worry of hypoglycaemia. Results showed no changes in the well-being index and hypoglycaemia fear or confidence.

External submissions

Medtronic submission

The Medtronic clinical effectiveness submission compared the (Advanced) HCL systems with real time CGM plus continuous subcutaneous insulin infusion (non-integrated). Find full details of the submission, including a critique by the EAG, on pages 115 to 119 in the external assessment report.

Dexcom submission

The Dexcom clinical effectiveness submission compared HCL with sensor augmented pump (SAP) systems, based on the results of 1 systematic review and NMA, and 8 RCTs. Find full details of the submission, including a critique by the EAG, on pages 119 to 123 in the external assessment report.

CamDiab submission

The CamDiab clinical effectiveness submission included 10 studies. Find full details of the submission, including a critique by the EAG, on pages 123 to 127 in the external assessment report.

Tandem submission

The Tandem clinical effectiveness submission included a poster and 2 papers (1 unpublished). Find full details of the submission, including a critique by the EAG, on pages 127 to 129 in the external assessment report.

3 Cost effectiveness evidence

The EAG did a systematic review to identify any published economic evaluations of hybrid closed loop systems for managing blood glucose levels in people with type 1 diabetes. Find the full systematic review results on pages 134 to 146 of the external assessment report. The EAG also constructed a de novo economic model to assess the cost effectiveness of hybrid closed loop systems for managing blood glucose levels in people with type 1 diabetes.

Systematic review of cost-effectiveness evidence

The EAG identified 6 studies that were included in the review, 5 were economic evaluations of hybrid closed loop (HCL) systems and 1 was a budget impact analysis. Four of the economic evaluation studies (Jendle et al. 2019, Jendle et al. 2021, Roze et al. 2021, and Serne et al. 2022) used the IQVIA CORE Diabetes Model (CDM). One study by the Scottish Health

Technologies Group (SHTG) used the Sheffield type 1 diabetes model (Harbour et al. 2022). The budget impact analysis was done by the Canadian Agency for Drugs and Technology in Health (CADTH) and used a customised Microsoft Excel tool.

The economic evaluation studies compared the cost effectiveness of HCL systems with various diabetes management technologies (for example, isCGM plus MDI, CSII and self-monitoring of blood glucose). Two of the 6 studies were done in Sweden (Jendle et al. 2019 and Jendle et al. 2021), and 1 each in the UK (Roze et al. 2021), Netherlands (Serne et al. 2022), Scotland (Harbour et al. 2022) and Canada (CADTH, 2021). The studies were assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and Phillips checklists where applicable.

The EAG said that there was substantial heterogeneity in the choice of baseline cohort data and treatment effects data. Only the SHTG study used baseline data for its population of interest.

The EAG said that structure of the models used in the cost effectiveness studies were good quality. The IQVIA CDM and the Sheffield type 1 diabetes model are validated models for evaluating diabetes technologies. It also said that the IQVIA CDM is capable of capturing both long and short term clinical complications and costs associated with T1DM and has been extensively validated for use in this condition.

The EAG said that in 4 of the cost effectiveness studies, the base case results were very sensitive to the severe hypoglycaemic rates (SHE) and changes in the assumptions relating to the quality-of-life benefit associated with reduced fear of hypoglycaemia (FOH). It also said that the cost effectiveness acceptability curves from these studies showed that HCL systems are expected to be cost effective compared with the comparator technologies at various hypothetical maximum acceptable thresholds.

Company cost effectiveness submissions

Medtronic submission

The Medtronic submission used the IQVIA CDM to compare the advanced HCL 780G Minimed pump with CSII using the 640G Minimed pump. Find full details of the submission and the EAG's observations on pages 154 to 156 of the external assessment report.

Dexcom submission

[redacted]. Find full details of the submission and the EAG's observations on pages 157 to 159 of the external assessment report.

CamDiab submission

The CamDiab submission presented two cost effectiveness modelling exercises, one based upon the Dan05 study among patients aged 6 to 18 years using the [redacted] and the other based upon the KidsAP02 study among patients aged 1 to 7 years using [redacted] Find full details of the submission and the EAG's observations on pages 159 to 163 of the external assessment report.

Tandem submission

The Tandem submission referenced the Dexcom submission economics and provided no additional cost effectiveness estimates.

Economic analysis

The EAG said that the IQVIA CDM and the Sheffield type 1 diabetes model are both suited to economic analyses of diabetes management technologies allowing for deterministic and probabilistic sensitivity analyses to be done. The IQVIA CDM uses time, time in state and diabetes dependent probabilities to simulate progression of diabetes and diabetes related complications with both diabetes and non-diabetes mortality accounted for. It allows clinical and cost

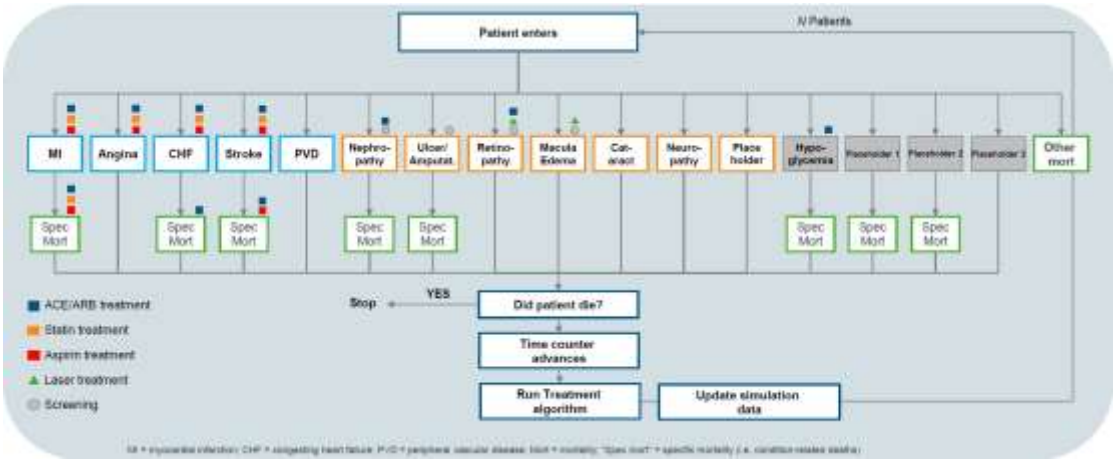
data to be inputted directly into the model or for default parameters to be used. The EAG preferred the IQVIA CDM. It used real world data from the UK as a simulation cohort. Further details on clinical and cost inputs are presented in the following sections.

Model structure

The modelled treatment pathway assumes that people remain on a single treatment option throughout: either CSII plus CGM (intermittently scanned or real time), PLGS or HCL.

In line with DG21 and NG17 the EAG used the IQVIA CDM to model the micro and macro vascular complications of diabetes and patients' overall survival. The IQVIA CDM predicts the progress of people with T1DM over their lifetime, modelling the incidences of the 11 macro and micro vascular complications, the likelihoods of which are affected by T1DM. Figure 20 shows the structure of the IQVIA CDM.

Figure 20 IQVIA CDM structure



The EAG said that the default and recommended setting is to sample 1,000 people from the patient characteristics and run each of these people through the model 1,000 times. The IQVIA team advised the EAG that for modelling a T1DM cohort only the non-specific mortality approach should be used. The IQVIA CDM models deaths from myocardial infarction, congestive heart

failure, stroke and renal disease. Therefore, the EAG removed deaths due to cardiovascular disease, cerebrovascular disease and renal failure from the England and Wales life table (2015 to 2017) to determine non-specific mortality estimates. Deaths due to hypertension were also removed in a scenario analysis.

The EAG said it had concerns about the reliability of using the IQVIA CDM to model a paediatric population due to key sources using data that relates to an adult population. It said that the model is affected by both the longer duration that is required for a lifetime horizon and the degree to which the risk equations of the model relate to a paediatric population. The EAG did an exploratory analysis using the NMA results for the subset of paediatric studies and a scenario analysis that applies the NHSE paediatric pilot results (see exploratory paediatric modelling results section). This analysis is shown in appendix 5 of the external assessment report.

Modelling of other clinical effects

The EAG said that there was a lack of clarity around the IQVIA CDM implementation of the quality of life decrements for non severe hypoglycaemic events (NSHEs). The EAG used the IQVIA CDM to model the effects of HbA1c on survival and the micro and macro vascular complications of diabetes. The IQVIA CDM overall survival curve for each technology is then coupled with technology specific treatment costs and comparator specific NSHE and severe hypoglycaemic event (SHE) rates (in scenario analyses). With the addition of the events' unit costs and disutilities this enables technologies' other effects to be incorporated into the cost effectiveness analysis.

Perspective, discount rates and time horizon

The perspective for costs is the NHS and PSS, the perspective for benefits is that of the patient, and costs and benefits are discounted at 3.5%. The base case assumes a 50 year time horizon which the EAG said is effectively a

lifetime horizon for most patients. Because of the uncertainty around the IQVIA CDM outputs for longer time horizons, the EAG did scenario analyses which explored time horizons of 8, 12 and 24 years.

Population

The EAG used data from the 2019 to 2020 National Diabetes Audit subgroup of those on pump therapy for the key baseline characteristics. In a scenario analysis it also used data from the NHSE adult pilot study. Table 2 shows the population baseline characteristics.

Table 2 Population baseline characteristics

Population characteristic	National Diabetes Audit Mean	National Diabetes Audit SD	NHSE adult pilot mean	NHSE adult pilot SD
Age	43.4	17.8	40	16.3
Duration diabetes	24.8	15.6	21	11.8
HbA1c	8.0	1.1	9.4	2.0
Male	42%	n.a.	33%	n.a.
White	97%	n.a.	96%	n.a.
Black	1%	n.a.	1%	n.a.
Asian	2%	n.a.	3%	n.a.

For other baseline characteristics needed as inputs to the IQVIA CDM, the EAG took them from NG17, which uses data from the Repose trial comparing pumps with multiple daily injections. These characteristics relate to a slightly more severe controlled group of people with a baseline HbA1c of 9.1%. Full details of these additional baseline characteristics are in table 39 (appendix 7) of the external assessment report.

Comparators

In addition to the intervention (HCL), the cost effectiveness analysis considered the 2 comparators in the EAG network meta-analysis (NMA):

- CSII plus CGM non-integrated

- LGS/PLGS

The EAG did not evaluate CSII plus CGM separately as CSII plus real time CGM (rtCGM) and CSII plus intermittently scanned CGM (isCGM). It assumed the balance to be 10% CSII plus rtCGM and 90% CSII plus isCGM for adult patients. However, the EAG said that this may underestimate CSII plus isCGM use. In the scenario analysis that uses the NHSE adult pilot data, the EAG assumed that CSII plus CGM was 100% CSII plus isCGM due to prior use of CSII plus isCGM being reported as a requirement. Because LGS/PLGS systems are no longer available to purchase in the UK, this may not be a relevant comparator.

Model inputs

Modelling of HbA1c effects: HbA1c progression

In the base case analysis the EAG assumed no annual worsening of HbA1c over time. However, as the IQVIA CDM default for HbA1c progression applies an annual worsening of 0.045%, the EAG included this as a scenario analysis, applied to both the intervention and comparator arms.

HbA1c effects

In the base case, the EAG used the results of the RCT NMA (see section 2, intermediate outcomes -RCTs). Two scenario analyses were done. One that restricted the NMA evidence base to adult trials, and 1 where the mean HbA1c percentage change of the NHSE adult pilot was used (applied to the NHSE adult pilot baseline characteristics). The base case assumes that the HbA1c effect endures for the model time horizon of 50 years. Scenario analyses that use durations of 5 years, 10 years and 20 years were also done. Table 3 shows the mean HbA1c percentage changes for each technology.

Table 3 HbA1c percentage changes

Intervention/ comparator	NMA (base case)	NMA adult (scenario analysis)	NHSE adult pilot (scenario analysis)
HCL	-0.29% (0.033%)	-0.24% (0.043%)	-1.50% (0.051%)
PLGS	-0.06% (0.079%)	-0.01% (0.115%)	-
CSII plus CGM	0.00%	0.00%	-

Non severe hypoglycaemic event (NSHE) and severe hypoglycaemic event (SHE) rates

NSHE rates were not reported in the RCTs. The EAG did not include NSHE or SHE effects in its base case. The EAG did scenario analyses that estimate NSHE and SHE rates based upon estimates in the literature coupled to the EAG NMA results for time below range.

For NSHEs the EAG did a scenario analysis that couples the annual NSHE rate for HCL of 20.8 (Brown et al. 2019 and Breton et al. 2022) with the EAG NMA time below 3.0 mmol/litre net effect estimates, the weighted mean of the end of trials' time below 3.0 mmol/litre for the CSII plus CGM and the assumption that the number of NHSEs is proportionate to the time below 3.0 mmol/litre. The EAG estimates of NSHEs and SHEs used in the main scenario analysis are shown in table 4.

Table 4 EAG estimates of NHSEs and SHEs for main scenario analysis

Intervention/ comparator	Time below 3.0mmol/litre NMA net	Time below 3.0mmol/litre Absolute	Time below 3.0mmol/litre Ratio	NSHE	SHE
HCL	-0.14%	0.46%	100%	20.8	0.26
PLGS	-0.16%	0.44%	96%	19.9	0.25
CSII plus CGM	Reference	0.60%	130%	25.9	0.32

Scenarios of annual NSHE rates of 57.2 (from Abraham et al. 2021) and 13.0 (from Kariyawasam et al. 2021) for HCL are also presented. For SHEs, the EAG used the same approach in exploratory scenarios that assume SHE rates are proportionate to time below 3.0 mmol/litre, coupled with the annual SHE rate for HCL of 0.26 (reported in McAuley et al. 2020). Find details of NSHE and SHE rates on pages 169 to 175 of the external assessment report.

Inputs for exploratory paediatric modelling

In the exploratory analysis the EAG revised the key baseline characteristics to reflect the NHSE paediatric pilot baseline data. These are shown in Table 5.

Table 5 Exploratory paediatric modelling: baseline characteristics

Population characteristic	NHSE paediatric pilot mean	NHSE paediatric pilot SD
Age	12	3.5
Duration diabetes	6.6	3.7
HbA1c	7.9%	1.1%
Male	58%	n.a.
White	94%	n.a
Black	3%	n.a.
Asian	3%	n.a.

The base case used the NMA HbA1c results for the subset of paediatric studies and a scenario analysis was done that used the HbA1c results from the NHSE paediatric pilot study. The HbA1c model inputs are shown in table 6.

Table 6 Exploratory paediatric modelling: HbA1c (s.e.) changes

Intervention/ comparator	NMA (base case)	NMA paediatric studies	NHSE paediatric pilot (scenario analysis)
HCL	-0.29% (0.033%)	-0.31% (0.059%)	-0.70% (0.019%)
PLGS	-0.06% (0.079%)	-0.11% (0.125%)	-
CSII plus CGM	0.00%	0.00%	-

Because of the lower mean baseline age, the EAG extended the time horizon to 80 years. The EAG also assumed that paediatric patients had not developed any of the complications associated with diabetes and modelled by the IQVIA CDM.

Costs

Training costs

The EAGs base case does not include training costs involved from moving from MDI plus CGM to CSII plus CGM or to HCL, because estimates for these in terms of staff time and outpatient visits were the same. However, moving from CSII plus CGM to HCL, with most patients moving from isCGM to rtCGM results in a training cost of £1,132.

Treatment costs

The EAG used current list prices for the technologies provided by the NHS Supply Chain. It said that the costs of HCL pumps and consumables differ slightly between systems but the total 4 year costs are similar, except for 1 system which is around an annual average of £500 more than the unweighted average. This also applies to the LGS/PLGS systems.

The EAG used the unweighted averages for year 1 and years 2, 3 and 4 (see table 7) and provides a scenario analysis which increases these by £500 for both HCL and LGS/PLGS. To account for potential reductions in CGM sensor durations, the EAG increased the cost of all CGM sensors by 5%.

Table 7 Pump and consumable costs

Intervention/ comparator	Year 1	Years 2 to 4	4 year total	Average
HCL	£7,931	£5,015	£22,975	£5,744
PLGS	£7,135	£4,455	£20,498	£5,125
CSII plus CGM	£5,480	£3,751	£16,734	£4,184

For insulin costs, the EAG added an additional annual average of £315 to all regimes based on a daily average of 50 IU.

Companies indicated that prices will change for the next financial year and some products have confidential volume discounts. The EAG has addressed these aspects in the separate confidential appendix.

Ongoing visits and costs of micro and macro vascular complications

The EAG assumed that that without complications the average patient once established on treatment is seen in an outpatient clinic once per quarter, at an annual routine outpatient cost of £640. Other ongoing routine management costs and costs of micro and macro vascular complications are taken from NG17 and inflated to 2019 to 2020 prices. Find details of these costs in tables 27 and 28 (pages 200 to 201) in the external assessment report.

NSHE and SHE costs

Where NSHEs and SHEs are included in scenario analyses, the EAG applied a cost of £1.83 for SHEs not requiring outside medical attention and of £542 for those requiring medical attention. It assumed that 37.9% of SHEs require medical attention. The EAG also did a scenario analysis that increased the cost of SHEs not requiring outside medical attention to £36 and those requiring medical attention to £628. Another scenario analysis costs all SHEs at the 2021 updated cost of £381 of NG17.

Health-related quality of life and QALY decrements

The EAG used a value of 0.839 for quality of life without complications for patients with T1DM. This was based on the EQ-5D baseline average reported by Peasgood et al. 2016.

Disutilities of micro and macro vascular complications

Disutilities of micro and macro vascular complications are taken from the default values of the IQVIA CDM, in line with NG17. Find details of these in table 23, page 187 of the external assessment report.

Disutilities of hypoglycaemia events

The EAG said that for the disutility of NSHEs (used only in scenario analyses), the studies by Gordon et al. and Currie et al. provide estimates that conform most closely to the NICE reference case.

Hypoglycaemia events and carer disutilities

The EAG did not identify any data that quantified disutilities associated with impact of hypoglycaemic events on parents and carers. It said that a reasonable upper limit for the effect upon carers might be to assume that they have the same disutility as the person with T1DM that they are caring for. The EAG did a scenario analysis that doubles the disutilities associated with hypoglycaemia events to reflect possible effects on carers.

Base case results

The base case modelling disaggregate results are shown in table 29 of the external assessment report (see page 203). These results showed that compared with CSII plus CGM, the use of HCL is estimated to increase undiscounted survival by 0.458 years. Discounting reduces the net survival gain to 0.149 years, giving a patient gain of 0.160 QALYs. The net treatment cost of £31,185 is partly offset by renal savings of £421 and eye savings of £3,085, resulting in a net cost of £28,628.

Cost effectiveness of HCL

The base case results suggest that PLGS is extendedly dominated by HCL, and that HCL has a cost effectiveness estimate of £179k per QALY gained. The EAG's base case cost effectiveness estimates are shown in table 8.

Table 8 Base case cost effectiveness estimates

Technology	Life Years Undiscounted	Total QALYs	Total Costs	ICER compared with CSII
CSII	32.499	14.232	£134,661	-
PLGS	32.685	14.291	£152,706	£305,852
HCL	32.957	14.392	£163,289	£178,925

The EAG said that the IQVIA CDM does not allow periodic capital costs to be modelled, so for the deterministic modelling it used the modelled OS curves to estimate treatment costs.

Analysis of alternative scenarios

Find the full list of the EAG's scenario analyses on pages 205 to 206 of the external assessment report.

Scenario analyses

In the scenario analyses, the EAG said that PLGS was extendedly dominated throughout and therefore was not shown in the results. Table 9 shows the ICERs for HCL compared with CSII plus CGM.

Table 9 Scenario analyses' ICERs: HCL vs CSII+CGM

Scenario	Change in costs	Change in QALYs	ICER compared with CSII+CGM
Base case	£28,628	0.160	£179k
SA01a: Only adult studies	£28,734	0.141	£204k
SA01b: Benhamou excluded	£28,096	0.169	£166k
SA02a: NHS adult pilot baseline characteristics	£25,775	0.205	£126k
SA02b: NHS adult pilot characteristics and effect	£12,447	1.004	£12,398
SA02c: SA02b + reduced complication costs	£21,669	1.004	£21,583
SA03a: 8 year time horizon	£12,740	0.014	£910k
SA03b: 12 year time horizon	£16,601	0.025	£664k
SA03c: 24 year time horizon	£23,975	0.073	£328k

SA04a: 5 year HbA1c effect	£29,571	0.045	£657k
SA04b: 10 year HbA1c effect	£28,887	0.068	£425k
SA04c: 20 year HbA1c effect	£28,369	0.115	£247k
SA05a: NSHEs with HCL 20.8 annual	£28,628	0.170	£169k
SA05b: NSHEs with HCL 57.2 annual	£28,628	0.173	£166k
SA05c: NSHEs with HCL 13.0 annual	£28,628	0.168	£170k
SA06: HEs: NSHEs and SHEs	£28,325	0.174	£163k
SA07a: SA06 + SHEs Currie values	£28,325	0.235	£121k
SA07b: SA06 + SHEs Nauck values	£28,325	0.260	£109k
SA08a: SA06 + £36/£628 SHE cost	£28,246	0.174	£162k
SA08b: SA06 + £381 SHE cost	£28,069	0.174	£161k
SA09: SA06 + HEs double quality of life effect	£28,325	0.188	£151k
SA10a: CSII 85% isCGM 15% rtCGM	£27,117	0.160	£169k
SA10b: CSII 95% isCGM 5% rtCGM	£30,139	0.160	£188k
SA11: HCL/PLGS annual cost £500 more	£38,244	0.160	£239k
SA12: CSII to HCL training cost £1,132	£29,760	0.160	£186k
SA13a: All-cause mortality	£27,846	0.139	£200k
SA13b: Non-specific mortality excluding hypertension	£28,556	0.171	£167k
SA14: Annual 0.045% HbA1c worsening	£27,694	0.181	£153k

The scenarios with the largest effect on the ICERs were when the NHS adult pilot baseline characteristics and HbA1c effects were used, either with or without reducing the modelled complication costs (SA02b and SA02c). These scenarios reduced the ICERs to £12,398 per QALY and £21,583 per QALY, respectively. All other scenarios that used baseline characteristics from the 2019 to 2020 National Diabetes Audit and HbA1c effects from the NMA had ICERs above £100k, ranging from £109k to £910k per QALY.

Threshold price analyses

The EAG did a threshold price analysis around the average annual cost of HCL that would result in ICERs of £20,000 and £30,000 per QALY. This is shown in the confidential appendix.

Exploratory paediatric modelling

The exploratory paediatric modelling base case disaggregate results are shown in appendix 5 table 34 in the external assessment report. A summary of the exploratory paediatric modelling base case results is shown in table 10.

Table 10 Exploratory paediatric modelling: base case cost effectiveness estimates

Technology	Life Years Undiscounted	Total QALYs	Total Costs	ICER compared with CSII
CSII	60.123	19.252	£176,628	-
PLGS	60.291	19.301	£198,572	£447,834
HCL	60.942	19.448	£209,595	£168,196

As for the adult modelling, PLGS was extendedly dominated by HCL. Compared with CSII plus CGM, the use of HCL is estimated to increase undiscounted survival by 0.819 years. The additional treatment costs of £40,606 are partially offset by savings in renal complications of £2,459 and eye diseases of £5,143 resulting in total net costs of £32,966. With the gain of 0.196 QALYs this gives an ICER of £168,196 per QALY gained.

The EAG did a range of scenario analyses, with resulting ICERs ranging from £25,868 to £191k per QALY. Including only paediatric RCT studies reduced the ICER to £116k per QALY. Using the NHSE CYP pilot HbA1c change of -0.7% improved the ICER to £54,727 per QALY. Including the quality-of-life effects of the improvements reported in the hypoglycaemia fear survey (HFS2-ws) during the pilot further improves the cost effectiveness to £35,259 per QALY. If both parents also have a similar quality of life improvement for 15

years it improves to £25,868 per QALY. Reducing the cost of complications to account for their possible overestimation worsens the cost effectiveness to £69,013 per QALY. Full details of the scenario analyses and results are in appendix 5 table 36 in the external assessment report. The EAG said that in all the scenario analyses the HbA1c effect, the HFS2-ws effect and the composition of CSII+CGM may change as the patient moves from childhood into adulthood

4 Summary

Clinical effectiveness

There were relatively few studies in the clinical effectiveness review (12 RCTs) and studies were heterogeneous. They were of small size including a total of around 450 HCL recipients followed for between 4 and 26 weeks, accumulating around 110 person years of observation. Inclusion criteria were relatively narrow and most participants had reasonably good glycaemic control at entry, as indicated in most of those studies reporting baseline time in range (3.9 to 10 mmol/litre) at greater than 50% (range 47% to 62%), and baseline HbA1c at between 7% and 8%.

The NHSE adult pilot study included a broader spectrum of patients with worse glycaemic control at baseline (HbA1c around 9.4%).

Compared with CSII plus CGM, the NMA showed that the HCL arm of the RCTs had a statistically significant improvement (reduction) in HbA1c percentage of -0.29 (95% CI: -0.37 to -0.21). There was a statistically significant increase in percentage time in range between 3.9 to 10 mmol/litre, with a mean difference of 8.6 (7.03 to 10.22). The NMA also showed that percentage time above range (over 10.0 mmol/litre) was significantly decreased, with a mean difference of -7.2 (-8.89 to -5.51). Control arms also showed improvement, but this was less than that seen with HCL. The outcome estimates reported for observational studies were quantitatively

broadly in line with those from the RCTs. In the NHSE pilot, transfer to HCL resulted in larger improvements than observed in other studies (decrease in HbA1c of 1.5%), which may be due to the poorer baseline status.

The RCT data suggests that the gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia, however the power to detect small event sizes was limited because of the small size of study groups and relatively short treatment duration.

Adverse events were reported in some studies and were mainly low. Patient reported outcomes were assessed using various methods and did not result in clear trends.

Cost effectiveness

The key model inputs that impacted on results were:

- The net effect upon HbA1c
- The duration of the net effect upon HbA1c
- The model time horizon
- Treatment costs

The modelled cost effectiveness of HCL compared with CSII plus CGM is driven by the change in HbA1c and how long that change persists. It is assumed that the HbA1c effect persists for the patient lifetime, and therefore the baseline age determines the duration of the HbA1c effect. In the base case, the national diabetes audit mean age of those on pumps is used, sampling this using the standard deviation.

With the NMA estimated HCL effect on HbA1c of -0.29% compared with CSII plus CGM, the net total cost was estimated to be £28,628 after accounting for fewer complications (reduced eye and renal complications). There was a net undiscounted survival gain of 0.458 years, contributing to a gain of 0.160 QALYs. This resulted in a base case deterministic ICER of £179k per QALY

gained and a probabilistic central estimate of £186k per QALY gained. The EAG said the probability of HCL being cost effective at £20k per QALY and £30k per QALY thresholds were 21% and 31%, respectively.

The ICER was reduced to £126k per QALY gained if the NHSE adult pilot baseline patient characteristics were used. When the NHSE adult pilot change in HbA1c of -1.5% was used this resulted in an ICER of £12,398 per QALY gained. The EAG said that the incidences of renal and eye complications may be overestimated in the model. Adjusting these (that is, reducing by their possible overestimation) increased the ICER to £21,583 per QALY gained.

The modelling of longer term effects was uncertain. Time horizons of 8, 12 and 24 years led to increased ICERs of £910k, £664k and £328k per QALY gained, respectively. The duration of the HbA1c effect was also uncertain. Limiting this to 5, 10 and 20 years while retaining a time horizon of 60 years led to increased ICERs of £657k, £425k and £247 per QALY gained, respectively.

There was high uncertainty around NSHE and SHE annual event rates. There was also a lack of evidence that HCL had an effect on these. When NSHEs were included in a scenario analysis, with an annual rate for HCL of 20.8 (27.1 for CSII plus CGM), the ICER was reduced to £169k per QALY gained. Including SHE's reduced the ICER further to £163k per QALY gained. Using alternative sources for SHE disutility estimates from Currie et al or Nauck et al, further reduced the ICER to £121k and £109k per QALY, respectively.

Other model inputs used in scenario analyses had a limited effect on the ICER results. These included:

- Doubling the quality of life effect of hypoglycaemia events to reflect possible carer effects.
- Reducing the proportion of CSII plus CGM that is intermittently scanned CGM from 90% to 85%.

- Increasing the annual cost of HCL systems by £500.
- Applying an additional training cost of £1,132 for transferring from CSII plus CGM to HCL
- Revising non-specific mortality to also exclude deaths due to hypertension or to all-cause mortality.
- Applying an annual 0.045% worsening of HbA1c.

The exploratory modelling of a paediatric population very broadly mirrored the adult results, but the EAG had reservations about the reliability the IQVIA CDM for modelling a paediatric population.

5 Issues for consideration

Clinical effectiveness

Differences in baseline characteristics between RCTs and NHSE pilot led to different estimated HbA1c percentage changes

The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.29%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. Participants in the RCTs had reasonably good glycaemic control at entry (HbA1c between 7% and 8%), whereas the NHSE pilot baseline characteristics included a broader patient base with worse baseline HbA1c levels (around 9.4%). Therefore, this population had greater improvements after HCL treatment (decrease in HbA1c of 1.5%). The EAG used the network meta-analysis result in the base case.

Issues around the RCT and NHSE pilot evidence and generalisability

Clinical effectiveness analysis prioritised RCT evidence. However, the RCTs were of small size with numbers of participants ranging from less than 20 to 135. RCTs were also heterogeneous in terms of trial design, number and age

of participants, and other demographics including run-in times, duration of observation periods, and number and types of previous treatments. Three of the RCTs used in the NMA used the Minimed 670G which is an older HCL system and may be expected to result in a smaller reduction/improvement in HbA1c.

NHSE pilot studies were non-randomised studies with no control group and with a before-after study design. The EAG said this could limit the scientific value of the evidence due to greater risk of bias due to lack of randomisation, lack of a true control, and selection bias.

Population subgroup data

In the RCT children and young adults subgroup (under 18 years), the change in HbA1c percentage for HCL was greater (-0.31 [-0.43, -0.20]) than the adult subgroup (-0.24 [-0.32, -0.15]). In the NHSE children and young people pilot, the net HbA1c change was –0.7%. Data was not presented on specific child age groups as were included in the scope (that is, 5 years and under, 6 to 11 years and 12 to 19 years). There was very limited evidence on pregnancy and the effectiveness of HCL in pregnant women remains unclear.

Cost effectiveness

Using the NHSE adult pilot data for HbA1c change results in a large decrease in the ICER

The base case analysis using the NMA estimated HbA1c change resulted in poor cost effectiveness estimates with an ICER of £179k per QALY gained. Using the NHSE adult pilot HbA1c change of -1.5% (along with the pilot baseline patient characteristics) resulted in an ICER of £12,398 per QALY gained.

Differences between rtCGM and isCGM

Most of the clinical evidence had a comparator that used rtCGM, but the model base case assumed 90% isCGM and only 10% rtCGM. Therefore, for

the comparator the model is using the clinical effectiveness of rtCGM with the lower cost of isCGM and so may be underestimating the cost-effectiveness of HCL.

The time horizon is a key driver of model results

In the base case the time horizon was 50 years, however modelling of longer term effects is more uncertain. Shorter time horizons explored in scenario analyses resulted in larger ICERs.

Duration of HbA1c effect

The duration of the HbA1c effect is another key driver of the model results. The base case assumes that the effect lasts for the lifetime of the model, however this is uncertain and reducing the duration in scenario analyses also reduces the cost effectiveness. The EAG noted that there is a lack of evidence on the long term effect of the hybrid closed loop system and especially on clinical outcomes such as cardiovascular disease.

Disutilities in the model

There was a lack of data on the effect of HCL on NSHEs and SHEs and also high uncertainty around annual event rates. Therefore, they were not included in the base case. Rates were inferred from the ratio of time below 3.0 mmol/litre for HCL compared to that of the other comparators, coupled with event rates for HCL. The reduction in mental burden and parental or carer anxiety provided by HCL systems may not be captured in the model.

Subgroup modelling

There is uncertainty in the exploratory paediatric modelling results due to the uncertainty around the modelled long term survival coupled with uncertainty about how much of the clinical data used in the IQVIA CDM construction was from a paediatric population. The EAG did not consider the cost effectiveness of HCL for pregnant women due to the lack of evidence.

6 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

- Some of the hybrid closed loop systems currently available in the UK are not licensed for use in children under 6 or 7 years old and in pregnancy.
- People with certain skin conditions or allergies may be unable to wear a sensor.
- People with learning difficulties and people whose vision or hearing does not allow recognition of pump signals and alarms may have difficulty in using the technologies.
- People who have had diabetes for many years and older people may have impaired awareness of hypoglycaemia.
- There may be a need for tighter glucose control in pregnant women.
- Younger children may need help to operate the device every time and toddlers may have more limited management options.
- People from ethnic minority are less likely to be offered technology as therapy; this may be because of a language barrier.
- People from deprived backgrounds and those who are less educated may be less likely to use the technology; this may be because of less awareness of their options.
- People with cystic fibrosis might be more likely to get diabetes.
- People with blood clotting disorders such as haemophilia might not be able to do finger prick testing.

7 Implementation

CCG funding variation and access

A variation in funding arrangements across Clinical Commissioning groups for continuous glucose monitoring technologies may lead to unequal access to

technologies for type 1 diabetes. It has been reported that many Clinical Commissioning groups do not have a policy for funding continuous glucose monitoring technologies or have decided not to fund (Choudhary 2019). In addition, some systems are not licensed in certain groups which may limit their options.

Technology requirements

The control algorithms apps for hybrid closed loop systems are typically hosted on smart phones. Some people may use old phones that cannot host these apps or may be unable to buy smart phones, thereby limiting their access to the technology.

System choice and manufacturer support

The choice of system a person prefers may be influenced by the level of support provided by the manufacturer to help resolve technical issues.

DIY closed loop systems

Even though DIY closed loop systems do not have regulatory approval, a growing number of people with type 1 diabetes continue to use these systems. A position statement offering clinical guidance for people who use DIY closed loop technologies has been developed.

8 Authors

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Glossary

Bolus

A dose of insulin taken at mealtimes to keep blood glucose levels under control following a meal.

Continuous subcutaneous insulin infusion (CSII)

Continuous subcutaneous insulin infusion is delivered through a subcutaneously inserted cannula connected to an external pump with a refillable storage reservoir. The insulin pump can be tethered, where insulin is sent from the pump to the cannula through a tubing, or patch where the pump is attached directly to the skin.

Diabetic ketoacidosis

An acute short-term complication faced by people with type 1 diabetes when there is insufficient insulin in the body to allow the entry of glucose into cells. This leads to the metabolism of alternative energy sources such as fat, resulting in the harmful build-up of ketones in the blood.

HbA1c

Glycated haemoglobin. It is a measure of average blood glucose levels over the previous 2 to 3 months.

Hybrid closed loop (HCL)

Systems that use a mathematical algorithm to automatically drive insulin delivery in response to real time continuously monitored interstitial fluid glucose levels. They aim to reduce the user and carer input required for insulin monitoring and dosing.

Hyperglycaemia

High blood sugar.

Hypoglycaemia

Low blood sugar.

Intermittently scanned continuous glucose monitor (isCGM)

Consists of a sensor and transmitter that automatically monitors interstitial fluid glucose levels throughout the day and night but gives glucose readings only when the sensor has been scanned.

Real time continuous glucose monitor (rtCGM)

Consists of a sensor and transmitter that automatically monitors interstitial fluid glucose levels throughout the day and night and sends real time readings to a receiver or smart device.

Time above range

Percentage of time that blood glucose is above 10 mmol/litre and denotes hyperglycaemia.

Time below range

Percentage of time that blood glucose is below 3.9 mmol/litre and denotes hypoglycaemia.

Time in range

A measure of glycaemic control. Usually refers to percentage of time that blood glucose is between 3.9 mmol/litre and 10 mmol/litre.

Title: **Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes**

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Please note that: *Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.* Depersonalised Data (DPD) is highlighted in pink.

ABSTRACT

Background: Hybrid closed loop systems are a new class of technology to manage type 1 diabetes. The system includes a combination of real-time glucose monitoring from a continuous glucose monitoring device and a control algorithm to direct insulin delivery through an insulin pump. Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families.

Aim: The aim of this appraisal was to assess the clinical and cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring.

Methods: a systematic review of clinical and cost-effective evidence following a pre-defined inclusion criteria informed by the aim of this review. An independent economic assessment using iQVIA CDM to model cost effectiveness.

Results: The clinical evidence identified 12 randomised controlled trials (RCTs) that compared HCL to CSII+CGM or SAP therapy. HCL arm of RCTs achieved improvement in HbA1c % (HCL decreased HbA1c % by 0.28 (-0.34 to -0.21), increased % TIR (between 3.9 – 10.0 mmol/L) with a mean difference of 8.6 (7.03 to 10.22), significantly decreased TIR (% above 10.0 mmol/L), with a mean difference of -7.2 (-8.89 to -5.51) but did not significantly affect % time within range (<3.9 mmol/L). Comparator arms also showed improvements but this was less than that observed in the HCL arm. Outcomes were superior in the HCL arm vs. comparator arm. The cost effectiveness search identified six studies which were included in the review systematic review. Studies reported subjective cost-effectiveness that was influenced by the willingness to pay thresholds. Economic evaluation showed that the published model validation papers suggest that an earlier version of the iQVIA CDM tended to overestimate the incidences of the complications of diabetes, this being particularly important for severe visual loss and ESRD. Medium term modelling of overall survival appeared good, but there was uncertainty about its longer term modelling.

Current prices suggest that HCL is around an annual average £1,500 more expensive than CSII+CGM, though this may increase by around a further £500 for some systems.

The EAG base case applies the EAG RCT NMA estimate of -0.29% HbA1c for HCL relative to CSII+CGM. There was no direct evidence of an effect upon symptomatic or severe hypoglycaemia events, therefore the EAG does not include these in its base case. The change in HbA1c results in a gain in undiscounted life expectancy of 0.458 years and a gain of 0.160 QALYs. Net lifetime treatment costs are £31,185, with reduced complications leading to a net total cost of £28,628. The cost effectiveness estimate is £179k per QALY. The EAG has some concerns about using the iQVIA T1DM to model a paediatric population. The EAG does not formally consider the cost effectiveness of HCL compared to CSII+CGM for pregnant women. It only notes the relationship between HbA1c and birth defects.

Conclusions: RCTs of HCL interventions in comparison CSII+CGM or sensor augmented pump therapy achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10 mmol/L, and in hyperglycaemic levels.

Word count: 526

SCIENTIFIC SUMMARY

Background

Type 1 diabetes was formerly known as insulin-dependent diabetes. It is the result of an autoimmune process leading to destruction of the insulin-producing beta cells in the pancreas. The cause of this auto-immune disease is not known. Diabetes is managed by lifestyle and education, glucose monitoring, and insulin delivery. Treatment with insulin is aimed at replicating the function of the pancreas. The aim of treatment is to control hyperglycaemia and avoid hypoglycaemia. The NICE target for type 1 diabetes is 48 mmol/mol (formerly 6.5%) but few people with T1DM achieve that. Interventions to manage diabetes include: education, continuous glucose monitoring (include a sensor, transmitter and display device), insulin therapy (multiple daily injections or continuous subcutaneous insulin infusion). Continuous subcutaneous insulin infusion (CSII) is an alternative therapy to multiple daily injections. CSII is an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. Sensor-augmented pump (SAP) therapy systems combine CGM with CSII. The systems are designed to measure interstitial glucose levels (every few minutes) and allow immediate real-time adjustment of insulin therapy. The systems may produce alerts if the glucose levels become too high or too low. SAP can operate in standard (manual) and advanced (automatic) modes. In the manual open loop mode, the continuous glucose monitor and glucose pump do not communicate with each other, and insulin doses are programmed by the user, who makes manual adjustments. Hybrid closed loop systems are a new class of technology that use a combination of real-time glucose monitoring from a continuous glucose monitoring device and a control algorithm to direct insulin delivery through an insulin pump. Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families.

Objectives

The intervention of interest is a class of automated insulin delivery systems which consists of three components – a CGM, a microprocessor with control algorithms, and a pump. The

overall objectives of this project are to examine the clinical and cost-effectiveness of hybrid closed loop systems for managing glucose levels in people who have T1DM.

1. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?
2. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Methods

Systematic review methods followed the principles outlined in the Cochrane Handbook of Diagnostic Test Accuracy and the NICE Diagnostic Assessment Programme manual.

A comprehensive search was developed iteratively and undertaken in a range of relevant bibliographic databases and other sources, following the recommendations in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions. Date limits have been used, in order to identify records added to databases since the searches for DG21 (run in 2014). Two reviewers screened titles and abstracts and assessed eligibility of studies. Studies that satisfy the following criteria were included:

Populations: People who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring

If evidence permits the following T1DM subpopulations will be included:

- Pregnant women and those planning pregnancies (excluding gestational diabetes).[b]
- Children (5 years and under, 6 – 11 years, 12 - 19 years).

- People with extreme fear of hypoglycaemia.

People with diabetes related complications that are at risk of deterioration.

Target: Type 1 diabetes mellitus

Intervention: Hybrid closed loop systems

Comparator: Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated).

Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.

Outcomes: Intermediate measures

- Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l)
- Time below and above target range
- Change in HbA1c
- Rate of glycaemic variability
- Fear of hypoglycaemia
- Rate of severe hypoglycaemic events
- Rate of severe hyperglycaemic events
- Episodes of diabetic ketoacidosis
- Rate of ambulance call outs
- Rate of hospital out-patient visits
- Rate of weight gain

Clinical outcomes

- Retinopathy
- Neuropathy

Intermediate measures

- Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l)
- Time below and above target range

- Change in HbA1c
- Rate of glycaemic variability
- Fear of hypoglycaemia
- Rate of severe hypoglycaemic events
- Rate of severe hyperglycaemic events
- Episodes of diabetic ketoacidosis
- Rate of ambulance call outs
- Rate of hospital out-patient visits
- Rate of weight gain

Clinical outcomes

- Retinopathy
- Neuropathy
- Cognitive impairment
- End-stage renal disease
- Cardiovascular disease
- Mortality

Additional clinical outcomes in women who are pregnant/have recently given birth:

- Premature birth
- Miscarriage related to fetal abnormality
- Increased proportion of babies delivered by caesarean section
- Macrosomia (excessive birth weight)
- Respiratory distress syndrome in the new-born

Device related outcomes

- Adverse events related to the use of devices

Patient-reported outcomes

- Heath-related quality of life
- Psychological well being
- Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)
- Anxiety about experiencing hypoglycaemia
- Acceptability of testing and method of insulin administration

Carer reported outcomes

- Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)

Study design: Hybrid closed loop systems studies included any design. All comparator studies: comparative effectiveness studies.

Healthcare setting: Self-use supervised by primary or secondary care

Publication type: Peer reviewed papers

Language: English

Prioritization for full text assessment: We applied a two-step approach for identifying and assessing relevant evidence. The elements used to prioritise evidence (study design, study length, sample size). The most rigorous and relevant studies (mainly RCTs) were prioritised for data extraction and quality assessment. Observational studies were recorded and reported narratively. Two reviewers extracted data independently, using a piloted data extraction form. Disagreements was resolved through consensus, with the inclusion of a third reviewer when required. The risk of bias of randomised trials was assessed using the revised Cochrane risk-of-bias tool for randomized trials. We synthesised the evidence statistically. The network meta-analysis was conducted under a frequentist approach using a random-effects model.

Results

Clinical

Systematic review

The clinical evidence identified 12 randomised controlled trials that compared HCL to CSII+CGM or SAP therapy. Studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining mean difference between intervention and comparators. Studies did not consistently describe comparators. Cross-over studies did not provide data at different cross-over time points. Overall, the HCL arm of RCTs achieved improvement in HbA1c % (HCL decreased HbA1c % by 0.28 (-0.34 to -0.21), increased % TIR (between 3.9 – 10.0 mmol/L) with a mean difference of 8.6 (7.03 to 10.22), significantly decreased TIR (% above 10.0 mmol/L), with a mean difference of -7.2 (-8.89 to -5.51) but did not significantly affect % time within range (<3.9 mmol/L). Comparator arms also showed improvements but this was less than that observed in the HCL arm. Outcomes were superior in the HCL arm vs. comparator arm. Available evidence from the RCTs suggests that these gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration.

External submissions

NHSE submitted two observational audit studies, the first audit was conducted in adults and the second in children and young people (CYP). The audit included adult participants that had [redacted]

[redacted]

Economics

Systematic literature review of cost effectiveness

The literature search identified six studies which were included in the review systematic review. Five of these studies were economic evaluations of hybrid closed loop systems, whereas one was a budget impact analysis that aimed at estimating the financial impact of reimbursing HCL systems for individuals with type 1 diabetes. These studies were assessed using the CHEERS and Phillips checklists where applicable. According to the assessment, four studies were identified as cost effectiveness analyses in their titles The structure of the models used in the cost effectiveness studies was judged to be of good quality. The studies clearly stated their decision problem/research question, the viewpoint of their analyses and their modelling objectives, which were coherent with the decision problem. Both the IQVIA CORE Diabetes Model and the Sheffield type 1 diabetes model are validated models for evaluating diabetes technologies. The studies that used the IQVIA CORE diabetes Model described the model as one with a complex semi-Markov model structure with interdependent sub-models, so more thorough, easier access to its reported features would be of benefit to the intended audience. None of the studies clearly showed the illustrative model structure, which depicted the clinical pathway for T1DM. All the cost effectiveness studies noted that hybrid closed loop systems were cost effective over the lifetime compared with their comparator interventions. This inference was, however, subjective as the studies chose arbitrary willingness to pay thresholds. A major limitation of most of the cost effectiveness studies is that their findings might not be generalisable. This is because the studies did not use baseline characteristics and treatment effects data for their target populations.

Company submission

The EAG received economic submissions from Medtronic, Dexcom and Camdiab. The Tandem submission referenced the economics of the Dexcom submission.

The Medtronic treatment costs applied the anticipated April 2023 CiC prices rather than current list prices. Using the iQVIA CDM it estimated that compared to the 640G system with rtCGM the 780G HCL system improved HbA1c by 0.8% which resulted in a saving of £5,816, patient gains of 0.21 QALYs and dominance for HCL. For the comparison with CSII+isCGM the same HbA1c improvement was applied alongside an annual reduction of 0.9 severe hypoglycaemia events. This resulted in a net cost of £13,057, a patient gain of 0.70 QALYs and a cost effectiveness of £18,672 per QALY.

Dexcom used the [redacted]

The Camdiab submission presented [redacted]

Independent economic assessment

Due to the complexity of modelling T1DM the EAG does not build a de novo model. There are two main T1DM economic models available, the Sheffield T1DM model and the iQVIA CDM. In common with NG17 and DG21 and most of the company submissions, the EAG uses the iQVIA CDM to model cost effectiveness. The published model validation papers suggest that an earlier version of the iQVIA CDM tended to overestimate the incidences of the complications of diabetes, this being particularly important for severe visual loss and ESRD. Medium term modelling of overall survival appeared good, but there was uncertainty about its longer term modelling. It is not known whether these issues persist in the current iQVIA CDM.

The EAG assesses the cost effectiveness of HCL, PLGS and CSII+CGM. PLGS is extendedly dominated throughout and for this summary the EAG does not consider it further.

Direct treatment costs are supplied by the NHS supply chain using current list prices. The EAG provides a cPAS appendix that applies the confidential possible future prices. Current prices suggest that HCL is around an annual average £1,500 more expensive than CSII+CGM, though this may increase by around a further £500 for some systems. CSII+CGM is cheaper than HCL in large part due to 90% or more of adult patients using isCGM sensors rather than rtCMG sensors.

Patient baseline characteristics for the EAG base case are drawn from the National Diabetes Audit subgroup of T1DM patients on pumps.

The EAG base case applies the EAG RCT NMA estimate of -0.29% HbA1c for HCL relative to CSII+CGM. Due to there being no direct evidence of an effect upon symptomatic or severe hypoglycaemia events the EAG does not include these in its base case.

The change in HbA1c results in a gain in undiscounted life expectancy of 0.458 years and a gain of 0.160 QALYs. Net lifetime treatment costs are £31,185, with reduced complications leading to a net total cost of £28,628. The cost effectiveness estimate is £179k per QALY.

The EAG provides scenario analyses that estimate symptomatic and severe hypoglycaemia events based upon the differences in the time below 3.0mmol/l for HCL and CSII+CGM. These improve the cost effectiveness of HCL to £163k per QALY if valued using the EAG preferred source, to £121k if valued using the same source as NG17 and to £109k if valued using other credible sources.

These results show are sensitive to time horizons of less than the patient lifetime, durations of HbA1c effect of less than the patient lifetime and higher HCL treatment costs which tend to worsen the cost effectiveness of HCL. If mortality for those without complications is higher than that of the base case or there is an annual worsening of HbA1c this tends to improve the cost effectiveness of HCL. All the resulting cost effectiveness estimates are above £100k per QALY.

If the NHSE adult pilot change [redacted] is assumed to be the net effect of HCL compared to CSII+CGM the undiscounted gain in life expectancy more than doubles to 1.004 years, and the patient gain to 3.103 QALYs. Net lifetime treatment costs increase to £35,912 due to the greater life expectancy, but considerable cost savings from reduced eye complications of £16,442 and reduced renal complications of £6,731 lead to a net total cost of £12,447 and a cost effectiveness of £12,398 per QALY. Reducing the modelled complication costs by their possible overestimation worsens the cost effectiveness to £21,583 per QALY. This does not take into account any quality of life effects and survival effects from possible overestimation of complication rates.

The key model inputs are:

- The net effect upon HbA1c.
- The duration of the net effect upon HbA1c.
- The model time horizon.
- Treatment costs.

Other important model inputs are:

- Hypoglycaemia event rates.
- What source is used to value the disutilities of hypoglycaemia event rates.

- What non-specific mortality is applied.
- Whether HbA1c worsens annually among T1DM patients and if so by how much.

The key modelling uncertainties are around:

- Overall survival gains.
- Severe visual loss and its effects upon survival, quality of life and costs.
- ESRD and its effects upon survival, quality of life and costs.

The EAG has some concerns about using the iQVIA T1DM to model a paediatric population. Exploratory modelling of a paediatric population broadly mirrors that of the adult population, though the NHSE paediatric pilot reported [redacted] change between baseline and six months with a corresponding [redacted] in the cost effectiveness estimate for this scenario.

The EAG does not formally consider the cost effectiveness of HCL compared to CSII+CGM for pregnant women. It only notes the relationship between HbA1c and birth defects. If HCL reduces HbA1c in pregnant women to the same extent as in the adult population the short-term additional costs of HCL will have some immediate cost offsets from reduced birth defects, with the potential for additional benefits to the child at no additional cost. It also seems likely that the baseline age of pregnant women is below the national diabetes audit mean age which is likely to further improve cost effectiveness. If after giving birth women remain on HCL into the long term the cost effectiveness estimate of HCL may trend towards that of the adult female T1DM population of the same age, but will remain superior to it.

Conclusions

RCTs of HCL interventions in comparison CSII+CGM or sensor augmented pump therapy achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10

mmol/L, and in hyperglycaemic levels. The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range (3.9 to 10 mmol/L), and % time above range >10 mmol/L all improved on transfer to HCL. There is a research need of well designed studies because identified studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining mean difference between intervention and comparators. Future research should clearly describe comparators because this is not clear in the current literature.

Word count: 3182

PLAIN ENGLISH SUMMARY

Type 1 Diabetes (T1DM) is a life-long condition where the individual's pancreas significantly reduces \ stops producing the hormone insulin that manages blood glucose levels. As a result, the individual must self-administer insulin, monitor their blood glucose levels, and take into consideration many multiple variables to achieve a tight blood glucose control range.

With the challenge of self-management, blood glucose levels may swing high (hyperglycemia) and low (hypoglycemia) multiple times a day. This can result in the individual experiencing confusion, fatigue, nausea and possible unconsciousness as part of their daily management. The long-term risks of high blood glucose levels include damage to blood vessels, impacting sight, sense of touch and other vital organs. During self management, the individual uses the information they have to administer the amount of insulin the body requires while limiting high and low blood sugar. The day-to-day management of diabetes can be difficult and, and at times people with diabetes may struggle to maintain control of their blood glucose level. This can put a significant burden on the patient and carers which can result in impact on quality of life and a feeling that the condition limits \ controls their abilities.

Management of Type 1 Diabetes

Type 1 Diabetes is managed via lifestyle adjustments and review of multiple sources of data to help calculate the amount of insulin that a person needs. This commonly covers the following:

- *Lifestyle*
    - A balanced diet including complex carbohydrates, fats and proteins and avoiding processed food slows the impact of food on the blood glucose level reducing the possibility of sudden highs or lows.
    - Exercise improves the body's sensitivity to insulin, therefore, reducing the amount to be injected. This can reduce the possibility of unexpected sudden blood glucose changes that a larger dose of insulin may bring, as well as general well-being in reducing stress that can cause insulin resistance.

- *Data*
    - Patients' understanding and monitoring of their body's reaction to insulin and foods to calculate their sensitivity to insulin and carbohydrates.
    - Monitoring of blood glucose levels via "finger pricks" where the individual draws a small amount of blood to get a point in time reading or continuous glucose monitors that provide a real-time reading of blood glucose.
- *Insulin Delivery*
    - Via daily injections or insulin pump that is connected to the body 24/7. Injections can be of rapid acting insulins that take effect within a short time frame (bolus) and long-acting insulins that release over a 12-to-24 hour period providing an amount of background insulin in the body (basal). Insulin pumps provide rapid acting insulin with the ability to deliver a bolus quickly and easily along with continuous background basal delivery that can be precisely adjusted for example every 5 minutes to form a unique 24-hour profile for the individual.

Processing of this information and deciding the best action is an ongoing challenge for the individual. Examples of such challenges include:

- Diet: Poor diet education, cost of access to fresh food and the challenge of avoiding easily accessible but cheap highly processed foods.
- Exercise: Lifestyle habits and motivation to exercise, along with the management of changes to insulin sensitivity, during and after exercise.
- Insulin Delivery: The inconvenience of injections and their limited control of insulin delivery, pumps with an overwhelming number of options for consideration.
- Blood Glucose Monitoring: This can be uncomfortable and provide a person with limited visibility of trend data. Compared to the data provided by manual blood glucose tests, continuous glucose monitors provide an overwhelming amount of real-time data for the individual to process.

- Alarm fatigue: insulin pumps can cause frustration, due to automatic alarms set to inform the individual of high or low blood glucose or lack of proactive information to prevent such events.
- Overtreatment: Miscalculation, frustration or unexpected sensitivity/resistance to insulin that can result in multiple blood sugar highs and lows within a short timeframe.
- Changes in sensitivity to insulin, and to food along with many other factors that can changes an individuals response to insulin over time and day to day.

Hybrid closed loop systems

Hybrid closed loop systems provide a control algorithm that reviews data, along with reviewing the impact of its past actions. It can action frequent minor adjustments of insulin delivery to allow blood glucose levels to be managed. The system is proactive versus reactive using the real-time feed of data provided by the continuous glucose monitor to make calculations and take actions and to take actions using a high level of controlled delivery offered by an insulin pump at a frequency that is unattainable by a human being. As a result, such systems can significantly reduce the burden on the patient by taking responsibility for handling the volume of data and technology required for management of their condition and providing intervention when needed.

The aim of the current project is to review the clinical and cost-effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM and are having difficulty managing their condition.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Term	Definition
AHCL	Advanced Hybrid Closed Loop
A&E	Accident and emergency
AID	Automated insulin delivery
BL	Baseline
CADTH	Canadian Agency for Drugs and Technology in Health
CDM	CORE Diabetes Model
CEAC	Cost effectiveness acceptability curve
CGM	Continuous glucose monitoring plus RT CGM
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CL	Closed loop
CSII	Continuous subcutaneous insulin infusion (insulin pump)
CV	Coefficient of Variation
CVD	Cardiovascular disease
DDS	Diabetes Distress Scale
DIY	Do It Yourself closed loop systems
DAFNE	Dose Adjustment for Normal Eating
DAFNE-HART	DAFNE-Hypoglycaemia Awareness Restoration Training
DBLHU	Diabeloop for Highly Unstable Diabetes
DKA	Diabetic ketoacidosis

DTSQ	Diabetes Treatment Satisfaction Questionnaire
EPOC	Effective Practice and Organisation of Care
EQ-5d	The most widely used multi attribute utility instrument for measuring health-related quality of life in cost-effectiveness analysis
FGM	Flash Glucose monitoring
FLAIR	Fuzzy Logic Automated Insulin Regulation
FoH	fear of hypoglycaemia
GMI	Glucose Management Indicator
HbA1c	Haemoglobin A1c or glycated haemoglobin
HCL	Hybrid Closed Loop
HFS	Hypoglycaemia Fear Survey
HTA	Health technology assessment
ICD10	International Classification of Disease
ICER	Incremental cost effectiveness ratio
IQR	Interquartile Range
isCGM	intermittently scanned continuous glucose monitoring
LGS	Low glucose suspend
MC	Multicentre
MD	Mean difference
MDI	Multiple daily injections
NHS	National Health Service
NHSE	National Health System England
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis

OL	Open Loop
PedsQL	Pedatric Quality of Life Inventory
PLGS	Predictive low glucose suspend
PLGM	Predictive Low-Glucose Management
PWT1D	people with type 1 diabetes
RoB	risk-of-bias tool for randomized trials
rtCGM	real-time continuous glucose monitoring (
T1DM	Type 1 diabetes mellitus
TIR	Time in Range
QALY	Quality adjusted life year
QoL	Quality of Life
RCTs	Randomised Clinical Trials
SADE	Serious adverse device effects
SAP-PLGS	Sensor-augmented pumps and it was followed by the predictive low glucose suspend feature
SBP	Systolic blood pressure
SHE	Severe hypoglycaemic rates
SHTG	Scottish Health Technologies Group
SEK	Swedish krona
SHEs	severe hypoglycaemic rates
SF-6D	A generic preference-based single index measure of health that can be used to generate QALYs and hence which can be used in cost-utility analysis
SMBG	Standard self-monitoring of blood glucose
SUCRA	Surface under the cumulative ranking curve

AHCL	Advanced Hybrid Closed Loop
UADE	Unanticipated adverse device effects
WTP	Willingness to pay

2 BACKGROUND

2.1 Description of health problem

Type 1 diabetes was formerly known as insulin-dependent diabetes. It is the result of an autoimmune process leading to destruction of the insulin-producing beta cells in the pancreas. The cause of this auto-immune disease is not known.

2.1.1 Aetiology, pathology and prognosis

Insulin is essential for survival. Diabetes is characterised by high blood glucose levels – hyperglycaemia. Injected insulin lowers blood glucose. It can cause abnormally low glucose – hypoglycaemia. The aim of insulin treatment is to keep plasma glucose as close to normal as possible and so prevent the development of the long-term complications of diabetes due to hyperglycaemia, including

- retinopathy, which can lead to visual impairment and blindness
- nephropathy which can lead to renal failure and dialysis
- neuropathy, which can cause various symptoms and increase the risk of amputation

Treatment also aims to reduce the increased risk of cardiovascular disease seen in diabetes. Deficiency of insulin can lead to diabetic ketoacidosis which can be fatal.

2.1.2 Epidemiology

Type 1 diabetes usually comes in late childhood or early adolescence but can develop at any age. Type 1 diabetes accounts for 5-10% of diabetes cases. The prevalence of type 1 diabetes is higher in adults than in children, the highest prevalence is observed in adults aged 30 years and above.[1, 2] There are about 250,000 people with T1DM in the UK.

2.1.3 Impact of health problem

Hypoglycaemia

Hypoglycaemia can be mild, moderate or severe.

People with diabetes are rightly scared of hypoglycaemia, and this fear may lead to them allowing blood glucose to run higher than is desirable which can increase the risk of long-term complications. The episodes of hypoglycaemia are usually called “hypos”.

The American Diabetes Association [3] defines hypoglycaemia as follows;

1) Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma.
2) Documented symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of 3.9 mmol/l).
3) Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration of 70 mg/dl (3.9 mmol/l).

Non-severe hypoglycaemia can be mild or moderate. Mild hypoglycaemia may present with symptoms such as sweating, shaking, hunger, and nervousness. Some symptoms are due to the release of adrenaline. Mild is easily self-managed by taking rapidly-absorbed carbohydrate.

Moderate hypoglycaemia can cause difficulty concentrating or speaking, confusion, weakness, vision changes and mood swings.

Mild and moderate hypos can usually be managed by the diabetic person themselves, but moderate hypos often lead to interruption of activities.

In the guidance on the Medtronic Veo suspend pump (DG21), NICE defined disabling hypoglycaemia as follows:

"People with type 1 diabetes may experience 'disabling hypoglycaemia', which is when hypoglycaemic episodes occur frequently or without warning so that the person is constantly anxious about having more episodes. This can have a negative effect on quality of life."

Severe hypoglycaemia can lead to cognitive impairment, unconsciousness and convulsions, and can be fatal. People having severe hypos need assistance and may need to attend an accident and emergency (A&E) department, seek support from paramedics. They may require admission to hospital. A population-based study in (2003) by Leese and colleagues [4] in Tayside found that on average, about 1 person in 14 had a hypo event each year which was severe enough to require NHS assistance, from the ambulance service, A&E, or admission.

In young children, repeated severe hypos can cause some cognitive impairment.

Hypoglycaemia can trigger an adrenergic response that acts as a warning that glucose should be consumed. Unfortunately, in some people, after repeated hypos, this warning may be lost.

This is known as hypoglycaemic unawareness, and such people are at increased risk of severe hypoglycaemia and its effects. These individuals are covered by the recommendation in DG21 [5] and in TA151,[6] in guidance on insulin pumps.

Nocturnal hypoglycaemia occurs during sleep and may not be detected. However it may disturb sleep and wake people up. It can have two adverse effects. One is rebound hyperglycaemia, the result of the body's reaction to hypoglycaemia such as release of other hormones that increase blood glucose, so that nocturnal hypoglycaemia may result in unusually high blood glucose levels around breakfast. The other consequence is that nocturnal hypoglycaemia may itself contribute to hypoglycaemic unawareness.

Past appraisals

In a technology appraisal (TA53) of long-acting insulin analogues (at that time only glargine),[7] the NICE Appraisal Committee accepted that both hypoglycaemic episodes, and the fear of such episodes recurring, caused significant disutility. A utility decrement of 0.0052 per non-severe hypoglycaemic event (NSHE) was accepted. As regards fear of hypos, the NICE Glargine guidance (TA53) [7] states:

"*The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. This is partly the result of an individual's objective fear of symptomatic hypoglycaemic attacks as indicated in the economic models reviewed in the Assessment Report. In addition, as reported by the experts who attended the appraisal meeting, individuals' quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemia and the benefits of longer-term glycaemic control. The Committee understood that improvement in this area of concern regarding the balance between hypoglycaemia and hyperglycaemia could have a significant effect on an individual's quality of life.*"

However, the guidance did not specify the amount of utility lost because of fear of hypos, and nor did the Technology Assessment Report [8] because it was based on the industry submission from Aventis, which was classed as confidential. But clearly the utility gain from reducing the fear of hypoglycaemia was enough to change a substantial cost per QALY to an affordable one. There is the probability that a reduction in the rate of severe hypoglycaemia events may reduce the fear of severe hypoglycaemia events, though the impact of this seems likely to be variable across patients. The quality-of-life impact arising from this would be

over and above the direct quality of life impact of the severe hypoglycaemia events in themselves.

Fear of severe hypos was estimated to reduce QoL by 0.020 in the development of type 2 guidelines in 2008. The assessment group (Waugh et al, Aberdeen [9]) considered the reasonableness of this

"This fear effect may only apply to a sub-group of patients, but as an illustration of the possible impact of this, the social tariffs derived by Dolan and colleagues [10] suggest that a move from level 2 within the anxiety subscale of EQ-5D to level 1 would be associated with a 0.07 QoL gain. In a similar vein, the coefficients derived by Brazier and colleagues [11] for the SF-6D questionnaire for the consistent model using standard gamble valuations suggest that a movement within the social dimension from health problems interfering moderately to not interfering would be associated with a 0.022 QoL improvement. Similarly, an improvement in the mental health subscale from feeling downhearted some of the time to little or none of the time would be associated with a 0.021 QoL improvement."

Studies of the disutility of hypoglycaemia

Brod et al [12] carried out a survey to estimate the effect of non-severe hypos on work – productivity, costs and a self-management. They used telephone interviews and focus groups, supplemented by a literature review. Respondents were required to have had a non-severe hypoglycaemic event (NSHE) in the previous month. NSHE was defined as a hypo event not requiring assistance from anyone else, with or without blood glucose measurement, and with or without symptoms. They were asked about duration, effect on work, and likely cause, and whether it occurred at work, at other times of day, or during sleep. 713 had type 1 diabetes, and half of this group had NSHEs at least once a week, with 27% having at least one a month. 22% had hypos only a few times a year.

About 95% of people identified hypos by symptoms, and about 60% of episodes were confirmed by a blood glucose test. The average duration of a NSHE was 33 minutes, but the effect on self-management lasted a week, with an extra six blood glucose tests, a reduction in insulin dose by an average of 6.5 units per day for 4 days in 25% of people, and an unplanned contact with a health care professional by 25%.

The effects on work included;

- Leaving early or missing a full day in 18%. The average work time lost was 10 hours.

- Missing meetings or being unable to finish a task – 24%

Work time was lost not only because of NSHEs occurring at work but also outwith work including nocturnal hypos. No breakdown by insulin regimen was reported such as CSII versus MDI.

Leckie et al [13] recruited 243 people with diabetes (216 people with T1DM and some with T2DM on insulin) who were in employment. Their insulin regimens included mostly MDI but 51 were on twice-daily mixtures of soluble and NPH. Over a 12-month follow-up, they recorded their hypo events, severity and effect on work, every month. A total of 1,955 NSHEs were reported, plus 238 severe hypos (some involving unconsciousness and seizures, and a few resulted in soft tissue injuries). However, 66% of patients had no severe hypos. Most (62%) of the severe episodes occurred at home, 52% during sleep, but 15% occurred at work. 55% of the NSHEs occurred at home and 30% at work. It should be noted that the mean HbA1c was over 9% in most patients, with the exception of patients having more than two severe hypos over the year, in whom it was 8.4% - still far above target.

Frier et al [14] carried out a survey amongst 466 people with T1DM of the frequency of non-severe hypoglycaemia and found that people with T1DM had an average of 2.4 episodes a week (median = 2), with around a quarter being nocturnal. The after-effects include fatigue and reduced alertness, and persisted longer after nocturnal NSHEs (10 hours) than after daytime episodes (5 hours). Amongst those in employment, 20% of NSHE led to loss of work time. Most did not contact their health care professionals. Self-testing of blood glucose increased in the week after the episode, with an average 4 extra tests. The survey showed that NSHEs are troublesome for patients and have effects lasting at least into the following day. The commonest after-effects were tiredness, reduced alertness and feeling emotionally down.

Choudhary et al [15] reported that use of pumps with a low glucose suspend facility meant that 66% of NSHEs lasted less than 10 minutes, and only 12% lasted for up to 2 hours. Nocturnal hypos were greatly reduced.

About 30% of people with type 1 diabetes have impaired awareness of hypos [16] and they are 3-6 times more likely to have severe hypos. The Gold scale rates awareness on a scale of 1 to 7 where 7 means complete absence of symptoms of hypoglycaemia. Structured education such as DAFNE restores awareness in about half of people with impaired awareness. Better control with avoidance of hypoglycaemia can also restore awareness. A trial by Little et al [17] (the HypoCOMPass trial) showed that better control for 24 weeks improved the Gold score

by one point and reduced the fear of hypo level from 58 to 45 (higher scores indicate greater fear, with the maximum being 132), without adversely affecting HbA1c.

Evans et al [18] used the time trade-off method to estimate the disutility of hypos on the HRQoL scale (0 to 1 where I is perfect health and 0 is death). They interviewed 551 people with type 1 diabetes and 8286 people with no diabetes. They note that hypos can affect HRQoL in two ways, firstly the direct effects of the episodes, and secondly through fear of future hypos which can lead to precautions such as insufficient insulin dose (increasing the risk of complications), restricting physical activity, over-eating. In addition, repeated hypos can lead to hypoglycaemic unawareness which increases the risk of future hypos. They estimated that daytime NSHEs reduce HRQoL in a range of 0.032 for one event a month to 0.071 for three episodes a week. Nocturnal NSHEs reduce it by slightly more. Severe events, even only once or twice a year, reduce HRQoL by about 0.08.

The general public valuation of disutility per event per year ranged from 0.004 for non-severe daytime hypos to 0.06 per severe event. People with type 1 diabetes had slightly lower estimates of the disutility of severe events, at 0.047.

Using data from this study, Lauridson et al [19] reported that the disutility of NSHEs may diminish if there are repeated events.

The study by Harris et al [20] reports the Canadian results from this study.

Levy and colleagues [21] elicited utility values for non-severe hypoglycaemia from 51 Canadians (but only half had T1DM) and non-diabetic controls. The disutility from a single NSHE was 0.0033. Levy et al argue that a minimum significant utility loss is 0.03, which would be reached by people having 10 NSHEs a year.

Adler et al [22] found that severe, frequent and nocturnal hypoglycaemia reduced quality of life, ranging from 0.84 in people with diabetes who had the least severe state) non-severe, daytime only, only once a year, not causing any worry) to 0.40 (severe frequent hypoglycaemia day and night, causing anxiety).

Currie and colleagues [23] surveyed 1,305 UK patients with type 1 and type 2 diabetes using both the Hypoglycaemia Fear Survey and the EQ-5D. Each severe hypoglycaemic event avoided was associated with a change of 5.9 on the Hypoglycaemia Fear Survey (HFS). Given a further estimate that each unit change on the HFS was associated with an EQ-5D quality of life change of 0.008 this led to an estimated benefit from reduced fear of severe hypoglycaemic events of 0.047 per annual event avoided. This was coupled with a direct

utility loss associated with a severe hypoglycaemic event in T1DM of 0.00118 to yield an overall patient benefit of 0.05 per unit reduction in annual severe hypoglycaemic events. Currie et al also reported direct disutilities in type 1 diabetes of 0.0036 per NSH event.

Conclusions on hypoglycaemia

Hypoglycaemia remains a major problem in type 1 diabetes and has not improved over recent decades. This may be because the increased emphasis on improving glycaemic control, through more intensive insulin treatment, has offset other advances in treatment; tightly managed diabetes can make it more likely that hypoglycaemia might occur. The frequency and severity of hypos can be reduced by structured education and by the use of CSII (insulin pumps) but they remain a problem leading to economic disutilities. For individual events, disutilities and costs are much greater for severe hypos but the much larger number of NSHEs lead to significant impacts on quality of life.

2.2 Current service provision

2.2.1 Management of disease

In people without type 1 diabetes, the pancreas produces a little insulin throughout the day but peaks of insulin release after meals. The release after meals is very fast and enables the body to handle and store nutrients. The pancreas releases insulin into the portal vein that goes into the liver, its main site of action.

Treatment with insulin is aimed at replicating the function of the pancreas. Insulin is injected under the skin – subcutaneously. Modern insulin regimens have two components – short-acting insulin to cover mealtimes, and long-acting insulin to cover the rest of the day, usually given twice a day. The long-acting form is called basal, and the combination is often referred to as “basal-bolus” insulin, or as MDI – multiple daily injections – with three injections of short-acting insulins and two of long-acting (glargine or detemir). However, subcutaneous insulin injections cannot achieve as rapid an effect as pancreatic insulin, and because of the slower onset of action and more prolonged effects, hyperglycaemia is common shortly after meals, often followed by later hypoglycaemia.

Good control of plasma glucose by intensified insulin therapy requires more than just insulin injections. It also requires regular monitoring of blood glucose by finger-pricking and measurement using a portable meter, or by using a continuous blood glucose measurement

(CGM) device, and then adjustment of insulin dose to take account of calorie intake from food and energy expenditure in exercise. People with diabetes almost always manage their own diabetes, supported by structured education packages such as DAFNE (Dose Adjustment for Normal Eating).

The aim of treatment is to control hyperglycaemia and avoid hypoglycaemia. Glycaemic control is assessed using glycated haemoglobin, HbA1c, which gives an average measure over 2-3 months. The NICE target for type 1 diabetes is 48 mmol/mol (formerly 6.5%) but few people with T1DM achieve that. With the spread of continuous glucose measurement (CGM) devices, "time in range" is increasingly used as another measure of glycaemic control.

The alternative to MDI is continuous subcutaneous insulin infusion (CSII) using an insulin pump. CSII was approved by NICE with restrictions (see Box 1).[6]

Box 1. NICE guidance: Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus [TA151]

Continuous subcutaneous insulin infusion (CSII or 'insulin pump') therapy is recommended as a treatment option for adults and children 12 years and older with type 1 diabetes mellitus provided that:

- attempts to achieve target haemoglobin A1c (HbA1c) levels with multiple daily injections (MDIs) result in the person experiencing disabling hypoglycaemia. For the purpose of this guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life

  or

- HbA1c levels have remained high (that is, at 8.5% [69 mmol/mol] or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

CSII therapy is recommended as a treatment option for children younger than 12 years with type 1 diabetes mellitus provided that:

- MDI therapy is considered to be impractical or inappropriate, and
- children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years.

The guidance on the use of the Veo pump also had restrictions (see Box 2).[5]

Box 2: NICE guidance: Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) [DG21]

1. The MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if: • they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion,

2. The MiniMed Paradigm Veo system should be used under the supervision of a trained multidisciplinary team who are experienced in continuous subcutaneous insulin infusion and continuous glucose monitoring for managing type 1 diabetes only if the person or their carer: • agrees to use the sensors for at least 70% of the time • understands how to use it and is physically able to use the system and • agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.

3. People who start to use the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set.

The guidance did not comment on reduction of severity of hypos.

In non-diabetic people, hypoglycaemia is rare, because if the blood glucose drops, a counter-regulatory mechanism kicks in, including release of glucagon (which raises blood glucose) and adrenaline, and cessation of insulin release. In people on MDI, there are pools of long-acting and short-acting insulin under the skin (subcutaneous) which unlike pancreatic insulin, cannot be switched off. In people on CSII, there is only a little short-acting insulin, so stopping the pump gives a quick response. (There can be a hazard here, in that should a pump fail, the patient soon has no insulin and is at risk of hyperglycaemia and diabetic ketoacedocis (DKA).

Interventions to reduce hypoglycaemia

One intervention to reduce the risk of hypoglycaemia is structured education such as the DAFNE Programme. Structured education is recommended in NG17 (Recommendations | Type 1 diabetes in adults: diagnosis and management | Guidance | NICE). The assessment report for the original appraisal of patient education in diabetes has been published in the HTA Monograph series (Loveman et al 2003)

Iqbal and Heller [24] provide a recent review of the role of structured education and hypoglycaemia. They note that until recently, the frequency of severe hypoglycaemia had not fallen over the last 20 years despite advances in treatment. They conclude that structured education can reduce the incidence of severe hypoglycaemia by about 50%, and that there is some evidence, albeit from an observational study with no control group, that the DAFNE-Hypoglycaemia Awareness Restoration Training (DAFNE-HART) programme can reduce hypoglycaemia even in patients with hypoglycaemia unawareness.

Continuous glucose monitoring

There are various forms of CGM. The term "continuous" is slightly misleading – glucose levels are measured every few minutes. The device measures the level of glucose under the skin ("interstitial glucose") which reflects the level in the blood, but with a slight delay.

There are three elements in CGM

- A sensor that sits just underneath the skin and measures glucose levels.
- A transmitter attached to the sensor and sends the results to a display device.
- A display device that shows the glucose level.

The diabetic person checks the CGM data and adjusts insulin dose, calorie intake or activity levels to maintain blood glucose levels.

So, the traditional "loop" involves CGM, the patient using the data, and insulin dosage.

Autosuspend pumps

The mechanism here is that the CGM – patient – pump loop is augmented by direct communication between CGM device and the pump. If blood glucose is falling too low, the CGM device communicates with the pump and switches off the insulin infusions, for say 2 hours. This is particularly useful in nocturnal hypoglycaemia when the patient is asleep.

Closed loop systems

This term refers to systems with three components – CGM, a microprocessor with algorithms, and a pump. In effect, the microprocessor replaces the person. The microprocessor (in effect a small computer) receives data from the CGM and adjusts the infusion rate from the pump.

Devices such as the Veo only control the pump when hypoglycaemia is occurring. They may switch off the insulin infusion when blood glucose falls to low, or if it is heading in that direction.

Closed loop systems can also control insulin infusion if blood glucose is too high. The most advanced system is the iLet from BetaBionics which is a dual pump which infuses insulin if blood glucose is too high, and glucagon if it is too low.

2.2.2 Variation in services and/or uncertainty about best practice

At diagnosis, the diabetes professional team should work with adults with type 1 diabetes to develop a plan for early care. Individual care plans include diabetes education, including dietary advice, insulin therapy, (including dosage adjustment, self-monitoring, avoiding hypoglycaemia and maintaining hypoglycaemia awareness), family planning, cardiovascular risk factor monitoring and management, complications monitoring and management, and communicating with the diabetes professional team. There are different factors that should be taken into account to offer an appropriate glucose monitoring device for any person. Based on individual preferences, needs, characteristics, and the functionality of the devices available, adults with type 1 diabetes may be offered a choice of glucose monitoring. Modes include real-time continuous glucose monitoring (rtCGM) or intermittently scanned

continuous glucose monitoring (isCGM, commonly referred to as 'flash'), these measurement systems are coupled with multiple daily injection basal–bolus insulin regimens, or insulin pumps (Continuous subcutaneous insulin infusion (CSII) therapy), using Rapid-acting insulin, and/or Mixed insulin.[2]

People with type 1 diabetes may experience significant improvements in their lives as a result of the rapidly evolving technologies such as closed loop systems and artificial pancreas.[25] Demand for these technologies is increasing, with many people with type 1 diabetes anticipated to benefit from an artificial pancreas or closed loop system in the future.[25] There is evidence using key outcomes, such as HbA1c, time in range and severe or nocturnal hypoglycaemia, to demonstrate whether devices provide clinical benefits over standard self-monitoring of blood glucose. However, quality or sample size of the studies is frequently not good enough to clearly show the clinical benefits of one technology over another.

2.2.3 Relevant national guidelines, including National Service Frameworks

NICE guideline [NG17] covers care and treatment for adults (aged 18 and over) with type 1 diabetes, including advice on diagnosis, education and support, blood glucose management, cardiovascular risk, and identifying and managing long-term complications.[2] Evidence reviews by NICE evaluated the most effective method of glucose monitoring to improve glycaemic control in adults with type 1 diabetes. Overall, 17 studies were included in clinical effectiveness analysis to examine rtCGM vs isCGM , rtCGM vs standard self-monitoring of blood glucose (SMBG), and isCGM vs SMBG. Two UK studies among 14 primary studies that contained cost utility analyses were included in this evidence review. Results show time in range (TIR) to be a better measure than HbA1c as it captures variation and can be more directly linked to risk of complications. There was a clinically meaningful positive effect on time in range for rtCGM vs both isCGM and SMBG, as well as is CGM vs SMBG, on the pre-set minimally important difference (MID) of a 5% change.[26] The authors clarified that the service user should consult with a member of the diabetes care team with expertise in the use of CGM. This guideline reported both published UK cost-effectiveness studies (one on rtCGM and one on isCGM) found these technologies to be cost-effective compared to intermittent capillary blood glucose monitoring. Based on the results of economic modelling (using clinical data from the RCTs included in the clinical review), isCGM glucose monitoring was clearly cost-effective for the overall population of people with type 1 diabetes, and this finding was robust to all the sensitivity analyses undertaken.[26]

The Scottish Health Technology Group (SHTG) review examined the cost-effectiveness of using closed loop systems and the artificial pancreas for the management of type 1 diabetes compared with current diabetes management options, and considered clinical effectiveness, safety and patient aspects.[25]

The evidence reviewed on the clinical effectiveness consisted of small cross-over RCTs that tested the use of closed loop systems over relatively short periods of time, in people with well controlled diabetes who had had the condition for several years and who often had experience with using insulin pumps. The results of an NMA and three pairwise meta-analyses show significant improvements in mean percentage time in range for people with type 1 diabetes using a closed loop system compared with other insulin-based therapies. The pairwise meta-analyses also reported statistically significant reductions in mean percentage time spent in hyperglycaemia and hypoglycaemia. High heterogeneity was present in all meta-analyses, for all outcomes. This is potentially a result of small study size, multiple different closed loops systems in the intervention group, and use of a variety of methods of insulin therapy in the control groups. It should be noted that some of the secondary evidence reviewed may be based on technologies that have since been superseded by newer models because of the rapidly changing nature of these systems.

Also, adverse events were rarely reported in either the closed loop system or control groups.

The SHTG economic model, showed that closed loop systems were associated with the highest costs and QALYs in a Scottish adult population with type 1 diabetes, except in the comparison with CGM plus CSII. Base case results showed that the technology is cost-effective compared with CGM plus CSII, but not cost-effective in comparison with flash or continuous glucose monitoring combined with multiple daily injections in people with well controlled type 1 diabetes. There are some uncertainties because of a lack of published studies underpinning assumptions in the model.

2.3 Description of technology under assessment

2.3.1 Summary of Intervention

The intervention of interest is a class of automated insulin delivery systems called hybrid closed loop systems which consist of three components – a CGM, a microprocessor with control algorithms, and a pump. The microprocessor receives data from the CGM and adjusts the infusion rate from the pump, to help keep glucose levels in a healthy range. These systems are

aimed at reducing user or caregiver input in insulin dosing and some only require users to deliver meal boluses by entering the estimated amount of carbohydrates for meals at the time they are eaten.

There are several hybrid closed loop systems available in the UK. Some of these systems have received regulatory approval for a fixed combination of CGM, control algorithm, and insulin pump. However, some systems involve combining interoperable devices. The following systems are representative of the intervention of interest and have been identified by NICE as currently available in the UK.

Advanced HCL

HCL systems use control algorithms to automate basal insulin delivery based on glucose sensor values, in order to increase the time that a patient spends in the target range and thus reduce the frequency and duration of hypoglycaemia. The user of the HCL system is required to enter their carbohydrate intake before each meal, so that the appropriate meal-time insulin bolus can be delivered by the system.

Advanced HCL (AHCL) systems have additional features that include automated correction of bolus insulin delivered up to every 5 minutes when glucose levels are elevated. These systems may also enable greater personalisation of insulin delivery and monitoring and can include meal detection modules that allow the system to deliver more aggressive auto correction boluses.[27]

2.3.1.1 MiniMed 670G

MiniMed 670G (Medtronic) is a CE marked hybrid closed loop system that uses a control algorithm called SmartGuard. SmartGuard technology has a manual mode and an auto mode. In manual mode, the 670G works just like other sensor-augmented pump systems. In auto-mode function, blood glucose data measured by the CGM (Guardian sensor) is sent wirelessly to the insulin pump (670G), to enable adjustment of basal insulin every five minutes to maintain sensor glucose levels near a target glucose of 120 mg/dL (6.7 mmol/L). The system requires some user interaction to administer mealtime bolus doses. The 670G is not licensed for use in children under 7 years old. The device is also not to be used in people who require less than a

total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

2.3.1.2 MiniMed 780G

MiniMed 780G (Medtronic) is a CE marked hybrid closed loop system launched in 2020. It has an advancement on the algorithm used in the 670G system and has Bluetooth connectivity. The system includes different glucose targets, according to the users' needs. In addition to the target glucose of 120 mg/dL (6.7 mmol/L), users can also select to achieve a tighter glucose target of 5.5 - 6.1 millimoles per litre. In contrast to its predecessor system, the 780G has an 'autocorrection feature' that delivers correction boluses automatically when sustained hyperglycemia is detected. This requires minimal user or carer interaction. The CGM (Guardian sensor) is connected to the MiniMed mobile app via Bluetooth, which optionally automatically uploads data to the CareLink connect system to notify carers or for clinician review. The 780G is not licensed for use in children under 7 years or for people who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

2.3.1.3 Control IQ

The Control-IQ (Tandem Diabetes Care) is a CE marked system that combines t:slimX2 insulin pump and Control-IQ technology. This system can be interlinked with a compatible CGM to form a hybrid closed loop system which suspends insulin delivery in response to predicted hypoglycaemia, or gives a correction bolus in response to predicted hyperglycaemia. Control-IQ has 6 settings, including optional settings for sleep and exercise, to adjust basal insulin delivery depending on user need. Mealtime bolus doses are administered manually. Data from Control-IQ can be uploaded on the Diasend or Tidepool data clouds for clinician review. Control-IQ is not licensed for use in children under 6 years or for people who require less than a total daily insulin dose of 10 units per day or who weigh less than 55 pounds, as those are the required minimum values needed to operate safely.

2.3.1.4 CamAPS FX

CamAPS FX (Camdiab) is a CE marked android app developed at the University of Cambridge. The app can be interlinked with a compatible CGM (Dexcom G6) and insulin pump (Dana RS or Dana-I) to form a hybrid closed loop system. CamAPS FX can operate on an auto mode 'off' whereby basal insulin delivery is pre-programmed by the user or an auto mode 'on' where

insulin delivery is directed by the app. In auto mode on, a bolus dose calculator embedded in the app allows the user to initiate the delivery of mealtime insulin dose. If the auto mode 'on' feature is prevented from coming on, an auto mode 'attempting' feature is initiated in which insulin delivery is reverted to pre-programmed basal rates. Data from CamAPS FX can be uploaded to the Diasend data cloud, for clinician review. CamAPS FX is licensed for use in people aged 1 year and older and in pregnancy, however, other age restrictions may apply depending on the chosen CGM and insulin pump.

2.3.2 Identification of important sub-groups

The NICE scope (March 2022) states the following subgroups if evidence permits:

- Women with type 1 diabetes who are pregnant and those planning pregnancy (not including gestational diabetes). *Note that in this assessment this subpopulation is not required to fulfil the criteria of prior use of at least 1 technology.*
- Children with type 1 diabetes.
- If possible, evidence should be analysed based on the following age groups:
- 5 years and under,
- 6 - 11 years
- 12 -19 years
- People with extreme fear of hypoglycaemia
- People with diabetes related complications that are at risk of deterioration

2.3.3 Current usage in the NHS

The management of T1DM involves lifestyle adjustments, monitoring of blood glucose levels, and insulin replacement therapy, with the aim of recreating normal fluctuations in circulating insulin concentrations. Blood glucose levels are monitored to determine the type and amount of insulin needed to regulate blood glucose levels and reduce the risk of complications.

NICE guidelines recommend that adult and pregnant women with T1DM should be empowered to self-monitor their blood glucose, supported by structured education packages (e.g., Dose Adjustment for Normal Eating) on how to measure glucose levels and interpret the results.[2] NICE also recommends that children and young people with T1DM and their families or carers should be offered a continuing programme of education from diagnosis. Several systems of monitoring glucose levels and delivering insulin are available in clinical practice. The system

recommended for individuals is based on the individual's age, whether they are pregnant, their glycaemic control, and personal preferences (Figure 1).

Management of type 1 diabetes mellitus (T1DM)

Education and Information

NICE guidelines recommend that all people with T1DM should be offered continuing programme of education from diagnosis

Glucose monitoring to obtain information on blood glucose levels and ensure a therapeutic insulin regimen

Glucose monitoring

Finger-prick capillary blood glucose monitoring	Real-time continuous glucose monitoring (rtCGM) using a sensor, transmitter and display device	Flash glucose monitoring using a sensor and scanner
NICE recommends routine monitoring of blood glucose levels at fingertips for all adults, children and young people and pregnant women with T1DM as first line management together with MDI.	NICE recommends automated rtCGM with alarms (low or high glucose level warnings) for: • adults with T1DM when standard management of blood glucose levels has not worked resulting in poor glycaemic control with severe hypoglycaemia or impaired hypoglycaemia awareness • pregnant women with T1DM • children and young people with T1DM, for specific indications	NICE recommends intermittently scanned CGM (flash monitoring) without alarms to pregnant women with T1DM who are unable to use rtCGM or express a clear preference for it. NICE guidelines for adults, children and young people does not comment on the use of flash glucose monitoring.

Insulin regimen to achieve glycaemic control (measured as glycated haemoglobin levels) in order to minimize the risk of chronic diabetes complications

Insulin regimen

Multiple daily insulin injections (MDI)	Continuous subcutaneous insulin infusion (CSII)
NICE recommends MDI insulin regimens as the insulin injection regimen of choice for all adults, children and young people with T1DM.	NICE recommends CSII for: • adults and children 12 years and older with T1DM provided that they have not been able to reach target glycated haemoglobin levels with MDI or have disabling hypoglycaemia • children younger than 12 years with T1DM if MDI therapy is considered to be impractical or inappropriate • pregnant women with insulin-treated diabetes who are using MDI and do not achieve blood glucose control without significant disabling hypoglycaemia

Integrated sensor-augmented pump therapy systems (SAP)

Using a CGM which "talks to" the pump to automatically suspend insulin rate when blood glucose levels are dropping

Integrated

NICE recommends SAP as an option but not routinely for adults and children 12 years and older with T1DM provided that they have not been able to reach target glycated haemoglobin and have episodes of disabling hypoglycaemia despite optimal management with CSII.
People who have started using the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained.

Figure 1. Management of type 1 diabetes mellitus (www.nice.org.uk/guidance/ng17)

2.3.3.1 Blood glucose monitoring

Capillary blood glucose monitoring

Blood glucose concentrations in diabetes can vary considerable from day-to-day and over the course of a 24-hour period. Routine blood glucose testing is typically done using capillary blood glucose monitoring. Capillary blood glucose monitoring involves pricking a part of the body (usually the finger) with a lancet device to obtain a small blood sample at certain times of the day. The drop of blood is then applied to a test strip which is inserted into a blood glucose meter for automated determination of the glucose concentration in the blood sample at the time of the test. Blood glucose measurements are taken after several hours of fasting, usually in the morning before breakfast, and before and after each meal to measure the change in glucose concentration.

NICE recommends routine self-monitoring of blood glucose levels at fingertips for all adults with T1DM at least 4 times a day, including before each meal and before bed.[2] For pregnant women with T1DM, the NICE recommendation is to test fasting, pre-meal, 1-hour post-meal, and bedtime blood glucose levels daily. The NICE recommendation for children and young people with T1DM is capillary blood glucose testing 5 times per day.[28]

Real time continuous blood glucose measurement (rtCGM)

rtCGM is an alternative to routine finger-prick blood glucose monitoring for people (including pregnant women) aged 2 and over, who have diabetes, have multiple daily injections of insulin or use insulin pumps, and are self-managing their diabetes. This involves measuring interstitial fluid glucose levels throughout the day and night.

A rtCGM system comprises three parts:

- A sensor that sits just underneath the skin and measures glucose levels
- A transmitter that is attached to the sensor and sends glucose levels to a display device
- A display device that shows the glucose level (separate handheld device (known as "standalone" CGM) or a pump (known as an "integrated system")

For most rtCGM systems, calibration by checking the finger-prick blood glucose level is needed once or twice a day. rtCGM systems monitors glucose levels regularly (approximately every 5 minutes), and alerts can be set for high, low or rate of change.

NICE does not recommend offering rtCGM routinely to adults with T1DM. Instead, rtCGM with an alarm should be considered for adults with T1DM for whom standard management of blood glucose levels has not worked or been difficult, i.e., those with recurrent severe hypoglycaemia or impaired awareness of hypoglycaemia. The users must also be willing to commit to using the technology at least 70% of the time and to calibrate it as needed. For children and young people with T1DM, NICE recommends that ongoing rtCGM with alarms should be offered to those who continue to have severe hypoglycaemia or impaired hypoglycaemia awareness, or those who are not able to recognise or communicate symptoms of hypoglycaemia. The NICE recommendation is to offer rtCGM to all pregnant women with T1DM to help them meet their pregnancy blood glucose targets and improve neonatal outcomes.

Flash/intermittently scanned glucose monitoring

Flash glucose monitoring systems comprise a reader and a sensor applied to the skin to measure interstitial fluid glucose levels. It only provides a reading or trends when the sensor is scanned. The NICE guidelines for adults and children with T1DM do not comment on the use of flash systems for intermittent interstitial fluid glucose monitoring.

For pregnant women with T1DM, the NICE recommendation is to offer intermittently scanned flash monitoring to those who are unable to use rtCGM or express a clear preference for it. In standard practice and in accordance with the NHS long-term plan, most centres offer flash and/or CGM to pregnant women with T1DM.

HbA1c

Longer-term control is measured by glycated haemoglobin levels (HbA1c), which reflect the average blood glucose levels over 2 to 3 months. HbA1c is correlated to CGM results over the preceding 8-to-12 weeks.[29] NICE guidelines on diabetes (type 1 and type 2) in children and young people, adults, and diabetes in pregnancy recommend that people with T1DM should

aim for a target HbA1c level of 6.5% (48 mmol/mol) or lower to minimise the risk of long term complications from diabetes. Poor glycaemic control may trigger a discussion about different options for insulin administration.

2.3.3.2 Insulin regimens

Multiple daily injections (MDI)

Insulin is injected subcutaneously. Modern insulin regimens have two components – short-acting insulin to cover mealtimes, and long-acting insulin to cover the rest of the day, which is usually given twice a day. The long-acting form is called basal, and the combination is often referred to as "basal-bolus" insulin, or as multiple daily injections (MDI), with three injections of short-acting insulins and one or two of long-acting insulin. However, subcutaneous insulin injections cannot achieve as rapid an effect as pancreatic insulin, and because of the slower onset of action and more prolonged effect, hyperglycaemia is common shortly after meals, often followed by hypoglycaemia later.

The NICE recommendation is to offer MDI basal–bolus insulin regimens for all adults, children and young people with T1DM. For pregnant women with diabetes, NICE recommends that rapid-acting insulin analogues should be considered.

Continuous subcutaneous insulin infusion (CSII)

The alternative to MDI is continuous subcutaneous insulin infusion (CSII) using an insulin pump. It makes use of an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. CSII was approved by NICE as a treatment option for adults and children 12 years and older with T1DM provided that:

- attempts to achieve target HbA1c levels with MDIs result in the person experiencing disabling hypoglycaemia. For the purpose of this guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life, or
- HbA1c levels have remained high (that is, at 8.5% (69 mmol/mol) or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

CSII therapy is recommended as a treatment option for children younger than 12 years with T1DM provided that:

- MDI therapy is considered to be impractical or inappropriate, and
- children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years.

For pregnant women with T1DM, NICE recommends that CSII should be offered to women who are using MDI and do not achieve blood glucose control without significant disabling hypoglycaemia.

Integrated sensor-augmented pump therapy systems (SAP)

Integrated sensor-augmented pump therapy systems combine rtCGM with CSII. The systems are designed to measure interstitial glucose levels (every few minutes) and allow immediate real-time adjustment of insulin therapy. The systems may produce alerts if the glucose levels become too high or too low. NICE's diagnostic guidance (DG21) on integrated sensor-augmented pump therapy systems for managing blood glucose levels in T1DM recommends the MiniMed Paradigm Veo system as an option for managing blood glucose levels in people with T1DM only if they have episodes of disabling hypoglycaemia despite optimal management with CSII.[5] As with other pumps the user can program one or more basal rate settings for different times of the day/night. A built-in bolus calculator works out how much insulin is needed for a meal following the input of carbohydrates consumed. The advanced feature of sensor-augmented pump is that the rtCGM – patient – pump loop is augmented by direct communication between the rtCGM device and the pump. If blood glucose is falling too low, the rtCGM device communicates with the pump and automatically switches off (suspends) the insulin infusions. Depending on the device, the user either must restart insulin delivery or the pump resumes insulin delivery after 2 hours.

LGS/PLGS

SAP systems can operate in standard (manual) and advanced (automatic) modes. In the manual open loop mode, the continuous glucose monitor and glucose pump do not communicate with each other, and insulin doses are programmed by the user, who makes manual adjustments.

In advanced, automatic mode, the CGM device and pump can communicate with each other automatically based on real-time glucose data, in order to adjust the insulin basal rate and suspend the insulin infusion without the input of the wearer in order to prevent potential hypoglycaemia. Glucose suspension can be a simple 'low glucose suspend' (LGS) function, in which insulin infusion is suspended when glucose monitoring systems detect that glucose levels have fallen below a specific hypoglycaemia threshold. In this case, insulin is suspended for a period of time and may resume when the system determines that glucose levels have returned to within target range or when the glucose suspension is overridden by the patient.

Predictive low glucose suspend (PLGS) is a more advanced use of technology in which prediction algorithms are used which essentially forecast future hypoglycaemia (e.g. within the next half hour), and pre-emptively suspend insulin delivery before hypoglycaemia develops. PLGS systems will then automatically resume insulin infusions if the user overrides the suspension, or if glucose levels begin to rise or rise above a specific threshold.[30, 31]

3 DEFINITION OF THE DECISION PROBLEM

3.1 Decision problem

3.1.1 Interventions

The interventions of interest are hybrid closed loop systems - a class of automated insulin delivery systems which consists of three components – a CGM, a microprocessor with control algorithms, and a pump.

There are several hybrid closed loop systems available in the UK such as MiniMed 670G and MiniMed 780G. The systems are representative of the intervention of interest and have been identified by NICE as currently available in the UK.

3.1.2 Population including sub-groups

Population and sub-groups are per NICE scope (published March 2022).

Populations	People who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring[ab] If evidence permits the following T1DM subpopulations will be included: • Pregnant women and those planning pregnancies (excluding gestational diabetes).[b] • Children (5 years and under, 6 – 11 years, 12 - 19 years). • People with extreme fear of hypoglycaemia. • People with diabetes related complications that are at risk of deterioration. [a] For the purpose of this review, difficulty refers to (1) not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below (for pregnant women/those planning pregnancies: not maintaining fasting plasma glucose levels of 5.2 mmol/l or below, or not maintaining non-fasting plasma glucose of 7.7 mmol/L (one hour after eating)/ 6.3 mmol/L (two hours after eating)), (2) not maintaining at least 70% time in range of 3.9 -10 mmol/l, or (3) repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life. [b] Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.

3.1.3 Relevant comparators

Comparator	• Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.

	Where evidence permits, scenarios assessing the following comparators will be presented for women with type 1 diabetes who are pregnant/planning pregnancy: • Real time continuous glucose monitoring with multiple daily insulin injections. • Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections. • Self-blood glucose monitoring with continuous subcutaneous insulin infusion.

3.1.4 Outcomes

Intermediate measures • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below and above target range • Change in HbA1c • Rate of glycaemic variability • Fear of hypoglycaemia • Rate of severe hypoglycaemic events • Rate of severe hyperglycaemic events • Episodes of diabetic ketoacidosis • Rate of ambulance call outs • Rate of hospital out-patient visits • Rate of weight gain
Clinical outcomes • Retinopathy • Neuropathy • Cognitive impairment • End-stage renal disease • Cardiovascular disease • Mortality
Additional clinical outcomes in women who are pregnant/have recently given birth • Premature birth

- Miscarriage related to fetal abnormality
- Increased proportion of babies delivered by caesarean section
- Macrosomia (excessive birth weight)
- Respiratory distress syndrome in the new-born

Device related outcomes

- Adverse events related to the use of devices

Patient-reported outcomes

- Heath-related quality of life
- Psychological well being
- Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)
- Anxiety about experiencing hypoglycaemia
- Acceptability of testing and method of insulin administration

Carer reported outcomes

Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)

3.2 Overall aims and objectives of assessment

The overall objectives of this project are to examine the clinical and cost-effectiveness of hybrid closed loop systems for managing glucose levels in people who have T1DM. The key questions for this review are provided in the box below.

Key question 1

What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Sub questions

1. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in pregnant women who have T1DM?

2. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in children who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

3. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, an extreme fear of hypoglycaemia, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

4. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, with diabetes related comorbidities that are at risk of deterioration, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Key question 2

What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Sub questions

1. What is the cost effectiveness of hybrid closed loop systems for managing glucose in pregnant women who have T1DM?

2. What is the cost effectiveness of hybrid closed loop systems for managing glucose in children who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

3. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, an extreme fear of hypoglycaemia, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

4. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, with diabetes related comorbidities that are at risk of deterioration, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

Systematic review methods followed the principles outlined in the Cochrane Handbook of Diagnostic Test Accuracy [32] and the NICE Diagnostic Assessment Programme manual.[33]

4.1 Methods for reviewing effectiveness

4.1.1 Identification of studies

4.1.2 Search strategy

The search strategy comprised the following main elements:

1) Searching of electronic bibliographic databases and other online sources,

2) Contacting experts in the field, and

3) Scrutiny of references of included studies, relevant systematic reviews, and the most recent NICE guidance on systems that combine CGM and CSII.[5]

A comprehensive search was developed iteratively and undertaken in a range of relevant bibliographic databases and other sources, following the recommendations in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions.[34] Search terms were related to T1DM (including a separate set of terms relating to pregnant women and women planning pregnancy) and technologies to manage blood glucose levels. Search strings applied in the previous technology assessment on integrated sensor-augmented pump therapy systems (DG21) [35] were used as the basis for developing selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections, and other systematic reviews informed the lines relating to pregnancy.[36-38] The main MEDLINE search strategies were independently peer reviewed by a second Information Specialist.

Date limits were used, in order to identify records added to databases since the searches for DG21 (run in 2014).[35] Searches were conducted in March and April 2021, and updated in April 2022, in the following resources: MEDLINE ALL (Ovid); Embase (Ovid); Science Citation Index and Conference Proceedings (Web of Science); Cochrane Database of Systematic Reviews (Wiley); CENTRAL (Wiley); Clinicaltrials.gov; HTA database (CRD); International HTA database (INAHTA); NIHR Journals Library; and the following websites:

- U.S. Food & Drug Administration (FDA)

- Medicines & Healthcare Products Regulatory Agency (MHRA)
- Agency for Healthcare Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Swedish Agency For Health Technology Assessment And Assessment Of Social Services (SBU)

The search was developed in MEDLINE (Ovid) and adapted as appropriate for other resources. Full search strategies are provided in Appendix 1: Record of searches – Clinical effectiveness (see section 10.1.1).

Records were exported to EndNote X9, where duplicates were systematically identified and removed. Where available, alerts were set up so that the team were aware of any new, relevant publications added to databases beyond the original search date.

4.1.3 Inclusion and exclusion criteria

Studies that satisfy the following criteria were included:

Populations	People who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring[ab] If evidence permits the following T1DM subpopulations will be included: • Pregnant women and those planning pregnancies (excluding gestational diabetes).[b] • Children (5 years and under, 6 – 11 years, 12 - 19 years). • People with extreme fear of hypoglycaemia. • People with diabetes related complications that are at risk of deterioration. [a] For the purpose of this review, difficulty refers to (1) not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below (for pregnant women/those planning pregnancies: not maintaining fasting plasma glucose levels of 5.2 mmol/l or below, or not maintaining non-fasting plasma glucose of 7.7 mmol/L (one hour after eating)/ 6.3 mmol/L (two hours after eating)), (2)

	not maintaining at least 70% time in range of 3.9 -10 mmol/l, or (3) repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life. [b] Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.
Target condition	Type 1 diabetes mellitus
Intervention	Hybrid closed loop systems
Comparator	• Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion. • Where evidence permits, scenarios assessing the following comparators will be presented for women with type 1 diabetes who are pregnant/planning pregnancy: • Real time continuous glucose monitoring with multiple daily insulin injections. • Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections. • Self-blood glucose monitoring with continuous subcutaneous insulin infusion.
Outcomes	<u>Intermediate measures</u> • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below and above target range • Change in HbA1c • Rate of glycaemic variability • Fear of hypoglycaemia

- Rate of severe hypoglycaemic events
- Rate of severe hyperglycaemic events
- Episodes of diabetic ketoacidosis
- Rate of ambulance call outs
- Rate of hospital out-patient visits
- Rate of weight gain

Clinical outcomes

- Retinopathy
- Neuropathy
- Cognitive impairment
- End-stage renal disease
- Cardiovascular disease
- Mortality

Additional clinical outcomes in women who are pregnant/have recently given birth:

- Premature birth
- Miscarriage related to fetal abnormality
- Increased proportion of babies delivered by caesarean section
- Macrosomia (excessive birth weight)
- Respiratory distress syndrome in the new-born

Device related outcomes

- Adverse events related to the use of devices

Patient-reported outcomes

- Heath-related quality of life
- Psychological well being
- Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)
- Anxiety about experiencing hypoglycaemia
- Acceptability of testing and method of insulin administration

Carer reported outcomes

	• Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)
Study design	Hybrid closed loop systems studies • Any design All comparator studies • Comparative effectiveness study designs
Healthcare setting	Self-use supervised by primary or secondary care
Publication type	Peer reviewed papers Abstracts and manufacturer data will be included only if they provide numerical data and sufficient detail on methodology to enable assessment of study quality/risk of bias. Further, only data on outcomes that have not been reported in peer-reviewed full text papers will be extracted and reported.
Language	English

Research papers were included where it could not be established if all study participants had difficulty managing their condition (defined by HbA1c, fasting plasma glucose, non-fasting plasma glucose, or time in range as above), if the group mean met this criterion.

Papers that fulfilled the following criteria have been excluded:

Non-human studies, letters, editorials, and communications. Qualitative studies. Studies conducted outside of routine clinical care settings, e.g., inpatient research facilities, diabetic summer camps. Studies where more than 10% of the sample did not meet the inclusion criteria (for example over 10% were inpatients). Studies without extractable numerical data. Studies that provided insufficient information for assessment of methodological quality/risk of bias. Articles not available in the English language. Studies evaluating individual components and

not complete hybrid close loop systems. Studies of DIY closed loop systems, which are not approved by regulatory bodies.[39] Studies evaluating automated insulin delivery systems which only suspend insulin delivery when glucose levels are low/ are predicted to get low.

4.1.4 Review strategy

4.1.4.1 Prioritization strategy for full text assessment

We applied a two-step approach for identifying and assessing relevant evidence. We applied stricter criteria at the point of data extraction/risk of bias than title and abstract assessment to prioritise and select the best available evidence.[40-42] The elements used to prioritise evidence (study design, study length, sample size) were chosen in collaboration with NICE and diabetes clinicians as those that will provide the most applicable evidence.

Step one: The studies were scoped in Endnote before deciding which studies qualified for full text assessment (step two). Records were coded in terms of study design and study duration. Randomised controlled trials (RCTs) were prioritised over controlled trials. Non-randomised controlled trials/comparative effectiveness studies were prioritised over non-comparative studies. Longer term studies (6 months or more) were prioritised (see section 4.1.4.1) over shorter-term studies.

Step two: studies identified from step one went through the standard systematic reviewing approach of full text assessment. We followed the pre-defined PICO (see for study 4.1.3 eligibility criteria) to assess the eligibility of studies.

4.1.4.2 Prioritization strategy for data extraction and risk of bias

Given the limited time and resources available, deprioritised studies i.e. the large number of observational studies which otherwise met the inclusion criteria for this review were narratively reported and listed. RCTs were prioritised for data extraction and quality assessment.[42].

4.1.5 Data abstraction strategy

We extracted the following study characteristics:

Details on study design and methodology, participant characteristics, intervention characteristics, comparator characteristics, outcomes, outcome measures, and additional notes (such as funding).

Two reviewers extracted data independently, using a piloted data extraction form. Disagreements was resolved through consensus, with the inclusion of a third reviewer when required.

4.1.6 Critical appraisal strategy

The risk of bias of randomised trials was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[43] Risk of bias in controlled trials, non-randomised trials, and cohort studies was assessed using the Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I) tool.[44] Risk of bias for case control studies and controlled before-and-after studies was assessed using Effective Practice and Organisation of Care (EPOC) RoB Tool.[45] Two reviewers assessed risks of bias. Disagreements were resolved through consensus, with the inclusion of a third reviewer if required.

4.1.7 Methods of data analysis/synthesis

We synthesised the RCT evidence statistically. The network meta-analysis was conducted using a frequentist approach and a random-effects model.

Subgroup analyses were undertaken where possible for the different combinations of interventions study participants had previously used to manage their blood glucose (i.e., flash glucose monitor and multiple daily insulin injections, flash glucose monitor and CSII, rtCGM and multiple daily insulin injections, rtCGM and CSII, self-blood glucose monitoring and CSII).

4.1.7.1 Pairwise and network meta-analysis

The analysis compared hybrid close-loop systems and relevant comparators for managing blood glucose levels in T1DM. The primary effectiveness outcome was HbA1c. Other clinically relevant outcomes include the 'time in target range' which gives the percentage of time that a person spends with blood glucose level in target range of 70 to 180mg/dl, and adverse events (e.g., severe hypoglycaemia, diabetic ketoacidosis).

Decisions about information to include in the NMA were informed by relevance to the decision problem and sufficient similarity across studies (e.g., patient characteristics and study design)

to reduce the risk of violating underlying assumptions of transitivity/coherence when pooling direct and indirect evidence across studies. We used an iterative process[46] to define the extent of the treatment network and to identify studies for inclusion. This involved first defining an initial core set of interventions that met the criteria set out in the projects' scope and included trials of such interventions in T1DM populations.

Publication bias was assessed visually using a comparison-adjusted funnel plot, where publication bias is present if the funnel plot is asymmetrical. Egger's test was also used, where publication bias is considered to exist if $p<0.05$.

Transitivity was assessed by looking at the distributions of potential effect modifiers across all studies included in the systematic review.

To check for consistency of each network, net splitting can be performed which splits the estimates in the network into direct and indirect estimates. Statistically significant inconsistency is present between the direct and indirect estimates if the p-value of the difference between effect estimates is <0.05. However, due to the small number of studies and treatments in each network, net splitting was not feasible. Loop consistency was also not tested as there were no closed loops in the networks for any of the outcomes.

Treatments were ranked using P-score, which measures the certainty that one treatment is better than another treatment, averaged over all competing treatments.

Statistical analyses were performed using RStudio version 4.1.0.

4.1.8 Dealing with missing data

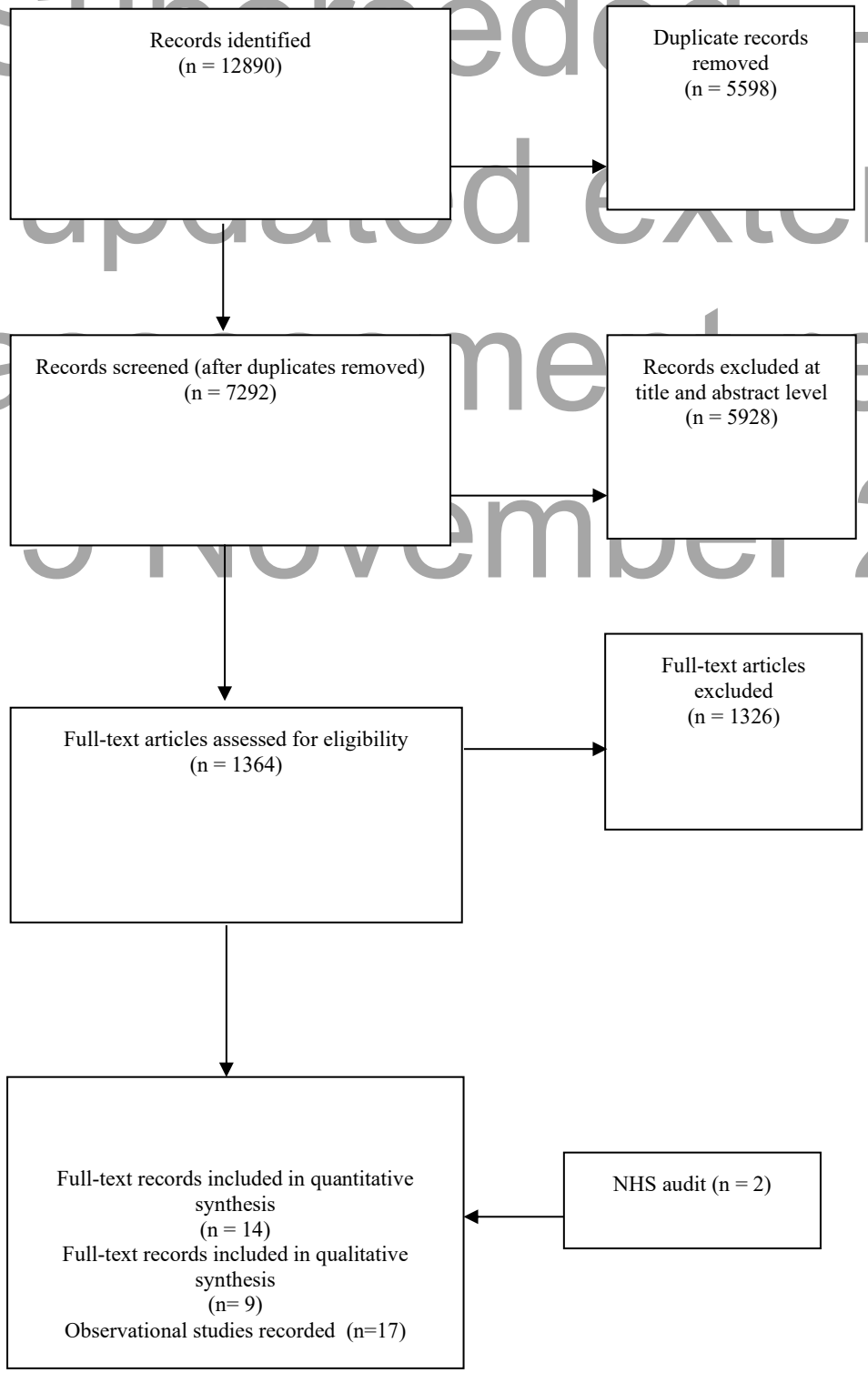
We conducted the review according to the registered protocol.

4.2 Results

4.2.1.1 Number of studies identified

The literature search provided 12890 records potentially related to the area of interest; 7292 records remained after removing duplicates. After the abstract screening, 1364 records were identified for full paper screening. A further 1326 articles were excluded at the full-text stage mainly due to incorrect intervention/comparators, study design, incorrect population, abstract/poster presentation only or further duplication identified. 14 records (12 RCTs) [27, 47-59] and 9 observational studies [27, 60-65] are presented for this systematic review of clinical

effectiveness. Three papers drew on the same study participants. External submissions, including NHS England evidence and company submissions are also presented in this report. The PRISMA flow diagram is shown in the figure below.



4.2.1.2 Number and type of studies included

Randomised controlled trials

Randomised studies

Eleven RCTs (one with two relevant intervention arms,54 13 records) 47-57, 59 were identified that yielded data of potential relevance to the decision problem assessing HCL against a comparator. RCTs in which HCL treatment was received for ≥ 4 weeks (range 4 to 26 weeks) were included if the comparator was relevant to the decision problem (comparators were classified as CSII + CGM and LGS/PLGS).

Most of these studies reported results for outcomes relevant to monitoring glycaemic control. These data were assembled using CGM technology that accumulates large amount of data and they assessed change in % time in range over a specified period of observation (baseline to final). Most studies reported change in HbA1c level (final minus baseline values). The RCTs thus provided quantitative data potentially amenable to network meta-analysis. Two Publications (Bergenstal 2021 27 and Weinzimer 2022 58) were derived from the FLAIR study and presented data comparing different types of AHCL; since HCL has been viewed here as a generic intervention the FLAIR study can be considered more similar to a single arm study (with two subgroups) than an RCT and is considered in the section describing single arm studies.

These RCTs were heterogeneous in multiple respects including trial design (parallel groups or cross over design with wash-out phase between different treatments), participants' age, number of participants, and other demographics including run-in times, duration of observation periods, and number and types of previous treatments. Studies screened relatively small numbers of patients. The number of participants randomised ranged from < 20 to 135.

Table 1 summarises the main characteristics of patients recruited in RCTs with treatment duration 4 to 26 months (additional RCT details are in 10.2. Most studies were conducted in children or young adults. For young children it would likely be difficult to clearly establish whether they were having difficulty in controlling glycaemia prior to recruitment. Only McAuley 2022 51 and Boughton 2019 48 looked at HCL use in elderly patients (age >60 years); in control arm for practical reasons and familiarity with method the participants continued with their previous method of glycaemic control which presumably was long

established (i.e. they were not "re-trained" in a new non-HCL method). In treatment arm participants were trained and then transferred to HCL. Both these studies in the elderly enrolled relatively few patients.

Table 1. Main characteristics of populations recruited in RCTs

Study	Inclusion criteria	Age description	N
Ware 2022a [56]	Diag: ≥ 0.5yr previous; pump ≥3 months; HbA1c < 11% no previous HCL..	Very young children 1 to 7 yr	74
von dem Berge 2022 [55]	Pump ≥3 months; total insulin > 8 U/day; HbA1c 7.4% (±0.9); no severe hypo in last 3 months.	Pre-school and school children; 2 to14 yr	38
Thabit 2015 children/adolescents arm[54]	Diag: ≥ 0.5yr previous; age ≥ 6 y; pump ≥3 months; HbA1c < 10%;	Children /adolescents 6 to 18 yr.	25
Ware 2022b [57]	Diag: ≥ 1yr previous; pump ≥3 months; HbA1c 7.5% to 10%;	Children /adolescents 6 to 18 yr	135
Tauschmann 2018 [53]	Diag: ≥ 1yr previous; age ≥ 6 to 20 yr ; pump ≥3 months; HbA1c 7.5% to 10%; no CGM previous 3 months	Children and young adults 22yr (13 to 26)	86
Thabit 2015 adults arm [54]	Diag: ≥ 0.5yr previous; age ≥18 y; pump ≥ 0.5y; HbA1c 7.5% to 10%;	Adults, 40 yr (±9·4)	33
Benhamou 2019 [66]	Diag: ≥ 2yr previous; aged ≥18 years ; ≤ 50 U per day; HbA1c ≤ 10%	Adults, 48·2 yr (±13·4)	63
Boughton 2019 [48]	Diag: ≥ 1 yr ; Age ≥ 60 yr; pump ≥3 months; HbA1c ≤10·0%. No current use of a closed-loop system, no more than 1 severe in preceding 6 months.	Elderly, 68 yr (62 to 70)	37
McAuley 2022 [51]	Diag: ≥ 10 yr ; Age ≥ 60 yr; using i pump; HbA1c ≤10.5% ; no dementia.	Elderly , 67 yr (± 5)	30
Collyns 2021 [49] and Wheeler 2022 patient reported outcomes based on Collyns [59]	Diag: ≥ 1 yr; age 7 to 80 yr ; pump ≥6 months ; daily insulin min 8 units ; HbA1c < 10% ; no pregnancy.	Children 7-13,N 19, adolescents14-21 N 14, adults 22- 80yr N 26	60
Kariyawasam 2022 [50]	Diag: ≥ 1 yr ; Age 6 to 12 yrs; pump ≥3 months; HbA1c ≤9·0%; hospital 3days then 6 wks post-hospital phase	Young, 6-12 years	22
Stewart 2018 [52]	Women (singleton pregnancy); Diag: ≥ 1 yr prior to pregnancy; age 18-45 yr; HbA1c (8% (±1.1); Excluded if insulin dose ≥ 1.5 units/kg.	Pregnant, 32.8 (±5) yr;	16

The major outcomes reported in the RCTs related to monitoring glycaemic control.

These included change in % HbA1c and % time within, above or below a defined blood glucose level (mmol/ litre) including: % time within range indicating satisfactory control (3.9 to 10 mmol/litre, % time in a hyperglycaemic range (> 10 mmol/litre), and % time in a hypoglycaemic range variously <3.9, <3.5, <3.3, <3.0 and < 2.8 mmol/litre depending on study. Low rates of severe hypoglycaemia and of ketotic episodes were also reported; it may be that the small number of participants and relatively short treatment periods mean that accurate estimates of the rates of these events is difficult. The outcomes reported in RCTs are summarised in Table 2. Additional outcomes are reported in

Table 2. Glycaemic-control outcomes reported in RCTs of potential relevance

Study	Change in HbA1c %	% time >10 mM	% time 3.9 to 10 mM	% time <3.9 mM	% time <3.5 mM	% time <3.3 mM	% time <3.0 mM	% time <2.8 mM	Hypo events	Ketotic events
Ware 2022a[56]	√	√	√	√	√		√		√	√
von dem Berge 2022[55]	√	√	√				√	√	√	√
Thabit 2015[54]	√	√	√	√				√	√	√
Ware 2022b [57]	√	√	√	√					√	√
Tauschmann 2018 [53]	√	√	√	√	√			√	√	√
Benhamou 2019[66]	√	√	√	√		√		√	√	√
Boughton 2019 [48]	√	√	√	√	√		√		√	√
McAuley 2022[51]	√	√	√	√		√	√		√	√
Collyns 2021 [49] and Wheeler 2022 [59]	√	√	√	√			√		√	√
Kariyawasam 2022 [50]	√	√	√	√					√	√
Stewart 2018 [52]	√	√	§					√		

§ Stewart report TIR 3.5 to 7.8 mmol/L.

Outcome results reported in the RCTs are summarised below in Table 2 and presented graphically in forest plots. Glycaemic control outcomes by study arm were reported in various ways, as mean (± sd) or median (IQR) values, often baseline values for each arm were not reported or were unclear so that change from baseline was sometimes and or

unreported and only end of treatment values were provided. Trials reported mean difference and 95% CI between arms whether this was derived from median or mean estimates for the outcome. These reported values were available for NMA. Where necessary some outcome results have been calculated from numerical data in the relevant published reports; these together with most other data reported, were often strongly rounded to only a few decimal places. Table 3 summarises the data extracted from the included RCTs. We present combined results of all RCTs together covering all subpopulations, before presenting results by individual subpopulations.

Superseded – see updated external assessment report (15 November 2022)

Table 3. Summary of main outcome measure reported in RCTs

	HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd* *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR*	*N hypo non-severe mean sd** **Median IQR*	*N hypo sev; mean sd**	*N DKA Event* *mean sd*
Tauschmann 2018 [53] HCL vs. CSII+CGM ;22 yr, 21 yr ; N =86 ; Tx 12 wks Lancet. 2021;392(10155):1321-9											
Inter Base	8.0 (0.6)	44 (11)	52 (10)	*3.5 (2.0,5.4)	*1.8 (0.8,3.2)	NR	NR	* 0.4 (0.1,1.0)			
Inter end	7.4 (0.6)	32 (8)	65(8)	* 2.6 (1.9,3.6)	* 1.4 (0.9,1.9)	NR	NR	* 0.3 (0.2,0.6)			
DIFF calc	-0.6 (0.125)	-12 (2.0)	13	* -0.9	* -0.4	NR	NR	* 0.1	NR	2	1
Comp base	7.8 (0.6) (	44 (11)	52 (9)	*3.3 (1.2, 5.5)	*1.9 (0.6,3.30	NR	NR	* 0.5 (0.1,1.0)			
Comp end	7.7 (0.5)	42 (10)	54 (9)	* 3.9 (1.7,5.3)	* 2.0 (0.9,3.0)	NR	NR	* 05.(0.2,0.9)	NR	*2*	0
DIFF calc	-0.1 (0.123)	-2 (2.35)	2	* 0.6	* 0.1	NR	NR	* 0.0			
Rep.Net effect 95%CI	*-0.36 (-0.53,-0.19)*	*-10 (-13.2,-7.5)*	*10.8 (8.2,13.5)*	*-0.83 (-1.4,-0.16)*	*-0.33 (-0.81,0.04)*	*NR*	*NR*	* 0.09 (-0.24,0.1)*		*0*	*+ 1*
Ware et al., 2022: [56] 5.6 yr ; HCL vs. CSII+CGM ; 5.6 yr (1.61) very young children ; N = 74 ; Tx 16 wks. N Engl J Med. 2022;386:209- 19											
Inter Base	7.3 (0.7)	*32.2 (24.0,42.7)	61.5 (9.5)	*4.5 (2.4,6.7)	NR	NR	*0.8 (0.2,1.8)	NR	NR		
Inter end	6.6 (0.6)	*22.9 (19.3,27.3)	71.6 (5.9)	*4.9 (3.3,6.7)	*2.6 (1.8,3.7)	NR	*1.0 (0.6,1.4)	NR	NR		
DIFF calc	-0.7 (0.16)	*-9.3	10.1	*0.3		NR	*0.2	NR	NR	1	0
Comp base	7.4 (0.6)	*36.7 (21.6,41.8)	60.8 (10.9)_	*3.9 (2.0,7.4)		NR	*0.6 (0.3,1.4)	NR	NR		
Comp end	7.0 (0.7)	*31.7 (23.4,40.1)	62.9 (9.0)	*4.5 (2.9,7.3)	*2.4 (1.4,4.2)	NR	*0.9 (0.4,1.6)	NR	NR		
DIFF calc	-0.4 (0.16)	*-5.0	2.1	*0.6		NR	*0.3	NR	NR	0	0
Net effect 95%CI	*-0.4 (-0.5,-0.3)*	*-8.5 (-9.9,-7.1)*	*8.7 (7.4,9.9)*	*0.1 (-0.4, 0.5) n.s*	*0.04 (-0.3,0.3) n.s*	NR	*0.02 (-0.1,0.1) n.s*	NR	NR	*1*	*0*

	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** **Median IQR	*N hypo sev; mean sd**	*N DKA Event* *mean sd
Ware et al., 2022b [57] HCL vs. CSII+CGM; children / adolescents: 13.1 yr (2.6) & 12.8 (2.9) yr; N = 135 ; Tx 6 months.											
Inter Base	*8.2 (0.7)*	46 (15)	47 (12)	*6.1(2.7,9.5)	NR	NR	NR	NR	NR	NR	NR
Inter end	7.6 (1.1)	38 (20)	54 (17)	*6.1 (3.0,12.1)	NR	NR	NR	NR	NR	NR	NR
DIFF calc	-0.6 (0.17)	-8 (3.1)	7	* 0	NR	NR	NR	NR	11	2	2
Comp base	8.3 (0.7)	47 (16)	46 (13)	*4.9(0.32,9.4),	NR	NR	NR	NR	NR	NR	NR
Comp end	8.1 (0.8)	46 (15)	47 (12)	*5.4 (2.0,12.0)	NR	NR	NR	NR	NR	NR	NR
DIFF calc	-0.2 (0.13)	-1 (2.6)	1	* 0.5	NR	NR	NR	NR	12	0	0
Net effect 95%CI	*-0.32 (-0.59,-0.04)*	*-7.0 (-12.5,-1.5)*	6.7 *(2.2,11.3)*	**-0.53 (-1.78,2.83)*	NR	NR	NR	NR	1	2	2
Benhamou et al., 2019: [66] HCL vs. CSII+CGM ; adult 48.2 (11.7) yr ; N=63; Tx 12 wks. X-over trial. Lancet Digit Health. 2019;1(1):e17-25											
HCL	-0.29 (0.6)	29.5 (10.2)	68.5 (9.4)	2 (2.40)	NR	0.8 (0.8)	NR	0.2 (0.8)	NR	5	0
Comparator	-0.14 (0.6)	36.3 (10.20	59.4 (10.20)	4.3 (2.40)	NR	2 (1.6)	NR	0.7 (0.8)	NR	3	0
Net effect 95%CI	*-0.15 (-0.33,0.03)*	*-6.8 (-9.7,-3.9)*	*9.2 (6.4,11.9)*	*-2.4 (-3.0,-1.7)*	NR	*-1.3 (-1.6,-0.9)*	NR	*-0.5 (-0.33,0.03)*	NR	*2*	*0*
Thabit 2015 children/adolescents: [54] HCL vs. CSII+CGM ; 12 (3.4) yr ; N = 25 ; Tx 12 wks. N Engl J Med. 2015 November 26; 373(22): 2129–2140											
Inter Base	7.8 (0.7)	NR	NR		NR	NR	NR		NR		2
Inter end	7.6 (1.1)	NR	NR		NR	NR	NR		NR		0
DIFF calc	-0.2	36.0 (12.5)	61.2 (11.9)	*2.9 (1.4,4.5)	NR	NR	NR	*0.2 (0.1,0.4)	NR	2; 1 pnt HCL off	2
Comp base	7.8 (0.6)	NR	NR		NR	NR	NR		NR		
Comp end	7..9 (10.6)	NR	NR		NR	NR	NR	*0.4 (0.2,0.7)	NR		
DIFF calc	0	44.5 (12.7)	51.6 (11.8)	*3.0 (1.8,6.1)	NR	NR	NR		NR		

	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** **Median IQR	*N hypo sev; mean sd**	*N DKA Event *mean sd*
Net effect 95%CI	*-0.3 (-0.6,0.1)*	*-7.7 (-11.0,-4.4)*	*8.9 (5.9,11.8)*	¥ *0.83 (0.62,1.1) P 0.18*	NR	NR	NR	¥ *0.47 (0.22,1.1)* ***P 0.05***	NR		
Thabit 2015 adults: [54] HCL vs. CSII+CGM ; 40 (9.4) yr ; N = 33 ; Tx 12 wks. N Engl J Med. 2015 November 26; 373(22): 2129–2140											
Inter Base	7.6 (0.9)	NR	NR		NR	NR	NR		NR		
Inter end	7.3 (0.8)	NR	NR		NR	NR	NR		NR		
DIFF calc	-0.3 (0.21)	29.2 (11.4)	67.(10.60)	*2.9 (1.4,4.5)	NR	NR	NR	*0.3 (0.1,0.7)	NR	1	1
Comp base	7.6 (0.8)	NR	NR		NR	NR	NR		NR		
Comp end	7.6 (1.1)	NR	NR		NR	NR	NR	*0.4 (0.1,0.9)	NR	0	1
DIFF calc	0 (0.24)	38.9 (16.6)	56.8 (14.2)	*3.0 (1.8,6.1)	NR	NR	NR		NR		
Net effect 95%CI	*-0.3 (-0.5,-0.1)*	*-9.6 (-13.0,-6.3)*	*11.0 (8.1,13.8)*	¥ *0.81 (0.68,0.96) P 0.02*	NR	NR	NR	¥ *0.45 (0.31,0.56)* ***P <0.001***	NR	*1*	*0*
¥ Net effect reported as ratio and 95% CI											
McAuley et al., 2022 : [51] intervention: HCL vs. LGS/PLGS; elderly adult 67 yr (5); N = 30 ; X over ; Tx 4 months.											
Inter Base	7.5 (6)	NR	NR	NR	NR	NR	NR	NR	NR		
Inter end	*7.3 (7.1,7.5)	23.6 (6.6)	75.2 (6.3)	*1.21 (0.6,1.68)	NR	*0.37 (0.12,0.49)	*0.13 (0.03,0.24)	NR	NR	3	0
DIFF	NR	NR	NR	NR	NR	NR	-NR	NR	NR		
Comp base	7.5 (6)	NR	NR	NR	NR	NR	NR	NR	NR		
Comp end	*7.5 (7.1,7.9)	29.0 (9.8)	69.0 (9.1)	*1.69 (1.0,2.54)	NR	*0.41 (0.2,0.78)	*0.16 (0.10,0.38)	NR	NR	2	*1*
DIFF	NR	NR	NR	NR	NR	NR	NR	NR	NR		

	*HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe mean sd* **Median IQR*	*N hypo sev; mean sd**	*N DKA Event *mean sd*
Net effect 95%CI	*-0.2 (-0.3, 0.0)*	*-5.4 (-7.3,-3.5)*	*6.2 (4.4, 8.0)*	**-0.47 (-1.05,-0.25)*	NR	**-0.19 (-0.36,-0.06)*	**-0.11 (-0.16,-0.05)*	NR	NR	*+1*	*-1*
In 12 months pre-trial there were N=5 single severe hypo events and N= 4 patients with ≥ 2 severe hypo events. A minimum of 13 severe hypo events in 30 person years ~ 0.43/person year. HCL rate was 0.3/person year and SAP rate 0.2/person year											
Boughton et al., [48] HCL (*CamAPS FX, CamDiab, Cambridge, UK*) vs. CSII+CGM ; Age 68 (63,70) vs 67 (62,70) ; N = 20 vs. N =17 ; Tx 16 weeks . Sci Transl Med. 2019;11(484)											
Inter Base	7.5 (1.0)	*25.5 (15.1,41.9)	69.6 (14.1)	*1.8(0.8,3.2)	NR	NR	*0.1 (0.0,0.4)	NR	NR		NR
Inter end	6.7 (0.7)	*16.7 (11.4,23.9)	79.9 (7.9)	*1.7 (1.3,2.4)	*0.7 (0.5,1.1)	NR	*0.2 (0.1,0.3)	NR	NR		NR
DIFF	-0.8 (0.27)	*-8.8	10.3	*-0.1	NR	NR	NR	NR	NR	0	NR
Comp base	7.4 (0.9)	*25.5 (15.9,39.8)	70.3 (13.7)	*1.6 (0.4,2.7)	NR	NR	*0.1 (0.0,0.4)	NR	NR		NR
Comp end	6.9 (0.9)	*21.4 (16.9,36.50	71.4 (13.2)	*1.7 (0.9,2.7)	*0.7 (0.4,1.2)	NR	*0.2 (0.1,0.3)	NR	NR		NR
DIFF	-0.5 (0.31)	*-4.1	1.1	*0.1	NR	NR	NR	NR	NR	2	NR
Net effect 95%CI	*-0.2 (-0.4,-0.10*	**-8.5 (-10.9,-6.1)*	*8.6 (6.3,11.0)*	**-0.1 (-0.3,0.2)*	**0.0 (-0.2,0.1)*	*NR*	**0.0 (-0.1,0.1)*	*NR*	*NR*	*-2 (17.6 / 100PYR)*	*NR*
von dem Berge 2022 [55] HCL vs. LGS/PLGS; N =38 : (age 2-6 yrs N 18) and (14- 17 yrs N 20) ; Tx 8 weeks. X-over trial Diabetes Obes Metab. 2022;1–9											
Inter Base	7.4 (0.9)	36.3 (14.5)	60.4 (12.3)	NR	NR	NR	0.8 (0.9)			0	0
Inter end	6.9 (0.5)	25.8 (8.1)	70.8 (7.2)	NR	NR	NR	0.8 (0.7)			0	0
DIFF calc	-0.5 (0.17)	-10.5 (2.7)	10.4	NR	NR	NR	0		<3.9mM**16 (13.5,19.0) < 3mM**4 (3.4,5.9)		NR
Comp base	7.4 (0.9)	36.3 (14.5)	60.4 (12.3)	NR	NR	NR	0.8 (0.9)			0	0
Comp end	7.1 (0.6)	36.5 (15.2)	60.3 (13.9)	NR	NR	NR	0.6 (0.50			0	0

	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** **Median IQR	*N hypo sev; mean sd**	*N DKA Event *mean sd*
DIFF calc	-0.3 (0.18)	-0.2 (3.41)	-0.1	NR	NR	NR	-0.2		<3.9mM **18 (13.7,20.6) <<3mM **3 (2.6,4.6)		NR
Net effect 95%CI	*P 0.0002*	*P <0.0001*	*P <0.0001*	*NR*	*NR*	*NR*	*n.s.*		*n.s. n.s.*	0	*NR*
Kariyawasam 2022 [50] HCL vs. CSII+CGM; N =20 (N=17 for 6 wk home phase) ; age 2-6 yrs ; Tx 6 weeks. Lancet digit Health; X-over RCT											
Inter Base	7.6 (0.52)	NR	NR	NR	NR	NR	NR	NR		0	0
Inter end	NR	31.1 (7.7)	66.19 (6.5)	2.62 (2.39)	NR	NR	0.57 (0.77)	NR		0	0
DIFF calc	NR	NR	NR	NR	NR	NR	NR	NR	* 13 (11.6) /person yr		NR
Comp base	7.4 (0.95)	NR	NR	NR	NR	NR	NR	NR		0	0
Comp end	NR	36.11 (7.7)	58.68 (6.5)	5.24 (2.39)	NR	NR	1.01 (0.77))	NR		0	0
DIFF calc	NR	NR	7.51	NR	NR	NR	NR	NR	* 24.57 (12) /person yr		NR
Net effect 95%C (calc) reported P	*NR*	*-5 (-10.2,0.18) P 0.015*	*7.51 (3.14,11.8) P <0.001*	*-2.62 (-4.22,-1.01) P <0.0001*	*NR*	*NR*	*-0.44 (-0.96,-.08) P 0.003*	*NR*	*-11.57 (-19.5,-3.6) P <0.0001*	0	*0*
Collyns 2021 [49] HCL vs. LGS/PLGS; N = 60 ; age 23.5 (7 to 65) ; Tx 4 weeks with 2 to 4 wk run in. ; X-over RCT; all 3 age groups. ALL 59 (completed)											
Inter Base	7.6 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inter end	NR	27.5(8.1)	70.4 (8.1)	2.1 (1.4)	NR	NR	0.5 (0.5)	NR	0	0	0
DIFF calc	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Comp base	7.6 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Comp end	NR	39.6 (12.1)	57.9 (11.7)	2.5 (1.6)	NR	NR	0.5 (0.5)	NR	0	0	1

	*HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe mean sd* **Median IQR*	*N hypo sev; mean sd**	*N DKA Event *mean sd*
DIFF calc	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Net effect 95%C (rep) reported P	*-0.6 (-1.38,0.18)*	*-12.1 (9.0) P<0.001*	*12.5 (8.5) P <0.001*	*-0.4 (1.3) P 0.0318*	*NR*	*NR*	*-0.1(0.4) P 0.025*	*NR*	*0*	0	*-1*
Collyns 2021 [49] HCL vs. LGS/PLGS; N = 19 ; age 7 to 13yr ; Tx 4 weeks with 2 wk run in. ; X-over RCT; children											
Net effect 95%C (rep) reported P	*NR*	*-11.2 (8.0) P<0.001*	*11.8 (7.4) P <0.001*	*-0.7 (1.8) P 0.1216*	*NR*	*NR*	*-0.2(0.5) P 0.067*	NR	NR	NR	NR
Collyns 2021 HCL vs. LGS/PLGS; N = 14 ; age 14 to 21yr ; Tx 4 weeks with 2 wk run in. ; X-over RCT; adolescents											
Net effect 95%C (rep) reported P	*NR*	*-14.0 (8.5) P<0.001*	*14.4 (8.4) P <0.001*	*-0.74 (1.1) P 0.1804*	*NR*	*NR*	*-0.1(0.3) P 0.2441*	NR	NR	NR	NR
Collyns 2021 HCL vs. LGS/PLGS; N = 26 ; age 22 to 80yr ; Tx 4 weeks with 2 wk run in. ; X-over RCT; adults											
Net effect 95%CI (reported P)	*NR*	*-11.8 (10) P<0.001*	*11.9 (9.5) P <0.001*	*-0.1 (0.9) P 0.5184*	*NR*	*NR*	*-0.0(0.2) P 0.5462*	NR	NR	NR	NR

	HbA1c %	% TIR >10 mmol/L	%TIR >7.8 mmol/L	% TIR 3.5-7.8 mmol/L	% TIR <3.5mmol/L	% TIR <2.8 mmol/L	Hypo events median (range) Unclear if IQR	N severe hypo	DKA event
Stewart 2018 [52] HCL vs. CSII+CGM; N = 16 ; age 32.8 (sd 5); Tx 4 weeks; X-over RCT; adult pregnant women; study reported TIRs that were in most cases atypical of other studies.									

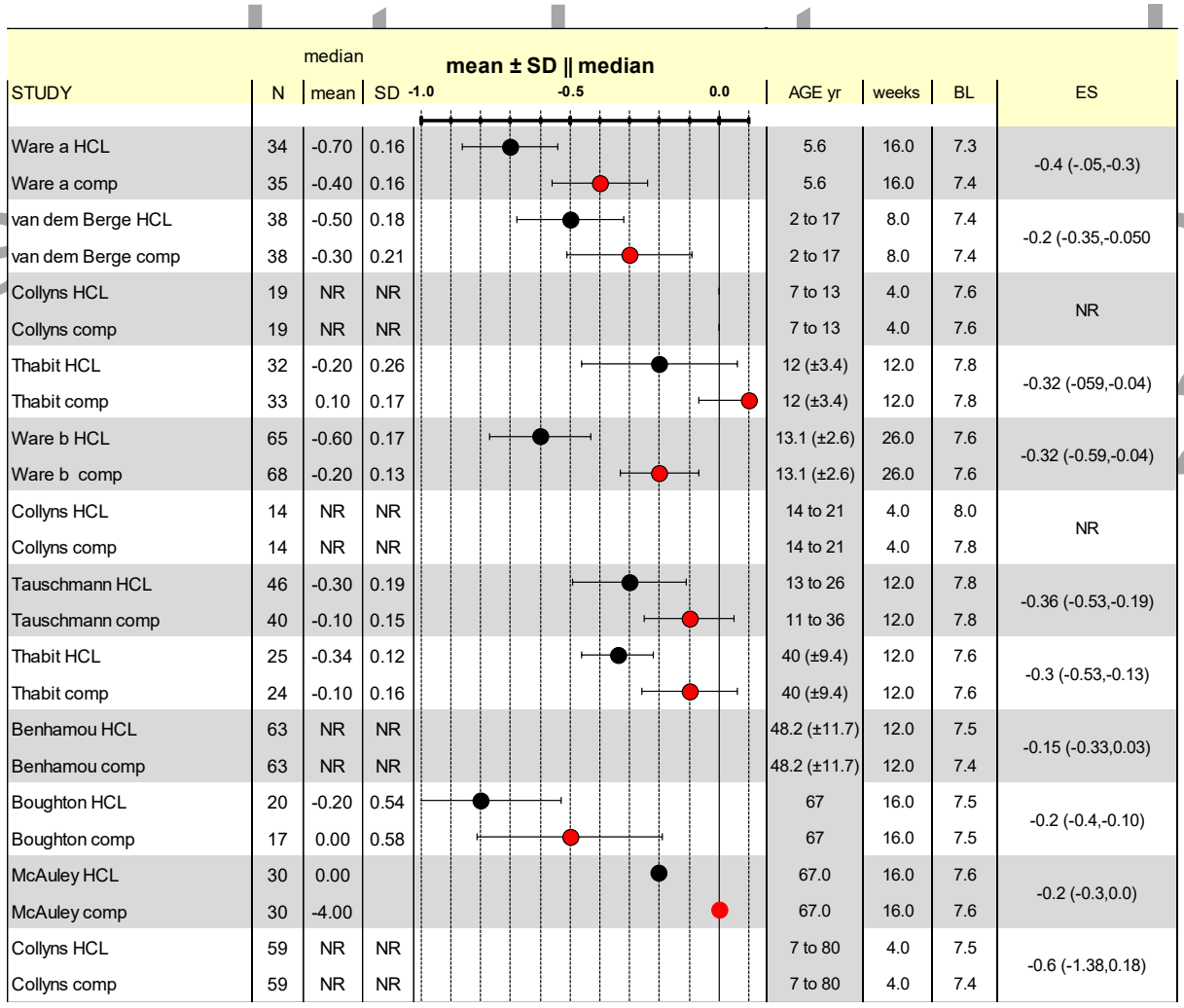
	*HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe mean sd* **Median IQR*	*N hypo sev; mean sd**	*N DKA Event *mean sd*
end INT	6.6%	14.6	36.1	62.3	1.6	0.2	8 (1 to 17)	0	NR		
end Comp	6.4%	14.8	36.6	60.1	2.7	0.5	12.5 (1 to 53)	0	NR		
Net effect 95%CI (rep) P	*P 0.15*	*-0.1 (-4.2,4.0) P 0.94*	*-0.6 (-7.4,6.30 P 0.86*	*2.1 (-4.1,8.3) P 0.47*	*-1.1 (-0.2 ,-2.1) P 0.02*	*-0.2 (-0.0,-0.5) P 0.03*	*P 0.04*		NR		
No statistically significant improvement in glycaemic control over 4 weeks except for less time in hypoglycaemic range possible reflected in fewer hypo (non severe) events											

DIFF = difference; DKA = diabetic ketoacidosis; IQR = inter quartile range; N = number of participants; Net effect = comparison HCL vs. comparator; sd = standard deviation; TIR = time in range ; Tx = treatment duration; wk = weeks; X over = RCT cross over design; yr = years.

4.2.2 %HbA1c - Forest plots

Figure 1 shows the change from baseline in %HbA1c for each arm over the treatment period. A negative effect estimate (ES), comparing HCL vs. comparator, infers superior glycaemic with HCL.

Figure 1. Change (mean ± sd or median) in %HbA1c over treatment period in RCTs



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Ware a HCL	34	-0.70	0.16	5.6	16.0	7.3	-0.4 (-.05,-0.3)
Ware a comp	35	-0.40	0.16	5.6	16.0	7.4	
van dem Berge HCL	38	-0.50	0.18	2 to 17	8.0	7.4	-0.2 (-0.35,-0.050
van dem Berge comp	38	-0.30	0.21	2 to 17	8.0	7.4	
Collyns HCL	19	NR	NR	7 to 13	4.0	7.6	NR
Collyns comp	19	NR	NR	7 to 13	4.0	7.6	
Thabit HCL	32	-0.20	0.26	12 (±3.4)	12.0	7.8	-0.32 (-059,-0.04)
Thabit comp	33	0.10	0.17	12 (±3.4)	12.0	7.8	
Ware b HCL	65	-0.60	0.17	13.1 (±2.6)	26.0	7.6	-0.32 (-0.59,-0.04)
Ware b comp	68	-0.20	0.13	13.1 (±2.6)	26.0	7.6	
Collyns HCL	14	NR	NR	14 to 21	4.0	8.0	NR
Collyns comp	14	NR	NR	14 to 21	4.0	7.8	
Tauschmann HCL	46	-0.30	0.19	13 to 26	12.0	7.8	-0.36 (-0.53,-0.19)
Tauschmann comp	40	-0.10	0.15	11 to 36	12.0	7.8	
Thabit HCL	25	-0.34	0.12	40 (±9.4)	12.0	7.6	-0.3 (-0.53,-0.13)
Thabit comp	24	-0.10	0.16	40 (±9.4)	12.0	7.6	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	7.5	-0.15 (-0.33,0.03)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	7.4	
Boughton HCL	20	-0.20	0.54	67	16.0	7.5	-0.2 (-0.4,-0.10)
Boughton comp	17	0.00	0.58	67	16.0	7.5	
McAuley HCL	30	0.00		67.0	16.0	7.6	-0.2 (-0.3,0.0)
McAuley comp	30	-4.00		67.0	16.0	7.6	
Collyns HCL	59	NR	NR	7 to 80	4.0	7.5	-0.6 (-1.38,0.18)
Collyns comp	59	NR	NR	7 to 80	4.0	7.4	

Weeks = treatment period; BL = baseline value ; comp = comparator; HCL = hybrid closed loop; N = number of participants; yr = years; ES = net effect size mean difference 95% CI [HCL vs. comparator]; medians have no error bars.

Range of mean baseline (BL) %HbA1c in the RCTs was narrow: 7.4 to 8.3. In all studies reduction in %HbA1c is greater for HCL than comparator. Change in %HbA1c over treatment (TX) period in HCL is modest (range -0.2 to -0.8). Net effect sizes (ES 95% CI; HCL vs. comparator) are modest ranging from -0.15 to -0.4. Relative to the NHS real world

pilot study BL is [redacted] and the net ES [redacted]. In the NHS pilot study (described in section 5.1) treatment with HCL brings the [redacted] seen in RCTs after HCL use. Not included in the forest plot is the FLAIR study [27] comparing two types of HCL with each other with BL %HbA1c = 7.9. Change from baseline was similar to the RCTs above: -0.5 (± 0.10) with one HCL and -0.3 (± 0.09) with the other.

4.2.3 %HbA1c – NMA

There were 12 estimates from 11 studies that were included in this NMA as estimates from Thabit study arms were split into adult and children estimates. The reference treatment class was CSII+CGM, where estimates >0 favoured CSII+CGM. The network map is presented in Figure 2 and the forest plot of the NMA is presented in Figure 3.

Compared to CSII+CGM, treatment with HCL decreased HbA1c % by 0.28 (-0.34 to -0.21). There was no statistically significant difference between CSII+GCM and LGS/PLGS.

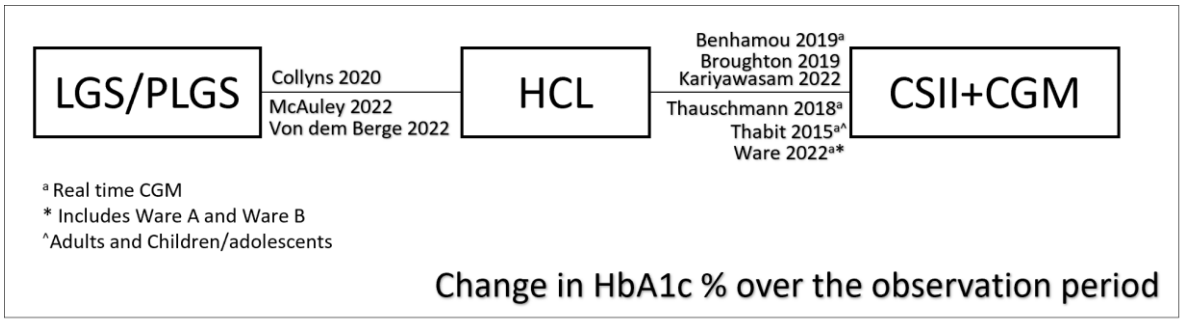


Figure 2. Network map of the outcome Change in HbA1c % over observation period

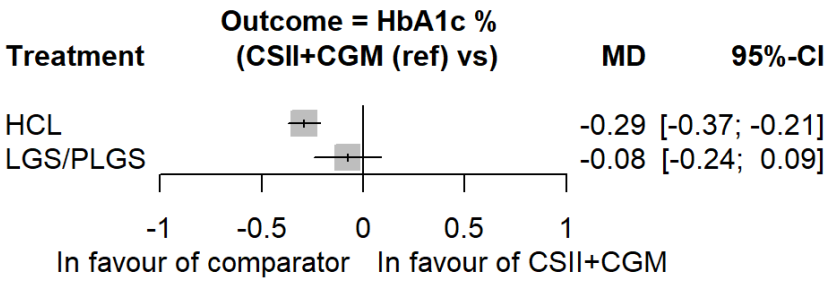
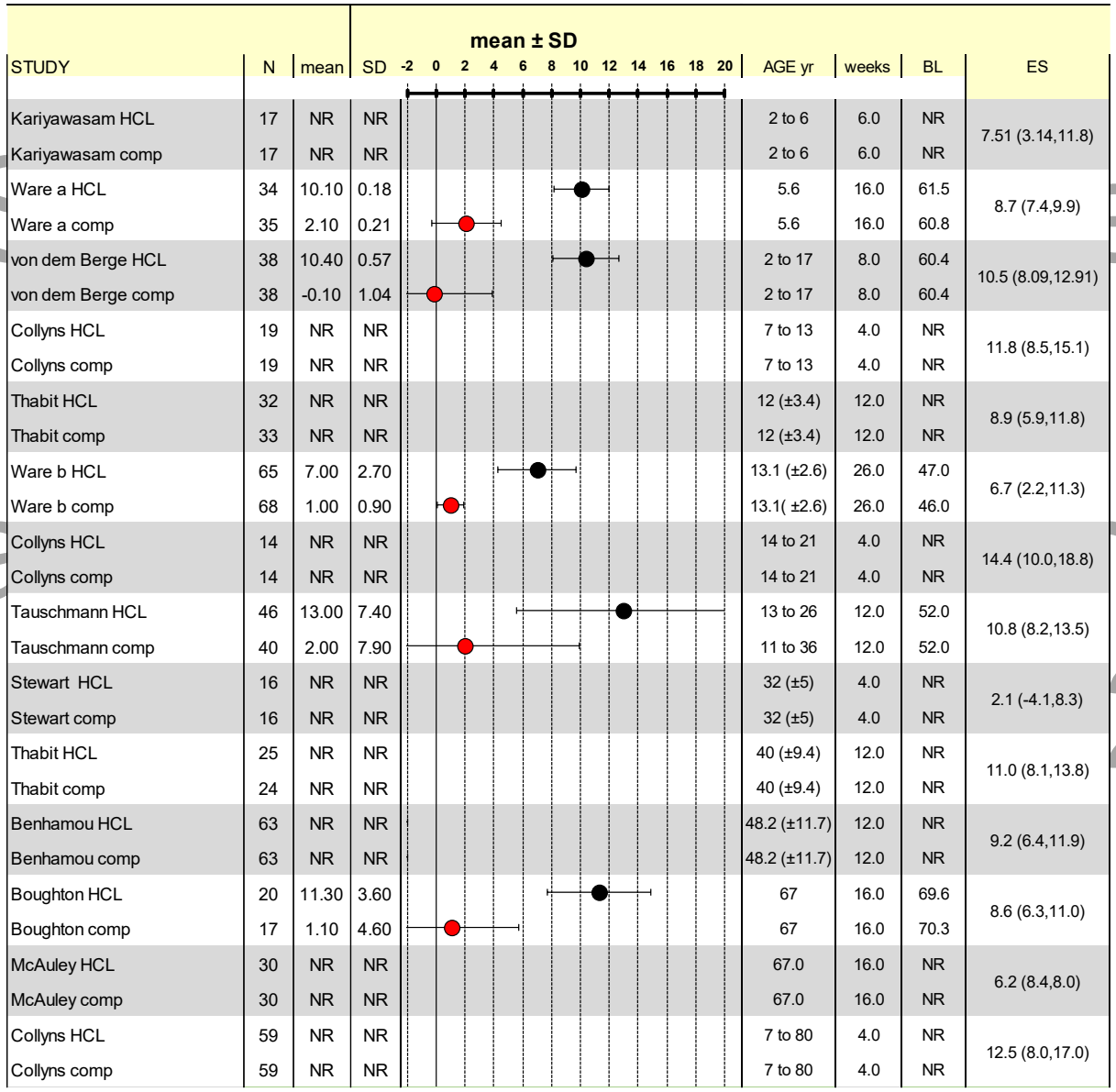


Figure 3. Results of the NMA of the outcome Change in HbA1c % over observation period

4.2.4 % time within range (between 3.9-10.0 mmol/L) - Forest plots

In all the RCTs the increase in % time in range was greater in the HCL arm than the comparator arm, in all cases reaching statistical significance (< P 0.05). The lowest mean BL % time in range was 40%, in all other studies it was > 50%. In the NHS Pilot study (described in section 6.1) [redacted]. The change from baseline in the HCL arm of RCTs with adults of similar age range as adult NHS Pilot (e.g. [53], [48]) ranged from 10% to 15%, approximately [redacted]. The size of improvement in % TIR appears to be greater the smaller the BL level.

Figure 4. change from baseline in % time in range (3.9 mmol/L to 10.0 mmol/L)



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	7.51 (3.14,11.8)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	10.10	0.18	5.6	16.0	61.5	8.7 (7.4,9.9)
Ware a comp	35	2.10	0.21	5.6	16.0	60.8	
von dem Berge HCL	38	10.40	0.57	2 to 17	8.0	60.4	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04	2 to 17	8.0	60.4	
Collyns HCL	19	NR	NR	7 to 13	4.0	NR	11.8 (8.5,15.1)
Collyns comp	19	NR	NR	7 to 13	4.0	NR	
Thabit HCL	32	NR	NR	12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR	12 (±3.4)	12.0	NR	
Ware b HCL	65	7.00	2.70	13.1 (±2.6)	26.0	47.0	6.7 (2.2,11.3)
Ware b comp	68	1.00	0.90	13.1(±2.6)	26.0	46.0	
Collyns HCL	14	NR	NR	14 to 21	4.0	NR	14.4 (10.0,18.8)
Collyns comp	14	NR	NR	14 to 21	4.0	NR	
Tauschmann HCL	46	13.00	7.40	13 to 26	12.0	52.0	10.8 (8.2,13.5)
Tauschmann comp	40	2.00	7.90	11 to 36	12.0	52.0	
Stewart HCL	16	NR	NR	32 (±5)	4.0	NR	2.1 (-4.1,8.3)
Stewart comp	16	NR	NR	32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR	40 (±9.4)	12.0	NR	11.0 (8.1,13.8)
Thabit comp	24	NR	NR	40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	9.2 (6.4,11.9)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	11.30	3.60	67	16.0	69.6	8.6 (6.3,11.0)
Boughton comp	17	1.10	4.60	67	16.0	70.3	
McAuley HCL	30	NR	NR	67.0	16.0	NR	6.2 (8.4,8.0)
McAuley comp	30	NR	NR	67.0	16.0	NR	
Collyns HCL	59	NR	NR	7 to 80	4.0	NR	12.5 (8.0,17.0)
Collyns comp	59	NR	NR	7 to 80	4.0	NR	

Weeks = treatment period; BL = baseline value ; comp = comparator; HCL = hybrid closed loop; N = number of participants; yr = years; ES = net effect size mean difference 95% CI [HCL vs. comparator]; medians have no error bars. NB. The population in Stewart et al., was pregnant women and the TIR refers to 3.5 to 7.8 mM rather than 3.9 to 10 mM.

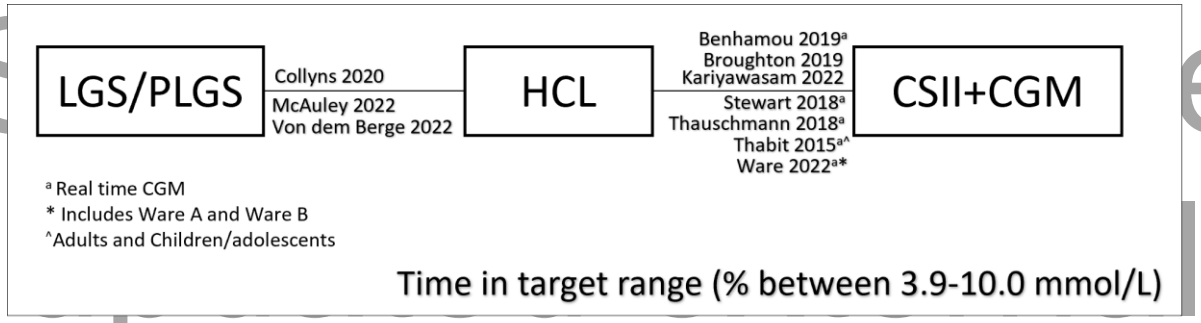
4.2.5 % time within range (between 3.9-10.0 mmol/L) – NMA

There were 13 estimates from 12 studies that were included in this NMA as estimates from Thabit were split into adult and children estimates. The reference treatment class was CSII+CGM, where estimates <0 favoured CSII+CGM. The network map is presented in Figure 5 and the forest plot of the NMA is presented in Figure 6.

Compared to the CSII+CGM treatment classification, HCL significantly increased % TIR (between 3.9 – 10.0 mmol/L), with a mean difference (MD) of 8.6 (7.03 to 10.22). There was

no statistically significant difference between CSII+GCM and LGS/PLGS.

Figure 5. Network map of the outcome Time in target range (% between 3.9 and 10.0 mmol/l)



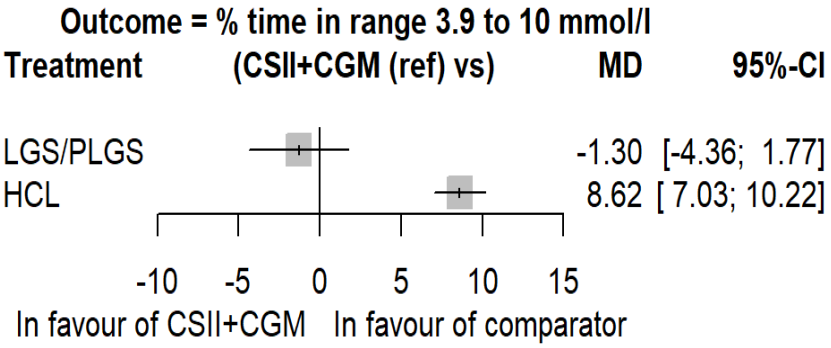
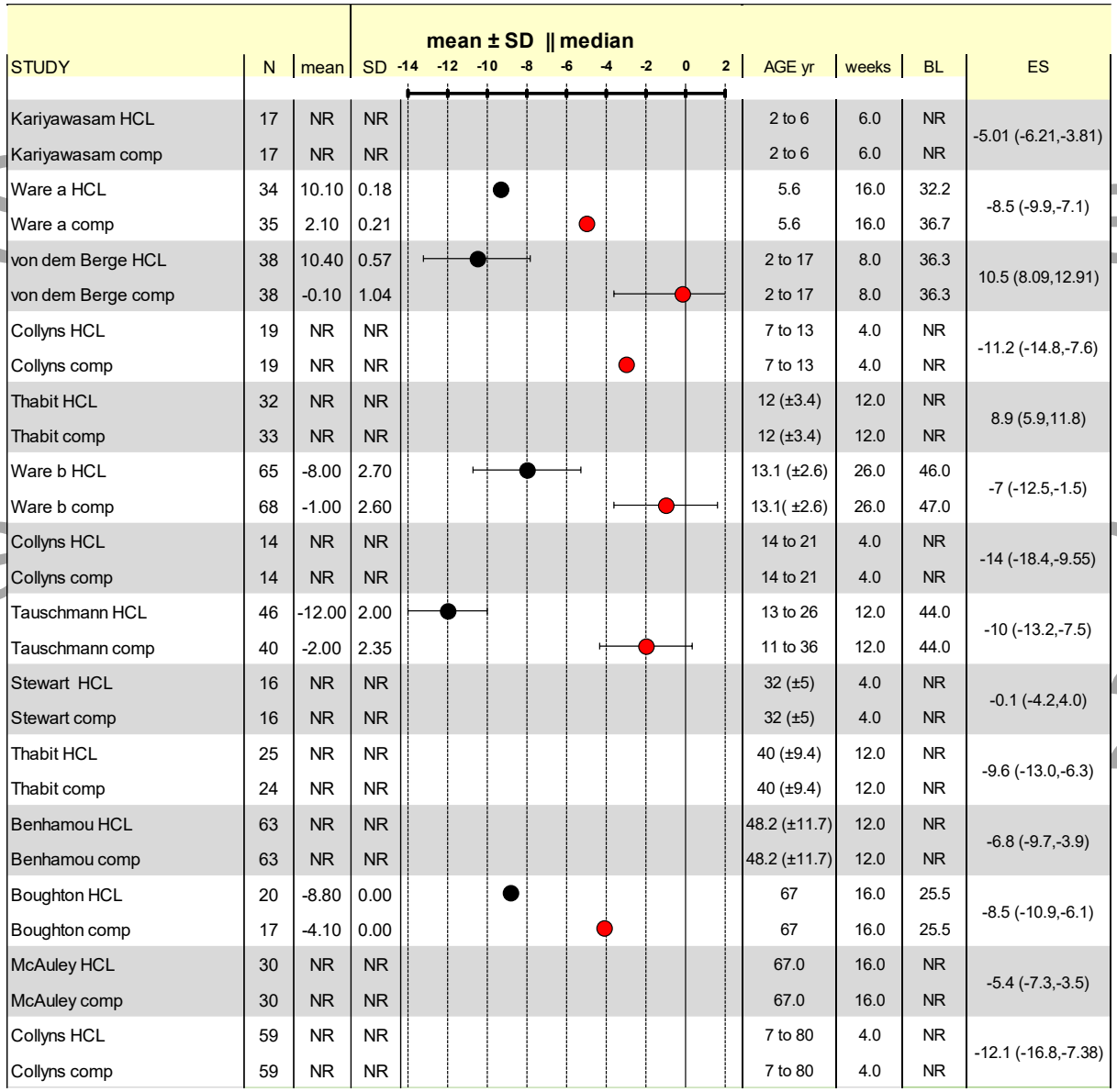


Figure 6. Results of the NMA of the outcome Time in target range (% between 3.9 and 10.0 mmol/l)

4.2.6 % time within range (>10.0 mmol/L) – Forest plot

Figure 7 shows the change from baseline in % time in hyperglycaemic range (> 10.0 mmol/L). Ware 2022 [56] and Boughton[48] reported BL and follow up % time in range as medians IQR without specifying the IQR for the change from BL, calculating IQR was problematical and not attempted. The studies of Benhamou [66] and Thabit [54] only reported net ES.

Figure 7. Change in % time in hyperglycaemic range (> 10.0 mmol/L) over treatment period in RCTs



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-5.01 (-6.21,-3.81)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	10.10	0.18	5.6	16.0	32.2	-8.5 (-9.9,-7.1)
Ware a comp	35	2.10	0.21	5.6	16.0	36.7	
von dem Berge HCL	38	10.40	0.57	2 to 17	8.0	36.3	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04	2 to 17	8.0	36.3	
Collyns HCL	19	NR	NR	7 to 13	4.0	NR	-11.2 (-14.8,-7.6)
Collyns comp	19	NR	NR	7 to 13	4.0	NR	
Thabit HCL	32	NR	NR	12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR	12 (±3.4)	12.0	NR	
Ware b HCL	65	-8.00	2.70	13.1 (±2.6)	26.0	46.0	-7 (-12.5,-1.5)
Ware b comp	68	-1.00	2.60	13.1(±2.6)	26.0	47.0	
Collyns HCL	14	NR	NR	14 to 21	4.0	NR	-14 (-18.4,-9.55)
Collyns comp	14	NR	NR	14 to 21	4.0	NR	
Tauschmann HCL	46	-12.00	2.00	13 to 26	12.0	44.0	-10 (-13.2,-7.5)
Tauschmann comp	40	-2.00	2.35	11 to 36	12.0	44.0	
Stewart HCL	16	NR	NR	32 (±5)	4.0	NR	-0.1 (-4.2,4.0)
Stewart comp	16	NR	NR	32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR	40 (±9.4)	12.0	NR	-9.6 (-13.0,-6.3)
Thabit comp	24	NR	NR	40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-6.8 (-9.7,-3.9)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-8.80	0.00	67	16.0	25.5	-8.5 (-10.9,-6.1)
Boughton comp	17	-4.10	0.00	67	16.0	25.5	
McAuley HCL	30	NR	NR	67.0	16.0	NR	-5.4 (-7.3,-3.5)
McAuley comp	30	NR	NR	67.0	16.0	NR	
Collyns HCL	59	NR	NR	7 to 80	4.0	NR	-12.1 (-16.8,-7.38)
Collyns comp	59	NR	NR	7 to 80	4.0	NR	

N = number of participants contributing data; yr = years; weeks = treatment duration; BL = mean baseline value ; ES = net effect size comparing reduction in % in range in HCL arm relative to control arm, n.b. the ES values reported were usually statistically adjusted. Benhamou and Thabit and only reported net ES. Median values have no error bars.

In all studies HCL reduced % time in hyperglycaemic range greater extent than in the comparator arms. Difference between arms (net effect size) was statistically significant in all cases ($P < 0.05$). The NHS Pilot study (described in section 5.1) reported an unadjusted

[redacted]

4.2.7 % time within range (>10.0 mmol/L) – NMA

There were the same 13 estimates from 12 studies in this NMA as for the outcome TIR % between 3.9-10.0 mmol/L. The reference treatment class was CSII+CGM, where estimates >0 favoured CSII+CGM. The network map is presented in Figure 8 and the forest plot of the NMA is presented in Figure 9.

Compared to CSII+CGM, HCL significantly decreased TIR (% above 10.0 mmol/L), with a mean difference (MD) of -7.2 (-8.89 to -5.51). There was no statistically significant difference between CSII+GCM and LGS/PLGS.

Figure 8. Network map of the outcome Time in target range (% above 10.0 mmol/l)

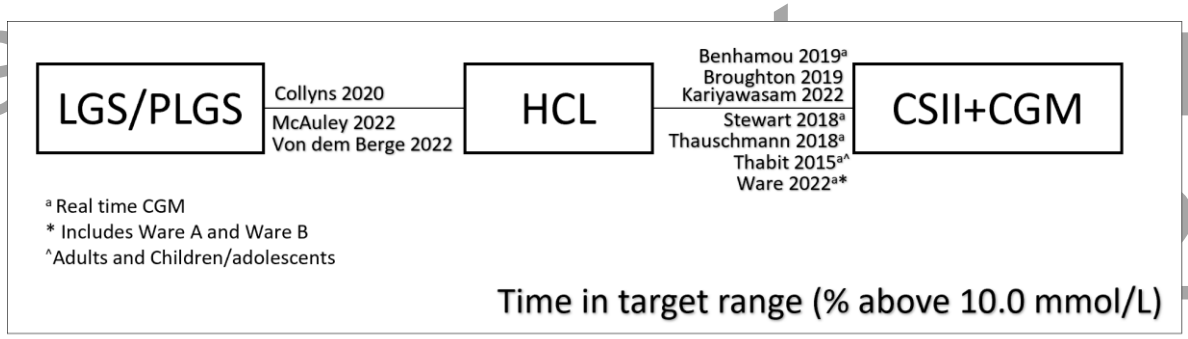
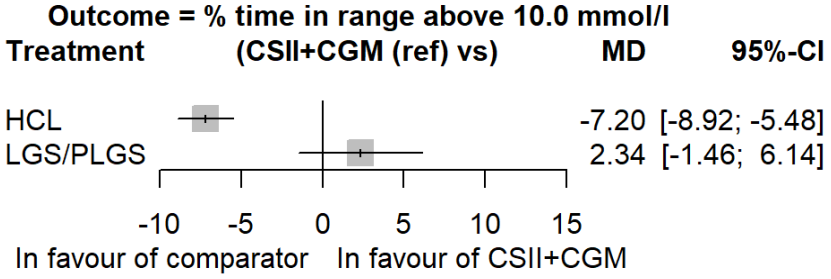


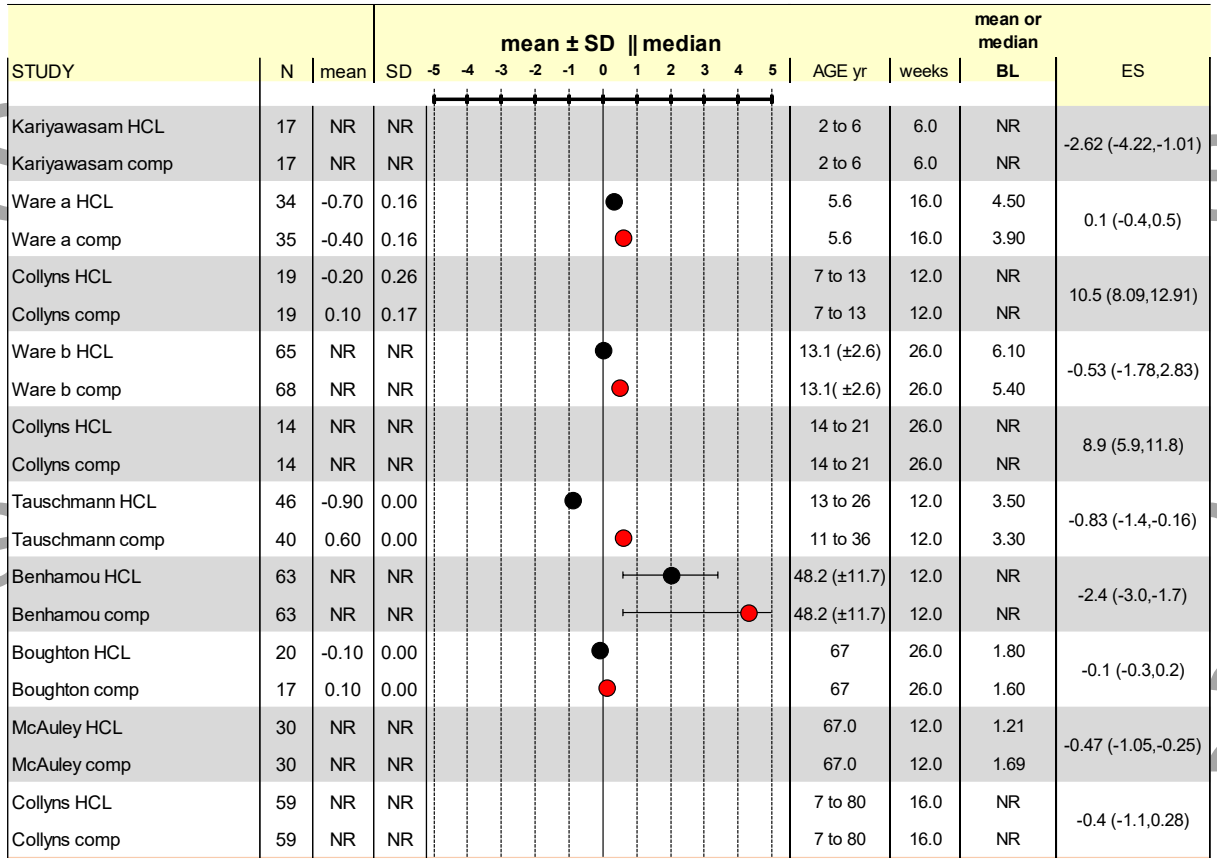
Figure 9. Results of the NMA of the outcome Time in target range (% above 10.0 mmol/l)



4.2.8 % time within range (<3.9 mmol/L) – Forest plot

Figure 10 summarises % time in hypoglycaemic range of <3.9 mmol/L. Because of skewed data results were mostly reported as medians with IQRs, only a few studies reporting mean ± sd. The plots show BL and follow up % time in specified range by each arm since this allows IQRs to be shown whereas reliably calculating IQR for BL vs. follow-up differences was problematical for most studies.

Figure 10. % time in hypoglycaemic range < 3.9 mmol/L



STUDY	N	mean	SD	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-2.62 (-4.22,-1.01)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16	5.6	16.0	4.50	0.1 (-0.4,0.5)
Ware a comp	35	-0.40	0.16	5.6	16.0	3.90	
Collyns HCL	19	-0.20	0.26	7 to 13	12.0	NR	10.5 (8.09,12.91)
Collyns comp	19	0.10	0.17	7 to 13	12.0	NR	
Ware b HCL	65	NR	NR	13.1 (±2.6)	26.0	6.10	-0.53 (-1.78,2.83)
Ware b comp	68	NR	NR	13.1(±2.6)	26.0	5.40	
Collyns HCL	14	NR	NR	14 to 21	26.0	NR	8.9 (5.9,11.8)
Collyns comp	14	NR	NR	14 to 21	26.0	NR	
Tauschmann HCL	46	-0.90	0.00	13 to 26	12.0	3.50	-0.83 (-1.4,-0.16)
Tauschmann comp	40	0.60	0.00	11 to 36	12.0	3.30	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-2.4 (-3.0,-1.7)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.10	0.00	67	26.0	1.80	-0.1 (-0.3,0.2)
Boughton comp	17	0.10	0.00	67	26.0	1.60	
McAuley HCL	30	NR	NR	67.0	12.0	1.21	-0.47 (-1.05,-0.25)
McAuley comp	30	NR	NR	67.0	12.0	1.69	
Collyns HCL	59	NR	NR	7 to 80	16.0	NR	-0.4 (-1.1,0.28)
Collyns comp	59	NR	NR	7 to 80	16.0	NR	

Thabit and Benhamou did not report before and after values; Thabit presented ES as a ratio of medians, Benhamoou ES was reported as -2.4 (95% CI: -3.0 to -1.7).

The NHS Pilot study (described in section 5.1) [redacted]

In both arms the mean or median % time in range was small (6% or less), the ES (difference between arms) was also small occasionally reaching statistical significance.

Figure 11 summarises % time in hypoglycaemic range of <3.0 mmol/L. Again study results were mostly reported as median with IQR, only a few studies reported mean ± sd.

Figure 11. % time in hypoglycaemic range < 3.0 mmol/L

STUDY	N	mean	SD	mean ± SD || median -0.40 -0.20 0.00 0.20 0.40	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR		2 to 6	6.0	NR	-0.44 (-0.96,0.08)
Kariyawasam comp	17	NR	NR		2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16		5.6	16.0	0.80	0.02 (-0.1,01)
Ware a comp	35	-0.40	0.16		5.6	16.0	0.60	
von dem Berge HCL	38	-0.20	0.26		7 to 13	12.0	0.80	0.2 (0.04,0.36)
von dem Berge comp	38	0.10	0.17		7 to 13	12.0	0.80	
Collyns HCL	19	NR	NR		13.1 (±2.6)	26.0	NR	-0.2 (-.42,0.02)
Collyns comp	19	NR	NR		13.1(±2.6)	26.0	NR	
Collyns HCL	14	NR	NR		14 to 21	26.0	NR	-0.01 (-0.26,0.06)
Collyns comp	14	NR	NR		14 to 21	26.0	NR	
Boughton HCL	20	NR	NR		13 to 26	12.0	NR	0.0 (-0.1,0.1)
Boughton comp	17	NR	NR		11 to 36	12.0	NR	
McAulery HCL	30	NR	NR		48.2 (±11.7)	12.0	NR	-0.11 (-0.16,-0.05)
McAuley comp	30	NR	NR		48.2 (±11.7)	12.0	NR	
Collyns HCL	59	5.00	NR		67	26.0	NR	-0.1 (-0.31,0.11)
Collyns comp	59	5.00	NR		67	26.0	NR	

The mean or median % time in range was < 1.5% in both arms and ES values (HCL vs. comparator) reported were very small. [redacted] in the NHS Pilot study (described in section 5.1). The [redacted]. A few studies reported alternative hypoglycaemic ranges (see Table 2) with similar results.

4.2.9 % time within range (<3.9 mmol/L) – NMA

There were 8 estimates from 8 studies that were included in this NMA. The reference treatment class was CSII+CGM, where estimates >0 favoured CSII+CGM. The network map is presented in Figure 12**Error! Reference source not found.** and the forest plot of the NMA is presented in Figure 13.

Despite a MD <0 for HCL compared to CSII+CGM, as the 95% CI crossed 0, there was no statistically significant difference between HCL and CSII+CGM, and similarly no statistically significant difference between CSII+CGM and LGS/PLGS.

Figure 12. Network map of the outcome Time in target range (% below 3.9 mmol/l)

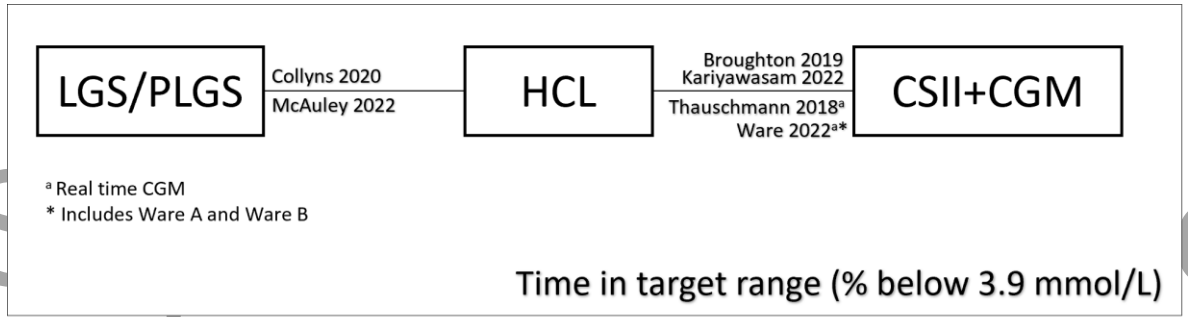
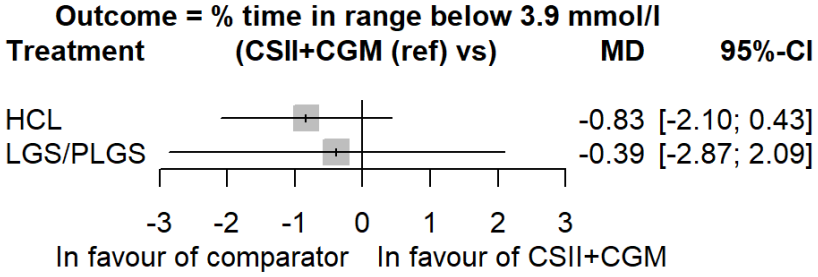


Figure 13. Results of the NMA of the outcome Time in target range (% below 3.9 mmol/l)



4.2.10 Observational studies (studies with no intervention other than HCL and or AHCL)

Nine observational studies are presented in Table 4 and provided outcomes indicating glycaemic performance in T1DM patients using HCL or AHCL (advanced HCL) systems. Two are NHS pilot studies, which are described in reports provided to the EAG (NICE, 17 June 2022) and seven are reported in published articles.[27, 60-65]

Table 4. Main characteristics of populations recruited in observational studies

Study	Population at recruitment / randomisation	Age description	N
NHS Pilot study adults. HCL (Report provided to EAG by NICE, 17 June 2022)	[redacted]	[redacted]	[redacted]
Forlenza 2022 HCL [65]	Diag: ≥ 0.25 yr; Pump ≥ 3 months; HbA1c < 10%; total insulin ≥ 8 U/day; no severe hypo in last 3 months.	children; 2 to <7yr	46
Beato-Vibora 2021a "group 4" HCL (MM670G) [61]	T1DM for 29yr (±9·4) Preg: women excluded. Cross sectional study	Adult 38yr (±11)	43
Bassi 2022; 2 AHCLs (A=MM780G; B= Control-IQ) [60]	Diag: ≥ 1yr ; previous CSII or MDI; use of CGM : ≥ one-months' before and after starting the AHCL. Drop outs from AHCL before one month of use were excluded.	24.4 yr (±15.7)	A 51 B 39
Beato-Vibora 2021b AHCL MM780G [62]	HbA1c % 7.23 (± 0.86); Preg: women excluded	Adult 43 yr (±12)	52
Breton 2021 AHCLAHCL slim X2 pump with Control-IQ [63]	Users of the AHCL US in "Tandem's Customer Relations Management database"	Range 6 to 91 yr	7801
Carlson 2022 AHCL MM [64]	Diag: ≥ 2 yr ; T1D for, at least, 2 years. Minimum daily insulin ≥ 8 U; HbA1c % < 10 ; willingness to use device. Excluded if history of severe hypos , diabetic ketosis.	Adolescents and adults. 38.3 yr (±17.6)	157
Bergenstal 2021; HCL MM 670G; AHCL as but with updated software. X over study [27]	Diag: ≥ 1 year; Age 14 to 29 yr ; HbA1c 7·0% to 11·0% ; Excluded if ≥ 1 severe hypo.	14 to 29 yr	112
NHS Pilot study CYP HCL (Report provided to EAG by NICE, 17 June 2022)	[redacted]	[redacted]	[redacted]

Most observational studies employed similar inclusion criteria to those used in the RCTs. The NHS Pilot adult (described in section 5.1.1) and CYP (described in section 5.1.2) pilot studies were [redacted].

The number of participants across these studies was greater than seen across the RCTs even when excluding the large survey study of Breton et al.[63] The adult pilot study [redacted] the CYP pilot [redacted]

Outcome results reported in observational studies are summarised below in Table 5 and presented graphically in forest plots in which the change from baseline is compared with that seen in the HCL arm of the RCTs.

Table 5. Outcome results reported in observational (single arm) studies

NHS Pilot CYP: [redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inter Base	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inter end	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DIFF (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Forlenza 2022 : [65] MiniMed™ 670G 2-6 yr ; N = 46 ; Tx 3 months

	% > 10 mmol/L	*o 10m mmol/L*	*% TIR < 3.9mmol/L*	*% TIR <3.0 mol/L [54mg/dl]*	*% TIR <2.8 mol/L [50mg/dl]*	*N hypo severe*
Inter Base	41.0 (14.7)	55.7 (13.4)	3.3 (2.5)	0.7 (0.8)	0.5 (0.5)	10 during run in 0.824/100 user days
Inter end	33.0 (9.90	63.8 (9.4)	3.2 (1.6)	0.7 (0.6)	0.5 (0.4)	39 during HCL 0.841/100 user days
DIFF	*-8.0* *P <0.001*	*8.1* *P <0.001*	*-0.1* *P 0.996*	*0* *P 0.679*	*0* *P 0.447*	*29* *0.017/100 user days*

Beato Vibora 2021 [61] "Cross sectional study" ; HCL system MiniMed 670G with Guardian Sensor Group 4, N = 43 ; Age 38 yr((± 11) ; Tx unclear

	HbA1c% *mean sd*	*> 10 mmol/L* *mean sd*	*TIR 3.9-10.0 mmol/L* *mean sd*	*TIR <3.9 mmol/ [70mg/dl]* *mean sd*	*TIR<3.0 mmol/L [54mg/dl]* *mean sd*
Inter Base	NR	NR	NR	NR	NR
Inter end	7.0 (0.42)	27 (9)	71 (10)	1.9 (1.6)	0.5 (0.6)
DIFF	*NR*	*NR*	*NR*	*NR*	*NR*

Bassi 2022. [60] 2 AHCL systems: Minimed 780G and Control IQ; N= 51 & N = 39 ; age 24.4 (±15.7) ; Tx 1 month; Retrospective, propensity matching.

	> 10 mmol/L	*3.9-10. mmol/L*	*3.9 mmol/L [70mg/dl]*	*<3.0 mmol/L [54mg/dl]*
Mean DIFF (95%CI)	-5.7 (-7.8, -3.5)	14.6 (11.4,17.9)	-0.2 (-0.6,0.2)	-0.2 (-0.4,0.0)
Mean DIFF 780G	*-7.3 (-10.6,-4.1)*	19.1 (14.3,23.9)	*0.37 (-0.21,0.94)*	*-0.08 (-.28,0.12)*
Mean DIFF Control IQ	*-3.8 (-6.7,-1.0)*	*9.8 (5.9,13.7)*	*-0.68 (-1.23,-0.12)*	*-0.27 (-0.63,0.09)*

Beato vibora 2021 [62] AHCL system: prospective study. Medtronic 780G Advanced Hybrid Closed-Loop N = 52 ; age 43 (±12) yr ; Tx 3 months

	HbA1c% *mean sd*	*> 10 mmol/L*	*% TIR* *10.0 mmol/L* *mean sd*	*% TIR <3.9* *mmol/L* *70mg/dl]* *mean sD*	*% TIR<3.0* *mmol/L* *54mg/dl]* *mean sd*	*Hypo* *rms per day* *mean sd*	*o severe* **mean* *sd*	*DKA* **mean sd*
Inter Base	7.23 (0.86)	29.4 (15.1)	67.3 (13.6)	3.4 (3.4)	0.9 (1.2)		NR	NR
Inter end	6.67 (0.61)	16.8 (8.4)	80.1 (7.5)	3.1 (2.5)	0.7 (0.9)	3.5 (3.0)	0	0
DIFF	*P <0.001*	*P <0.001*	*P<0.001*	*P 0.562*	*P 0.127*	NR	NR	NR

Breton 2021 [63] AHCL: slim X2 in pump with Control-IQ; 4% Type 2DM ; Tx 1 year (retrospective survey) ; results based on N = 7801 T1DM

	> 10 mmol/L Median IQR	*% TIR 3.9-10.0 mmol/L Median IQR*	*% TIR<3.0 mmol/L [54mg/dl] Median IQR*
Inter Base	25.2 (18.2,31.0)	63.2 (49.8,75.1)	0.01 (0.00,0.35)
Inter end	19.7 (14.3, 24.2)	73.5 (64.4,81.6)	0.02 (0.00,0.4)
DIFF (95% CI)	*P <0.001*	*P <0.001*	*P <0.001*

Time in range 3.9 to 10 mM improved; time in hyperglycaemic improved, less hyperglcaemia; hypoglycaemic time worsened, more time hypoglycaemic but events were rare authors state "*Although there was a statistically significant increase (due to the very large sample size) in time". %* TIR > 10 mM was actually % TIR 10 mM to 14 mM ; % time >250 : base 8.3 (3.1,16.9) , 12 months 4.7 (2.0,9.6) *i.e. better(less hyper) at 12 months.*

Carlson : [64] MiniMed AHCL ; N = 157 ; age 14-21yr ; (N 39) , Tx 3 months

	> 10 mmol/L	*% TIR 10.0 mmol/L mean sd*	*% TIR <3.9 mmol/L [70mg/dl] mean sd*	*% TIR<3.0 mmol/L 54mg/dl] mean sd*	*% TIR <2.8 mmol/L 50mg/dl] mean sd*	*hypo non-severe*	*hypo severe*	
Adults 22-75 yr (N 118)								
Inter Base	25.7 (10.2)	70.9 (9.8)	3.4 (3.0)	0.8 (1.1)	0.5 (0.7)	0	0	0
Inter end	22.6 (7.5)	75.1 (7.3)	2.3 (1.7)	0.5 (0.6)	0.3 (0.4)	0	0	0
DIFF(95% CI)	*-3.1 P<0.001*	*4.2 P<0.001*	*-1.1 P<0.001*	*-0.3 P 0.005*	*-0.2 P 0.006*	*0*	*0*	*0*
Adolescents14-21yr (N 39)								
Inter Base	34.3 (10.7)	62.4 (9.9)	3.3 (2.7)	0.9 (1.0)	0.6 (0.7)	0	1 *not device related*	*0*
Inter end	24.9 (5.7)	72.7 (5.6)	2.4 (1.8)	0.6 (0.6)	0.4 (0.5)	0		*0*
DIFF (95% CI)	*-9.6 P <0.001*	*10.4 P <0.001*	*-0.9 P 0.021*	*-0.3 P 0.106*	*-0.2 P 0.252*	0		*0*

Bergenstal 2021 [27] MiniMed 670G + previous software (HCL) and + updated software (AHCL).N 112; TX 12 weeks X-over (no washout);

Co-primary outcomes	*Daytime > 10mmol/L [180mg/L]* *mean sd*		*All day % TIR<3.0 mmol/L [54mg/dl]* *mean sd*	
	HCL	AHCL	HCL	AHCL
Inter Base	42 (13)	42 (13)	0.46 (0.42)	0.46 (0.42)
Inter end	37 (9)	34 (9)	0.50 (0.35)	0.46 (0.33)
DIFF (95% CI) calc	-5	-8	0.4	0.0

Secondary Outomes (all day)	*HbA1c %*		*% TIR >10.0 mmol/L* *mean sd*		*% TIR 3.9-10.0 mmol/L* *mean sd*		*% TIR<3.9 mmol/L [70mg/dl]* *mean sd*		*Hypo severe*	*DKA Event*
	HCL	AHCL	HCL	AHCL	HCL	AHCL	HCL	AHCL	HCL || AHCL	HCL || AHCL
Inter Base	7.9 (0.7)	7.9 (0.7)	41 (13)	41 (13)	57 (12)	57 (12)	2.3 (1.8)	2.3 (1.8)		
Inter end	7.6 (0.6)	7.4 (0.8)	34 (8)	31 8	63 (8)	67 (8)	2.1 (1.4)	2.1 (1.2)	0 || 1	0 || 0
DIFF (95% CI) calc	-0.3 (-0.13,-0.47)	-0.5 (-0.3,-0.7)	-7 (-9.8, -4.2,)	-10 (-12.8,-7.2)	6 (4.0,8.0)	10 (8.0,12.0)	-0.2 (-0.62, 0.22)	-0.2 (-0.60,0.2)	0 || 1	0 || 0

Figure 14 shows the change from baseline in HbA1c % experienced by HCL recipients reported in identified RCTs and observational studies. The range of change is narrow across RCTs and single arm trials (i.e. no intervention other than HCL and or AHCL). The improvement in HbA1c % level [redacted] in the NHS Pilot study; the baseline level was [redacted]. In the NHS Pilot with children and young people (CYP) [redacted]

Figure 14. Change in HbA1c % from baseline in study participants receiving HCL intervention

Figure 15 shows a forest plot for % time in range (between 3.9 and 10 mmol/L). At baseline in most studies time in range was above 50%. In the NHS Pilot adult study [redacted]; this likely reflects the broad inclusion of patients and indicates along with HbA1c baseline that [redacted]. Similarly in the NHS CYP Pilot [redacted]

[redacted]; this compares [redacted] with values in other observational studies of 63.8% (Forlenza), 71% (Beato-Vibora cross sectional study), 80 % (Beato-Vibora prospective study) 63% and 67% (Bergenstahl (HCL and AHCL respectively). Similarly in the CYP Pilot the [redacted]

Figure 15. Change from baseline of %time in range (3.9 to 10 mmol/L)

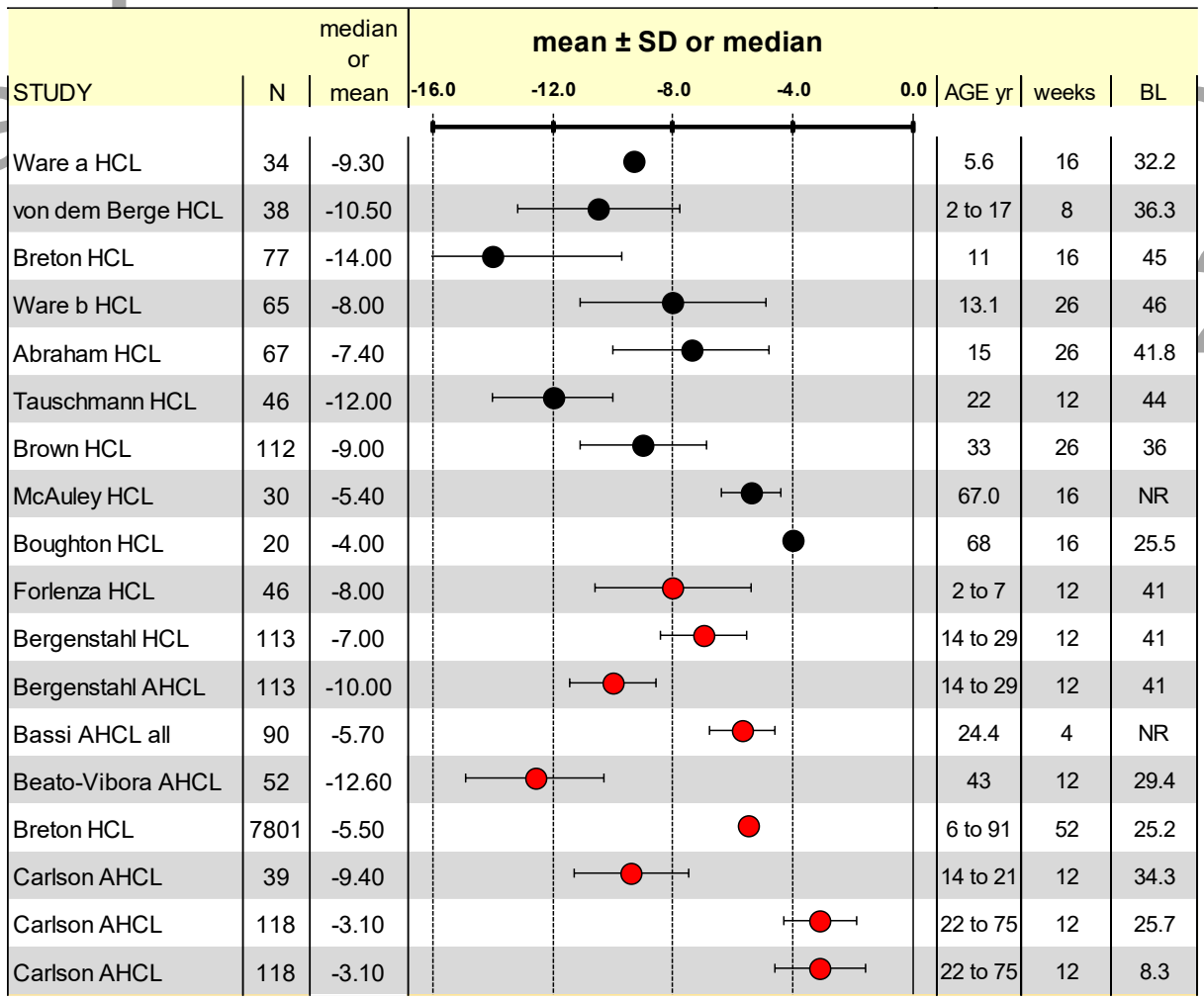
Median values have no error bars. RCTs shown include Abraham 2021[67] Brown 2019[68] Breton 2020 [69] details of these studies available in 10.4.

Figure 16 shows a forest plot of the change from baseline in the % time in the hyperglycaemic range of > 10 mmol/L. All studies reported an improvement from baseline; improvement ranged from (3.0% to 14 % reduction in % time in hyperglycaemic range). The NHS Pilot study [redacted]

[redacted]

Transfer to HCL resulted [redacted]

Figure 16. Change from baseline of %time in hyperglycaemic range (>10 mmol/L)



STUDY	N	median or mean	AGE yr	weeks	BL
Ware a HCL	34	-9.30	5.6	16	32.2
von dem Berge HCL	38	-10.50	2 to 17	8	36.3
Breton HCL	77	-14.00	11	16	45
Ware b HCL	65	-8.00	13.1	26	46
Abraham HCL	67	-7.40	15	26	41.8
Tauschmann HCL	46	-12.00	22	12	44
Brown HCL	112	-9.00	33	26	36
McAuley HCL	30	-5.40	67.0	16	NR
Boughton HCL	20	-4.00	68	16	25.5
Forlenza HCL	46	-8.00	2 to 7	12	41
Bergenstahl HCL	113	-7.00	14 to 29	12	41
Bergenstahl AHCL	113	-10.00	14 to 29	12	41
Bassi AHCL all	90	-5.70	24.4	4	NR
Beato-Vibora AHCL	52	-12.60	43	12	29.4
Breton HCL	7801	-5.50	6 to 91	52	25.2
Carlson AHCL	39	-9.40	14 to 21	12	34.3
Carlson AHCL	118	-3.10	22 to 75	12	25.7
Carlson AHCL	118	-3.10	22 to 75	12	8.3

Median values have no error bars.

Figure 17. Mean (95% CI) change from baseline in % time in range < 3.9 mmol/L

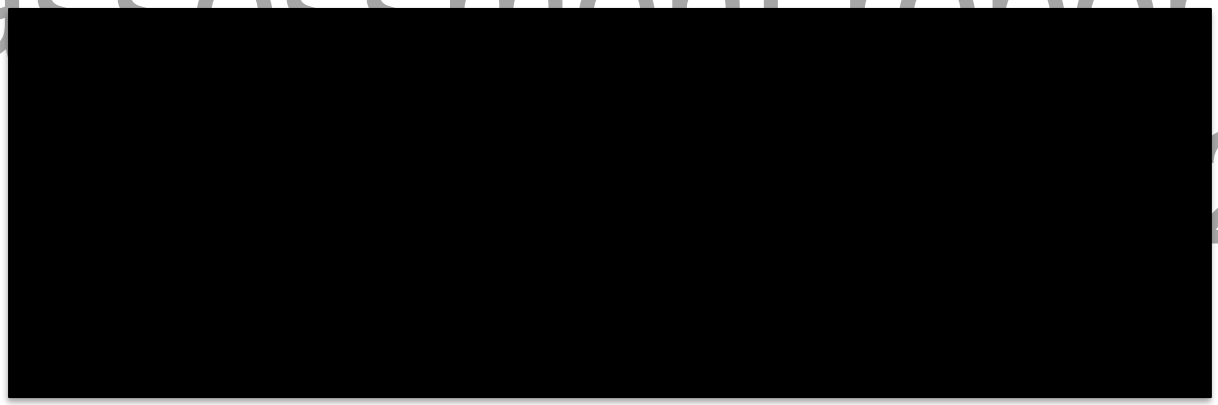
The change in % time in hypoglycaemic ranges (< 3.9 mmol/L and < 3.0 mmol/L) was reported in most observational studies.

Figure 17 shows the mean (95% CI) change from baseline in % time below 3.9 mmol/L; confidence intervals were wide. Both % time below 3.9 mmol/L at baseline ( ) and after HCL intervention were small, so that the resulting mean improvement was ~ -1% or less with CIs mostly crossing the null. The NHS Pilot adult study . The CYP Pilot . Only in one other study (Carlson, adult patients) was the change statistically significant at P <0.05.

Several single arm studies reported other outcomes indicative of hypoglycaemic status, most commonly % time in range < 3.0 mmol/L. The results are shown in

Figure 18.

Figure 18. Mean (95% CI) change from baseline in % time in range < 3.0 mmol/L



Changes from baseline were < 1% and with one exception did not reach statistical significance. The large survey study by Breton et al., (T1DM N = 7801) reported medians and IQR of: before HCL 0.01 (IQR (0.00 to 0.35) and after 0.02 (IQR 0.00 to 0.400) with a resulting P value of <0.001. These authors considered this small worsening in hypoglycaemia during HCL likely to be clinically meaningless.

4.2.11 Summary of observational studies

The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range (3.9 to 10 mmol/L), and % time above range >10 mmol/L all improved on transfer to HCL (or to an AHCL) without any strong evidence that hypoglycaemia became more of a problem; however changes in hypoglycaemia were mostly underpowered in these studies; in the largest studies (NHS Pilot audit study in adults and very large survey study by Breton et al.,) there was no persuasive indication of deterioration in hypoglycaemic states.

The NHS Pilot adult audit study [redacted]. Transfer to HCL resulted in [redacted] In the NHS Pilot study, the post HCL levels of measures of glycaemic control [redacted]. The NHS Pilot studies in adults and in CYP [redacted]; however it is unlikely all UK T1DM patients need to transfer to better control systems because many may be achieving good control with their current practice; it appears likely that by recruiting patients [redacted]. Whether discontinuation would increase with time is unknown but from a CE perspective permanent discontinuation represents a wastage of device(s). Discontinuations were reported in some RCTs; in most cases in RCTs the observation time on treatment to short and numbers of participants too small to get a meaningful idea of discontinuation rates in thee studies.

4.2.12 Assumptions

Publication bias was visually assessed using a funnel plot and statistically assessed using Egger's test for each of the outcomes. All four funnel plots were symmetric, suggesting a lack of publication bias, as well as the p-values of Egger's test, all of which were $p>0.05$. Consistency and inconsistency were measured using node-splitting, which compares the Direct and indirect estimates of the network. Loop-consistency was not measured as the Networks for each outcome had no closed loops. Node-splitting concluded that there were no Issues with consistency in the models.

4.2.13 Subgroup and sensitivity analyses

Results of the subgroup and sensitivity analyses (as specified in the protocol) are presented in Table 6.

A subgroup analysis was performed where studies were categorised based on mean or median age of participants at baseline. Mean or median age less than 18 years were classified as "Children and young adults", and studies with mean age greater than or equal to 18 years were classed as "Adults").

The following sensitivity analyses were performed:

Removing the Stewart 2018 study which was done on pregnant women only from the analysis.

Removing the Benhamou 2019 study from the analysis as it was identified as a potential outlier for the outcome "% time in range 3.9 – 10.0 mmol/L" as the difference in arms was around 31, but larger than the remaining studies.

Compared to the overall results, there were no statistically significant changes to the results when removing pregnant participants (excluding Stewart 2018), or when removing the outlying study (Benhamou 2019).

When splitting the study estimates into adults (18+ years) and under 18's. There were no statistically significant subgroups when compared to the overall NMA results. When comparing the subgroups separately, for the outcome TIR % between 3.9-10 mmol/L, HCL was significantly statistically worse compared to CSII+CGM (MD = -2.76, 95% CI = -5.33 to

-0.19) in the under 18's, but not statistically significant in the 18+ group.

Table 6. Results of the subgroup and sensitivity analyses compared to the overall NMA results

	HbA1c %	%TIR 3.9-10	%TIR > 10	%TIR < 3.9	%TIR < 3.0
Overall results					
HCL	-0.28 (-0.34, -0.21)	8.66 (7.33, 9.99)	-7.20 (-8.89, -5.51)	-0.83 (-2.10, 0.43)	-0.14 (-0.40, 0.12)
LGS/PLGS	-0.06 (-0.22, 0.09)	0.44 (-2.36, 3.24)	2.25 (-2.40, 6.90)	-0.39 (-2.87, 2.09)	-0.16 (-0.56, 0.24)
Excluding Stewart 2018 (pregnant participants)					
HCL	NA	8.90 (7.63, 10.17)	-7.81 (-9.33, -6.30)	NA	NA
LGS/PLGS	NA	0.73 (-1.89, 3.34)	1.76 (-2.38, 5.91)	NA	NA
Excluding Benhamou 2019 (outlying study)					
HCL	-0.29 (-0.36, -0.22)	8.58 (7.09, 10.07)	-7.24 (-9.12, -5.36)	-1.04 (-2.71, 0.63)	-0.21 (-0.60, 0.18)
LGS/PLGS	-0.08 (-0.23, 0.80)	0.33 (-2.66, 3.32)	2.17 (-2.70, 7.04)	-0.60 (-3.55, 2.36)	-0.23 (-0.76, 0.31)
Adults (18+)					
HCL	-0.24 (-0.32, -0.15)	9.28 (7.44, 11.13)	-7.28 (-10.06, -4.51)	-0.37 (-0.95, 0.21)	0.00 (-0.10, 0.10)
LGS/PLGS	-0.01 (-0.24, 0.21)	2.85 (-0.88, 6.58)	-0.27 (-9.75, 9.22)	0.09 (-0.80, 0.99)	0.11 (-0.01, 0.23)
Under 18 years old					
HCL	-0.31 (-0.43, -0.20)	7.74 (6.87, 8.62)	-6.97 (-9.31, -4.63)	-1.10 (-3.43, 1.22)	-0.21 (-0.66, 0.24)
LGS/PLGS	-0.11 (-0.36, 0.13)	-2.76 (-5.33, -0.19)	3.33 (-1.95, 8.61)	NR	-0.41 (-1.20, 0.38)

4.2.14 Additional outcomes

4.2.14.1 Adverse events

Studies did not consistently report additional outcomes (see section 10.3 for list of additional outcomes reported in RCTs). In the Benhamou trial, authors observed one severe hypoglycaemia and one ketoacidosis occurring in two different patients during the extension phase. The ketoacidosis occurred while the patient was under closed loop (CL) and presented with an acute infection of the ear, whereas the severe hypoglycaemia occurred while the patient had temporarily switched to Open Loop treatment. In this study several device malfunctions were reported, including 21 events related to the pump (in seven patients), six events related to the sensor (four patients), and four events related to the handset (three patients).[47]

In the Ware study, seven severe hypoglycaemia events were reported in total (four in the closed loop group, three in the comparator group), two diabetic ketoacidosis events (both in the closed-loop group), and two non-treatment-related serious adverse events (broken ankle in the control group and hospital admission for gastroenteritis in the closed-loop group) occurred after randomisation. There were 23 reportable hyperglycaemia events (11 in the closed-loop group, 12 in the control group), which did not meet criteria for diabetic ketoacidosis. A total of 155 adverse events were reported (67 in the closed-loop group, 88 in the control group).[57]

Tauschmann's study reported one diabetic ketoacidosis presenting in the closed-loop group due to infusion set failure which was not related to the closed-loop therapy. There were two severe hypoglycemia in both groups. [53]

Thabit 2015 reported safety outcomes. In this study one episode of severe hypoglycaemia occurred in an adult participant during the intervention period when the closed-loop system was not in use because of loss of connectivity (low battery) and the participant was receiving insulin at the rate supplied by the study insulin pump. In the study involving children and adolescents, one adolescent participant had two severe hypoglycaemic episodes (seizures) during the intervention period; these episodes required third-party assistance but did not result in hospital admission. During the two episodes, the closed

loop system was not in use (the participant was using sensor-augmented pump therapy).[54]

Seven adverse events were reported for seven (6%) of 112 participants during use of the 670G system and six events for six (5%) of 112 participants during use of the advanced hybrid closed-loop system (table 3). Severe hypoglycaemia occurred in one participant while using the advanced hybrid closed-loop system and none while using the 670G system. No cases of diabetic ketoacidosis were reported. Six cases of Hyperglycaemia was reported and that was in relation to infusion-set obstruction, and four cases were observed in the comparator group of adults. In children and adolescents, this was reported for two cases in the intervention group only. [27]

The FLAIR study reported two severe hypoglycemia events in the HCL. There were two hyperglycaemia events related to insulin pump issues (without diabetic ketoacidosis) in the HCL group.

The Boughton's study reported two events of severe hypoglycemia in SAP group. Four participants reported some adverse events in the HCL group and 7 participants in the SAP group.

The Kariyawasam's study reported a mean value of hypoglyceamic episodes 25.51 (5.42 SE) in the closed loop group and 48.19 (5.39 SE) in open loop group.

von dem Berge's study reported the median of Hypoglycaemic events (< 54 mg/dl), four in the intervention group and three in the comparison group.

Collyn's study reported five device related adverse events for each study arm.

Stewart study reported eight hypoglycemic events for the HCL group and 12.5 for the comparator (CGM+CSII) group.

Ware 2022 reported one serious adverse event of severe hypoglycemia that occurred during the

closed loop period.

Overall, the majority of the studies reported a low number of events for both trial groups. There was no clear difference between HCL vs comparator groups. Studies included a samll sample, were hetrogenious which limits a quantative synthesis.

4.2.14.2 Patient-Reported Outcomes and Perspectives

Tauschmann's study used the Pedatric Quality of Life Inventory (PedsQL) questionnaire which was administered to participants (participant version) and guardians of participants aged 17 years and younger (the parent proxy version) before and after the intervention period. The result showed –0·3 (95% CI: –4·1 to 3·4) a difference between groups regarding score of using PedsQL for assessing quality of life.

The FLAIR study, reported mean scores on the glucose monitoring satisfaction survey 2·76 points (SD 0·52) at screening, 2·65 points (0·63) at the end of the period using the HCL system, and 2·80 points (0·55) at the end of the period using the advanced HCL (p=0·0030 comparing HCL vs advanced HCL. The only two satisfaction subscales that changed and showed superiority of AHCL were emotional burden and behavioral burden[70]

Benhamou's study reported improved levels of satisfaction using the Diabetes Treatment Satisfaction Questionnaire score. The satisfaction improved significantly, with a DTSQ total score of 50.0 (Q1-Q3 48.5-53.5) at baseline in open loop, 65.0 (57-66.5) after the initial close loop period, and 60.0 (58.5-63) at the end of the extension period [47]

McAuley's recorded Hypoglycemia Fear Survey score. The total score was 7.5 (4–10) and 7.5 (5–10) for HCL and SAP therapy respectively. Difference between the two groups was not significant.

Wheeler's study compared technology satisfaction and sleep quality between AHCL vs. SAP + PLGM. overall treatment satisfaction was significantly higher for AHCL group compared to SAP+PLGM treated. There was no significant difference for anticipated worry of hypoglycaemia. Results showed no changes in the well-being index and hypoglycaemia fear/confidence were seen.

Several studies that used various tools and different survey approaches for technology satisfaction. Only one study (Benhamou), comparing an open loop to a closed loop system, found that user satisfaction had increased significantly. Other studies did not observe any significant changes.

4.2.1 Quantity and quality of research available

Of the 12 RCTs included in the analysis, seven were rated overall as having some concerns about their risk of bias, and two were rated overall as having a high risk of bias (von dem Berge, Collyns). Table 7 provides a visual summary of each domain. Risk of bias was noted for each domain as follows: high risk of bias was most common in relation to domain 2 (deviations from intended interventions). In this domain, 4/12 RCTs were deemed to be of low risk of bias (Tauschmann, Boughton, McAuley, Stewart); 6/12 had some concerns over risk of bias (Bergenstal, Thabit, Ware, Kariyawasam, von dem Berge, Collyns), and 2/12 RCTs were deemed to be at high risk of bias in this domain (Benhamou, Weinzimer).

In domain 1 (randomisation process), there were some concerns over risk of bias in 6/12 RCTs (Benhamou, Bergenstal, Thabit, Weinzimer, Kariyawasam, von dem Berge, Collyns), either because there was no information available to answer the signalling questions for the domain (Benhamou, Thabit, Weinzimer, von dem Berge); because of a lack of information on the randomisation process (Benhamou, Thabit, Weinzimer, von dem Berge, Collyns); issues with allocation concealment (Benhamou, Tauschmann, Thabit, Ware, Weinzimer, Boughton, von dem Berge, Collyns); or differences in the characteristics of participant groups at baseline (Bergenstal). The RCT by Collyns was deemed to be high risk of bias in relation to the randomisation process. The domains with the lowest risk of bias were in relation to missing outcome data (domain 3) and outcomes measurement (domain 4), where all 12 RCTs were considered to have low risk of bias for both domains.

In domain 5 (selection of the reported results), all but three RCTs were considered to have low risk of bias. Those that had some concerns over risk of bias were the studies by Benhamou, Boughton and von dem Berge).

Table 7. Risk of bias summary

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Benhamou (2021)	Some concern	High	Low	Low	Some concern	Some concern

Bergenstal (2021)	Some concern	Some concern	Low	Low	Low	Some concern
Tauschmann (2018)	Low	Low	Low	Low	Low	Low
Thabit (2015)	Some concern	Some concern	Low	Low	Low	Some concern
Ware (2022)	Low	Some concern	Low	Low	Low	Some concern
Weinzimer (2022)	Some concern	High	Low	Low	Low	Some concern
Boughton (2022)	Low	Low	Low	Low	Some concern	Some concern
Kariyawasam (2022)	Some concern	Some concern	Low	Low	Low	Some concern
McAuley (2022)	Low	Low	Low	Low	Low	Low
von dem Berge (2022)	Some concern	Some concern	Low	Low	Some concern	High
Stewart (2018)	Low	Low	Low	Low	Low	Low
Collyns (2021), Wheeler (2022)	High	Some concern	Low	Low	Low	High

Superseded – see updated external assessment report (15 November 2022)

5 External submissions

5.1 NHSE evidence

NHSE submitted two observational audit studies, the first audit was conducted in adults and the second in children and young people. [redacted]

Additionally, the findings [redacted]

5.1.1 NHS England Hybrid Closed Loop Pilot in Adults with Type 1 Diabetes

The study included adults with T1DM [redacted] Outcomes included in the analysis were [redacted] The primary outcome was [redacted]

Participants had [redacted]. Participants in the pilot study had [redacted] in comparison to the National diabetes audit (Table 8).[71] The National Diabetes Audit shows that 16% of people with T1DM have an HbA1c over 86mmol/mol or 10%.[71] This indicates that the pilot study participants [redacted]

Table 8. Baseline characteristics of the Audit vs. the National Diabetes Audit [71]

Variable	Audit in Adults	National Diabetes Audit*
Age (years)	[redacted]	43.4
Diabetes duration (years)	[redacted]	24.9
Gender (% male)	[redacted]	42
Ethnicity (%)		
White	[redacted]	87.2
Asian	[redacted]	2.1
Black	[redacted]	0.9
Mixed	[redacted]	0.8
Other	[redacted]	1.0
Unknown	[redacted]	8.1
HbA1c (mmol/L)	[redacted]	63.5
HbA1c (%)	[redacted]	8.0
*On insulin pump; **median		

[redacted] There are several points that require consideration:

1. Diabetes distress score measures were [redacted], however EQ-5D data measures were not collected. Therefore, utility measures are challenging to quantify.
2. The level and volume of patient education is not clearly defined. It is unclear if patients received structured education that may have improved glucose measures.
3. Patients enrolled in the study were on CSII therapy which is one of NICE criteria to switch to HCL. However, the length of pump therapy was not clear. NICE recommends the suspension of pump therapy when glycaemic improvements are not achieved.
4. Cost data were not provided.

5.1.2 NHS England Closed Loop Study in Children and Young People

The study recruited [redacted] with T1DM [redacted] (baseline characteristics Table 9). Participants were recruited from [redacted].

[redacted]

Table 9. Baseline characteristics of children and young people

Variable	Value
Age (years), mean (SD)	[redacted]
Diabetes duration (years), mean (SD)	[redacted]
Gender (% male)	[redacted]
Ethnicity (%)	
White	[redacted]

Asian	[redacted]
Black	[redacted]
Mixed	[redacted]
Other	[redacted]
HbA1c (mmol/L)	[redacted]
Time in range (%) 3.9-10mmol/L	[redacted]
Hypoglycaemia frequency (%)	[redacted]

[redacted]. There are several points that require consideration:

1. Pre-HCL treatments (such as pump and CGM) were not clearly described.
2. Extent of severe hypoglycaemia that may affect the Hypoglycaemia Fear Survey was not described.
3. Parental/carer EQ-5D data was not collected.
4. The level and volume of patient education was not clearly defined.
5. Cost data were not provided.

5.1.3 Medtronic submission clinical effectiveness

The Medtronic submission compared the (Advanced) Hybrid Closed Loop Systems with Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). They described a number of studies and edited extracts of their report are included in the box below:

1. Carlson et al.'s study [64] assessed safety and change in glycemia in adolescents and adults with type 1 diabetes (T1D) during the Medtronic Safety Evaluation of the Advanced Hybrid Closed Loop (AHCL) System. Both the run-in period and study phase involved use of the AHCL study device that included the MiniMed 670G insulin pump (version 4.0 algorithm) with CGM system (the Guardian™ Sensor [version 3] glucose sensor and Guardian Link [version 3] transmitter). This 3-month trial with a total 14,134 days of AHCL Auto Basal and Auto Correction use had no device-related SAEs and no serious or unanticipated device-related effects. There were no episodes of severe hypoglycemia or DKA during the Auto Basal and Auto Correction-enabled study phase. Glycemic outcomes of this study demonstrated reduced A1C and increased overall (24-h day) TIR in adolescents and adults using the AHCL system, when compared with a run-in period of SAP, PLGMs or automated basal insulin delivery use.

2.Da Silva et al. 2022,[72] in a report from 4120 users, analysed the safety and outcomes results of the MiniMed™ 780G system, which includes an advanced hybrid closed loop (AHCL) algorithm that provides both automated basal and correction bolus insulin delivery in real-world settings. An improvement was reported over standard of care based on the on-going trial (NCT03959423) which was confirmed by real world evidence: 80% of the first 4120 AHCL users have reached glycaemic targets, i.e., TIR >70% and a GMI <7.0%.

3. Vigereski et al. 2022 [73] analysed safety and effectiveness outcomes of individuals using the MiniMed™ 780G system with the no-calibration Guardian™ 4 sensor during the first three months of use. Data is based on the published poster. There is inadequate data on participant history.

4. The FLAIR study [27] compared the existing MiniMed 670G system with the new Medtronic advanced hybrid closed-loop system in adolescents and young adults with type 1 diabetes in a crossover trial at seven academic-based endocrinology practices (USA, and one each in Germany, Israel, and Slovenia). Both the MiniMed 670G and AHCL systems consisted of the same Medtronic 670G insulin pump and Guardian Sensor 3 continuous glucose monitor, with only the software differing between systems. The AHCL system was found to induce a greater reduction in hyperglycaemia during the day without an increase in hypoglycaemia than did the MiniMed 670G system. Time in the target glucose range increased from 57% to 67% with use of the advanced hybrid closed loop system compared with 57% to 63% with use of the 670G system.

5. For the comparison between AHCL to SAP 1 PLGM in a two-sequence crossover study in New Zealand, 59 participants (35 females), mean age 23.5 years, were recruited. AHCL improved %TIR 3.9–10.0 mmol/L (70–180 mg/dL) compared to SAP. There was one episode of mild diabetic ketoacidosis in the study, which occurred in the SAP 1 PLGM treatment period due to possible infusion set occlusion and a concurrent viral infection. There were no episodes of severe hypoglycaemia in the study.[49]

6. Petrovsky et al.'s study [74] described a structured initiation protocol of the MiniMed 670G HCL system in individuals with type 1 diabetes on MDI. This non-randomized single-centre study was conducted in

Doha, Qatar, and enrolled individuals aged 7–18 years with type 1 diabetes > 1 year, on MDI with SMBG, with or without RT-CGM or isCGM, with no prior pump experience, and with an HbA1c level < 12.5%. An improvement in TIR was observed after 3 days in Auto Mode, TIR continuously improved over time until reaching a plateau after 2 months. The authors reported that the improved clinical outcomes observed in the study were achieved in a safe manner, with no events of DKA, or severe hypoglycemia, and with no hospital admission, similar to the MiniMed 670G ~~pivotal~~ trials.

7. In an abstract Slover's et al [75] evaluated whether the MiniMed™ 780G AHCL system may be effective in adult individuals with T1D naive to CSII and CGM technologies. Report shows people with T1DM naive to CSII and CGM technologies who switched directly to AHCL improved their glycaemic control but there is no further information on participant history and intervention details.

5.1.3.1 Medtronic submission clinical effectiveness: EAG critique

The Carlson's study [64] was undertaken in the US context. The result on the extended study phase has not be published except in an abstract.

Da Silva's study reported data based on an ongoing trial of the MiniMed™ 780G AHCL system and it is the first report of outcomes.[72] There is a lack of demographic data, such as users' duration of diabetes and previous therapies. The results are limited by the follow-up duration of the cohort with a mean of 54 ± 32 days. There is some concern about reliability. The usability can only be inferred from the high percentage of time spent in AHCL and the low number of AHCL exits.

Medtronic suggest that there is consistent effectiveness of the MiniMed™ 780G system in current users (over 20,000 in June 2022), reporting improvements in performance, safety and usability compared to MiniMedTM 670G reducing the burden of people living with T1D. It seems these results are based on the same source as the ongoing trial. The source and history of participants is not clear.

Vigersky et al., 2022 reported safety and effectiveness outcomes following transition of participants to the MiniMedTM 780G system with the GuardianTM 4 sensor (NCT03959423).[73] The results relate to the US population. It is not clear whether they used the GuardianTM 4 System (GuardianTM 4 sensor plus GuardianTM 4 transmitter) or just the GuardianTM 4 sensor. The data is based on a poster presentation, and no more data was available about the patients.

The main issue with Arrieta et al., 2022 it is not clear whether patients with T1DM were on different previous treatments.[76] The only treatment information that was available is the percentage of MiniMedTM 780G system users, for two different age groups of people. Outcomes were analysed for three cohorts of users; cohort 1 (post-AHCL), cohort 2 (longitudinal), cohort 3 (pre- vs. post-AHCL). This study is related to several different countries' populations and results show differences with adults with T1DM in NHS England.

Choudhary et al., 2022 [77] is a retrospective analysis of CareLink™ (Medtronic, Northridge, California) data from people with Type 1 diabetes in the UK and was conducted to determine the real-world effectiveness of sensor-integrated pump therapy with the MiniMed Paradigm Veo or MiniMed 640G systems. Comparisons of SAP vs LGS, SAP vs PLGM, and LGS vs LGM was undertaken. There is not an HCL arm in this study. The initial analysis was based on treatment groups of different sizes and durations of treatment. The reasons for using SAP therapy without any suspension mode activated, and for switching to low glucose suspend, were not available. The analysis was purely descriptive, and no formal statistical comparison has been done.

The FLAIR study,[27] a randomized crossover trial conducted between June 3 and Aug 22, 2019, recruited 113 adolescents and young adults with type 1 diabetes. It was undertaken in the UK. The study period was only 3 months long; thus, it' is not possible to determine the sustainability of observed benefit over a longer period of time.

Collyn's et al.'s study [49] demonstrated a significant improvement in TIR, with no increase in hypoglycaemia for AHCL compared with SAP 1 PLGM during 4-week. The short study period limits the impact sustainability assessment. The age range of included participants is wide and no stratified data has been reported based on the age group.

Petrovski et al.'s study [74] assessed the use of a 10-day structured initiation protocol for MiniMed 670G HCL system in individuals with type 1 diabetes on MDI therapy. It was a single centre study with a small sample size for investigating clinical outcomes of using HCL for patients on MDI with SMBG, with or without RT-CGM or isCGM, with no prior pump experience.

Reported data in Farabi et al.'s study [78] was a systematic evaluation of the relationship between routine, unstructured physical activity, and glucose variations across wake and sleep periods for multiple days in young adults with T1DM in their natural home/work environment. This study is limited by the lack of a control group. The study did not have any exclusion criteria based on patients' history. There are also factors that can affect glucose levels such as structured physical exercise, which have not been considered in this study.

5.1.4 Dexcom submission clinical effectiveness

Dexcom compares HCL with SAP. This is based upon the results of one systematic review and network meta-analysis [79] and eight RCTs.[56, 57, 68, 69, 80-83] The review was based on 52 RCTs, including 3,975 participants, for T1D. Comparators were SAP (rt-CGM + CSII) and intermittently scanned glucose monitoring with CSII (FGM + CSII). The results of the NMA indicated that in terms of HbA1c reduction, there is no significant difference between CGM + CSII with a mean difference (MD) of −0.36 (95% CI: −0.90, 0.19). When simultaneously considering HbA1c and severe hypoglycaemia, integrated systems as well as MDI + CGM, appeared to provide the highest composite ranking in cluster analysis of surface under the cumulative ranking curve (SUCRA) values. Despite finding the most favourable results for HCL, it should be noted that the study authors recommended that "If only one technology is desired or practical, then CGM appears most favourable from composite ranking of A1c, hypoglycaemia, and QoL".[79]

All of the eligible trials included SAP as the main comparator; there were no studies that compared HCL with FGM + CSII. They described a number of studies and edited extracts of their report are included in the box below:

The iDCL Trial Research Group conducted several feasibility and pilot studies of the Control-IQ system and in 2019, Brown and colleagues published results of a 6-month randomised trial of this system.[68] A multicentre (MC) RCT conducted across several centres in the US evaluated a total of 168 patients who were randomly assigned in a 2:1 ratio to either the: Control-IQ system (n=112; HCL group) or control group (n=56; SAP therapy).

Breton and colleagues conducted a 16-week, RCT across four paediatric diabetes centres in the US.[69] A total of 101 patients were randomly assigned in a 3:1 ratio to either the: Control-IQ system (n=78; HCL group) or control group (n=23; SAP therapy). Patients in both groups attended follow-up visits at 2, 8, and 16 weeks.

Kanapka et al. (2021) further evaluated the efficacy and safety of the Control-IQ system in the same cohort of children aged 6-13 years with a 12-week extension phase.[83] A total of 100 patients who completed the 16-week RCT were entered into the extension phase and monitored for a further 12 weeks (a total of 28 weeks follow-up).

Ware et al. (2022) recently published a study with the aim of assessing the efficacy and safety of the Cambridge HCL algorithm in children and adolescents with T1D.[57] This study was a parallel, RCT conducted across seven UK and five US paediatric diabetes centres. A total of 133 patients were randomly assigned in a 1:1 ratio to either the: CamAPS FX system (n=65; HCL group) or control group (n=68; SAP therapy with or without glucose sensor). Patients in both groups attended follow-up visits at 13 and 26 weeks.

Some studies reported results of RCTs across different ski camps. Breton and colleagues' study was a multi-site, parallel, RCT conducted across two ski camps (5-day ski camp; ~5 hours skiing/day) in the US.[84] A total of 32 adolescents were randomised in a 1:1 ratio to either the: UVA AP system (n=16; HCL group) or control group (n=16; RM-SAP therapy. Ekhlaspour et al. conducted the first superiority trial of the Control-IQ system in children and adolescents aged 6-18 years under real-world conditions.[81] The study was a multisite, parallel, RCT conducted across three ski camps (2-day ski-camp; ~5 hours skiing/day) in the US. A total of 48 participants were randomised in a 1:1 ratio to either the: control-IQ system (n=24; HCL group) or control group (n=24; RM-SAP therapy).

Forlenza et al. conducted a 3-day home-use superiority trial in the 24 school children aged 6-12 years that participated in the 48-hours ski camp trial above.[82] The study was a multisite, parallel, RCT conducted during three days of home use at two clinical sites in the US. A total of 24 school children were randomly assigned in a 1:1 ratio to either the: Control-IQ system (n=12; HCL group) or control group (n=12; SAP therapy).

Ware et al.(2022), in a different study, aimed to evaluate the efficacy and safety of longer-term use of the Control-IQ system in young children using a larger sample size compared with previously conducted trials.[56] The study was a MC, cross-over, RCT conducted across diabetes centres in Europe over 16 weeks. A total of 74 children were firstly randomly assigned in a 1:1 ratio to either the: Control-IQ system (n=39; HCL group) or the control group (n=35; SAP therapy). As the trial used a cross-over design, participants

received their assigned initial therapy for 16 weeks and then crossed over to the second trial therapy after a wash out period of 1−4 weeks. Patients in both groups attended a follow-up visits every 4 weeks.

Boughton et al. recently conducted one of the only multinational study of HCL use specifically in older adults.[80] The study adopted a MC, randomised, cross-over (two-period) design across diabetes clinics at three UK centres and one Austrian centre. A total of 37 older adults were firstly randomly assigned in a 1:1 ratio to either the: CamAPS FX system (n= 20; HCL group) or control group (n= 17; SAP therapy). As the trial used a cross-over design, participants received their assigned initial therapy for 16 weeks and then crossed over to the second trial therapy after a wash out period of 4 weeks. Patients in both groups attended a follow-up visits every 4 weeks.

Overall, all studies, except Breton et al. (2020) [69] reported a statistically significant between-group difference in HbA1c (%) reduction in favour of HCL compared with SAP systems. Although statistical significance between systems was not reached in Breton et al.(2020),[69]. Also, all studies reported a statistically significant between-group difference in TIR (70–180 mg/dL) in favour of HCL compared with SAP systems.

The median number of hypoglycaemic events across trial periods was reported in two studies (Brown et al. 2019 and Breton et al. 2020).[68, 69], although statistical significance was not reached between groups. The difference in the median number of hypoglycaemic events per week in the iDCL study (Brown et al. 2019) was approaching statistical significance.[68]

The iDCL trial [68] included a number of PRO measures to assess user experience with diabetes technology and the impact of HCL and SAP system use on QoL. Total Diabetes Distress Scale [DDS] scores were significantly higher (less favourable) in the SAP compared with the HCL group at 3 months (P=0.04) but not at 6 months (P=0.30). Total Hypoglycaemia Fear Survey [HFS-II] scores showed no significant differences between the SAP and HCL group at 3 or 6 months. the HFS subscale scores also did not differ between study groups. However, scores on the two factors of the behaviour subscale (including a “maintain high blood glucose” and “avoidance” factor) were examined and showed lower (more favourable) scores in the HCL group on items, reflecting tendencies to maintain higher blood glucose level in certain situations to avoid hypoglycaemia (mean: 25) compared with the SAP group (mean: 35).

5.1.4.1 Dexcom submission clinical effectiveness: EAG critique

The EAG has some concerns about the results of the existing network meta-analysis.[79] Performance bias is challenging to asses because of impracticability of blinding

participants and clinicians to the devices being compared. Inconsistent reporting of TIR outcome made it impossible to meta-analyse this outcome.

The EAG has not managed to source the result reported in the submission from the iDCL trial because in this study multiple daily insulin injections were used by 35 (21%) patients.[68] The authors reported more unscheduled contacts in the closed loop group, which was attributed to the use of an investigational device, and the insulin pumps used by the control group did not have a feature to suspend insulin for predicted hypoglycaemia, which might have an effect on the amount of continuous glucose monitor–measured hypoglycaemia.

Breton's and Kanapka's study was similar to iDCL, with 21% of patients in the closed loop group and 17% in control group who had used MDI.[83] The amount of hypoglycaemia at baseline was unrepresentatively low in both treatment groups, which, in addition to the fact that most of the patients in the control group used a pump with a predictive low-glucose suspend feature, limited the ability of the trial to assess the effect of the closed-loop system on hypoglycaemia. On the other hand it's not possible to assess the sustainability of the treatment effect over a longer period because the trial period was only 4 months.

The EAG has some concerns about participants' characteristics. They came from a more advantaged socioeconomic background, and had more experience with diabetes technology, which may have a better effect on glycaemic control.

The EAG has some concerns about the monitoring method used because the researchers used remote monitoring that might have improved the glycemia compared to real world control. In addition, they reported an error in the software. Small sample size and the different context of the UK cause some concerns regarding generalisability.[81] There are some concerns about Forlenza et al.'s study.[82] because that study it was possible to achieve better control than could be seen in the real world. This occurred because a high degree of physician oversight was provided to both groups through continuous remote monitoring by a paediatric endocrinologist. This may have biased both the experimental and control groups, thereby limiting generalizability. There is risk of selection bias because subjects had enrolment HbA1c values of <7.5% on average in both groups, which may further limit generalizability.

There are some concerns about the generalisability of Ware et al.'s study on 'Closed-Loop Control in Very Young Children with Type 1 Diabetes'.[56] Highly motivated participants in closed-loop studies, and the crossover design, may limit the generalizability of these findings, because growth and development are rapid in very young children and may have affected trial results. Furthermore, additional exclusion criteria that were unrelated to diabetes applied to participants at sites in Germany, which potentially affected the reported treatment effect.

There are also concerns about the generalisability of Boughton et al.'s study [80] results because they enrolled participants that might not be fully representative of the general population of older adults with type 1 diabetes owing to the requirement for insulin pump therapy and the low baseline HbA1c. There was little ethnic diversity in the study population. The study participants had a relatively high level of educational attainment and might have had a higher level of technological proficiency than an age matched population which might limit generalisability of the results.

5.1.5 CamDiab submission clinical effectiveness

CamDiab presented 10 studies as clinical effectiveness evidence. They described a number of studies and edited extracts of their report are included in the box below:

Boughton et al.'s study [80] tested the hypothesis that use of the Cambridge closed-loop algorithm in older adults with type 1 diabetes is safe and improves glucose control compared with sensor augmented pump (SAP) therapy. The study was a multicentre, multinational, crossover design contrasting 16 weeks of hybrid closed-loop insulin delivery with 16 weeks of sensor augmented pump therapy in 38 participants at three centres in the UK (Cambridge, Manchester, and Birmingham) and one centre in Austria (Graz). The result shows HCL algorithm is safe, and significantly improves glycaemic control compared with sensor-augmented pump therapy, without increasing hypoglycaemia in older adults with type 1 diabetes. The time spent in the target glucose range (3·9–10·0 mmol/L) with closed-loop in this study population was high at 80%, and the 8·6 percentage point additional time in range compared to SAP therapy equates to an additional 2 h each day in target glucose range. Results show improvement in glycaemic control with closed-loop without any increase in hypoglycaemia and in the context of a population with tight glycaemic control at baseline (baseline HbA1c 7·4%; 57 mmol/mol).

Bally et al.'s randomised, crossover study,[85] recruited 31 adults (aged ≥18 years) attending diabetes clinics at Cambridge, UK and Graz, Austria. Participants were randomly assigned to receive either day-and-night closed-loop insulin delivery followed by usual pump therapy with blinded CGM, or vice versa. The results of the study show day-and-night hybrid closed-loop insulin delivery significantly improved overall glucose control while reducing hypoglycaemia progressively by 50–75% at lower glucose thresholds compared with usual insulin pump therapy. The findings of increased time spent in the glucose concentration target range, reduced hypoglycaemia, and decreased glycaemic variability were similarly observed during night-time and daytime periods. These outcomes were achieved without change in total insulin delivery.

Leelarathna et al.'s study [86] adopted a prospective multinational three-center randomized crossover design on seventeen adults with type 1 diabetes on insulin pump therapy over the 7-day home phase and 1-day stay at the clinical research facility.

Stewart et al. conducted a randomized, two-period crossover study in pregnant women with T1D to evaluate the safety, efficacy, and longer-term feasibility of day-and-night closed-loop insulin delivery versus SAP therapy.[52] Participants were randomly assigned to either 4 weeks of closed-loop (intervention) insulin delivery or 4 weeks of real-time CGM and CSII without the closed-loop system (SAP control) with a 1- to 2- week washout period before crossed to the alternate phase. No difference was found in the primary outcome of percentage of time in the target glucose range (63–140 mg/dL) during closed-loop and SAP therapy (62.3 vs. 60.1%, absolute difference 2.1% [95% CI 24.1 to 8.3]; P = 0.47). No episodes of severe hypoglycemia occurred. The mean (SD) HbA1c was 6.6% (2.8) (48.5 mmol/mol [7.5]), 6.4% (2.7) (46.3 mmol/mol [5.6]), and 6.3% (2.7) (45.9 mmol/mol [5.5]) at baseline, end of closed-loop, and end of SAP therapy, respectively.

Three studies by Tauschmann et al.'s reported results of a day-and-night closed-loop home trial in adolescents with type 1 diabetes under free-living conditions.[53, 87] One study is a randomized, two-period crossover design comparing automated closed-loop insulin delivery with sensor-augmented pump therapy over two 21-day periods in 12 subjects from paediatric diabetes clinics in UK.[87] Results show no serious adverse events or severe hypoglycemic episodes were observed during either study period. The proportion of time that sensor glucose was in the target glucose range of 3.9 to 10.0 mmol/L (primary end point), was increased during closed loop delivery compared with control period (P , 0.001). The mean glucose level was significantly lower with closed loop use (P = 0.001) as was the time spent above the target glucose range (P , 0.001).

The study extended findings from previous home trials in children and adolescents which were limited by a shorter intervention period. One of the previous trials was a prospective, single-centre, randomized crossover design contrasting automated closed-loop insulin delivery and sensor augmented pump therapy over 7 day.[88] Results show the proportion of time that the sensor glucose level was in the target glucose

range of 3.9– 10.0 mmol/L, significantly increased during closed-loop (P , 0.001). Closed-loop insulin delivery significantly reduced the mean glucose level (P = 0.028) and the time spent above target glucose level (P = 0.005) without increasing the time spent in hypoglycemia. No serious adverse events or severe hypoglycemic episodes were observed during either study period.

The Tauschmann's study published in 2018 was a randomised, parallel design in multiple centres,[53] from the UK and the USA for comparing day-and-night hybrid closed-loop (closed-loop group) or sensor-augmented pump therapy (control group) during free living over 12 weeks. The study reported a 10·8 percentage point increase in time with glucose concentrations within the target glucose range across all age groups. This improvement resulted from a reduction of time spent in hyperglycaemia without change in total insulin delivery. The researchers observed a lower amount of bolus insulin and a higher amount of basal insulin in the closed-loop group than in the control group. Post randomisation, no severe hypoglycaemia occurred in either study group.

Ware and colleagues (2022) [56] evaluated the efficacy and safety of longer-term use of the Control-IQ system in young children in an OL, MC, cross-over, RCT conducted across diabetes centres in Europe over 16 weeks. A total of 74 children were firstly randomly assigned in a 1:1 ratio to either the: Control-IQ system (n=39; HCL group) or the control group (n=35; SAP therapy). As the trial used a cross-over design, participants received their assigned initial therapy for 16 weeks and then crossed over to the second trial therapy after a wash out period of 1−4 weeks. Patients in both groups attended a follow-up visits every 4 weeks. The primary outcome was the between treatment difference in the % TIR of 70−180 mg/dL.

In a separate study, Ware et al. (2022) [57] adopted an open-label, multicentre, multinational, one-period, randomised design comparing hybrid closed-loop insulin delivery with insulin pump therapy, with and without glucose sensor, over 6 months. Participants were recruited from diabetes outpatient clinics at seven UK and five US paediatric diabetes centres. 133 eligible participants were randomly assigned to treatment (65 to the closed-loop group and 68 to the control group). Study reported a difference in efficacy between the two closed-loop system hardware configurations using the same algorithm, with an 11 ·5 mmol/mol (1 ·05%) reduction in HbA 1c in the CamAPS FX cohort compared with the control, and no reduction in HbA 1c in the FlorenceM cohort. No treatment effect in the cohort using the FlorenceM hardware was observed, contrasting with a treatment effect observed in the CamAPS FX cohort which used more reliable components and a factory-calibrated glucose sensor.

5.1.5.1 CamDiab submission clinical effectiveness: EAG critique

For Boughton et al.'s study [80] there are some concerns about generalisability of the results to the wider population of older adults with type 1 diabetes because there was little ethnic diversity in the study population. In the supplementary material, it is mentioned that the

study participants had a relatively high level of educational attainment and might have had a higher level of technological proficiency than an age matched population which might limit generalisability of the result.

For Bally et al.'s study [85] there may be some concerns around the duration of the study (for 4 weeks, in the order assigned at randomisation, with a 2–4 week washout period in between). This might have been insufficient to assess long-term compliance. Some exclusion criteria, such as participants with hypoglycaemia unawareness, have restricted assessment of the closed-loop system to those who might benefit greatly. The heterogeneity of sensor use in the control period might have confounded the reported glycaemic outcomes.

Leelarathna et al.'s study results are based on the a small sample size and a relatively short study duration.[86] In this study, the system used was an early generation closed-loop system (which was not a commercially available product). Some failures were observed using closed loop during the home phase because of unavailability of CGM data, a non-operational laptop, and unreliable Bluetooth communication between pump and the computer. All of these limitations could have affected the results.

Stewart et al.'s study included pregnant participants who had had intensive insulin treatment (either MDI or CSII), with equal numbers of pump and MDI users.[52] There are some concerns about duration of study (the short 4-week duration may have been insufficient for optimal closed loop training, particularly for device-naïve participants and those with less-advanced self-management skills). It was the prototype version of the closed-loop system, which had frequent errors, and reduced the time that closed-loop was operational.

One of Tauschmann et al.'s 2016 studies included a small sample size and the need to carry multiple devices during the closed-loop intervention, in addition to the study duration cause concerns about the finding.[87] Another study by Tauschmann et al. cause the same concerns, and also mention that the intervention was a prototype version of a closed-loop system and there was some restriction in use of this system during strenuous exercise.[88]

The main concerns about Tauschmann et al. 2018 [53] were the number of devices comprising a hybrid closed-loop system, which increased the risk of device and connectivity problems.

This issue resulted in more frequent non-protocol contacts to address technical issues. Another concerns is about systematic exclusion of participants with HbA1c outside the range of 7·5–10·0% and other groups, such as those with an impaired awareness of hypoglycaemia or a history of recurrent severe hypoglycaemia.

Ware et al. 2022 (Cambridge hybrid closed-loop algorithm in children and adolescents with type 1 diabetes) [57] used two different glucose sensors in the two closed-loop hardware configurations, although both have been shown to be similarly accurate in the hypoglycaemic range (glucose <3·9 mmol/L), it needs to be considered for interpreting the results. A prespecified analysis has been done to compare the entire closed-loop group with the control group, rather than each closed-loop system separately; the findings should be interpreted with caution.

The EAG's main concerns about the other Ware et al. 2022 study (Closed-Loop Control in Very Young Children with Type 1 Diabetes) is the generalisability of data.[56] Insulin-pump use was a prerequisite for trial participation and sensor use at enrolment was higher than average. Glycated haemoglobin level of less than 11.0% (97 mmol per mole) was required for trial participation, which potentially limited access to enrolment. Also, children from ethnic minorities were underrepresented. Investigators were free to adjust insulin therapy according to clinical judgment before randomization, which may have affected baseline characteristics. Research participants in closed-loop studies tend to be highly motivated, which may also limit generalizability. A crossover design was used, but because growth and development are rapid in very young children, this may have affected trial results. Additional exclusion criteria that were unrelated to diabetes applied to participants at sites in Germany, which potentially affected the reported treatment effect.

5.1.6 Tandem submission clinical effectiveness

Tandem presented three recent pieces as clinical effectiveness evidence in their submission. They described a number of studies and edited extracts of their report are included in the box below:

[redacted]

[redacted]

[1] GMI = 3.31 + 0.02392 × [mean glucose in mg/dL]. The average glucose is calculated over the entire time a customer used a Tandem pump in accordance with the guidelines above.

5.1.6.1 Tandem submission clinical effectiveness: EAG critique

[redacted]

5.1.7 Assessment of effectiveness

5.1.7.1 Summary of information

The clinical evidence identified 12 randomised controlled trials that compared HCL to CSII+CGM or SAP therapy.

Studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining MD between intervention and comparators. Studies did not consistently describe comparators. Cross-over studies did not provide data at different cross-over time points.

Overall, the HCL arm of RCTs achieved improvement in HbA1c %, time in in range (3.9 to 10 mmol/L), and hyperglycaemic levels. Comparator arms also showed improvements but this was less than that observed in the HCL arm. Irrespective of type of intervention used in the comparator arms, these outcomes were statistically superior in the HCL arm vs. control arm. Available evidence from the RCTs suggests that these gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration.

The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range, and % time above range all improved on transfer to HCL (or to AHCL) without any strong evidence that hypoglycaemia became more of a problem; however changes in hypoglycaemia were mostly underpowered in these studies; in the [redacted] and survey study by Breton et al.,) there was no persuasive indication of deterioration in hypoglycaemic states.

The inclusion of RCTs was based on the presence of a relevant comparator arm, the inclusion of at least 90% HCL recipients in the intervention arm, and the reporting of outcome measures applicable to NMA. The aim of the RCTs was generally to demonstrate improvement of glycaemic control with use of HCL. The study by Stewart of pregnant women included only 16 participants followed for 4 weeks; the population, study design and outcomes in this study were clearly different from other studies so that transitivity in NMA including Stewart is threatened.

There were relatively few studies, they were of small size encompassing a total of ~450 HCL recipients followed for between 4 and 26 weeks accumulating approximately 110 person years of observation. Inclusion criteria applied for the studies were relatively narrow and most participants had reasonably good glycaemic control at entry, as indicated in most of those studies reporting baseline TIR (3.9 to 10 mmol/L) at greater than 50% (range 47% to 62%), and baseline HbA1c at between 7% and 8%. There was considerable heterogeneity across studies regarding the age of participants, some studies presented results stratified by age groups. The relevance of the RCT populations and outcome measure results for the decision problem is debatable and not easy to judge.

The quality of studies assessed according to Cochrane criteria (Table 7) was associated with some concern.

In the HCL arm of RCTs the intervention achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10 mmol/L, and in hyperglycaemic levels. Control arms also showed improvement but this was less than that seen with HCL. Irrespective of type of intervention used in the control arms these outcomes were statistically superior in the HCL arm vs. control arm. Available evidence from the RCTs suggests that these gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration. The NHS adult Pilot study [redacted]

[redacted]. In the NHS Pilot study [redacted]

5.1.7.2 Discussion

The evidence on closed loop systems has been based largely informed by short duration studies, small number of participants and some uncertainty of the methodological quality of included studies. Closed loop systems have been previously reviewed and showed effectiveness in in treating patients with type 1 diabetes [2]. In this review, the HCL arm of RCTs achieved improvement in HbA1c %, time in in range (3.9 to 10 mmol/L), and hyperglycaemic levels. Comparator arms also showed improvements but this was less than that observed in the HCL arm. Irrespective of type of intervention used in the comparator arms, these outcomes were statistically superior in the HCL arm vs. comparator arm. In the NHS Pilot study, [redacted]. The 2022 Scottish Health Technologies Group (SHTG) [25] found significant improvements in mean percentage time in range for people with type 1 diabetes using a closed loop system compared to other insulin-based therapy. We found similar trends to the SHGT work. However, it should be noted that the scope of the SHGT group differs from this work. Our NMA synthesis demonstrated a significant decrease in TIR (% above 10.0 mmol/L), increase in % TIR (between 3.9 – 10.0

[2] Bekiari, E., Kitsios, K., Thabit, H., Tauschmann, M., Athanasiadou, E., Karagiannis, T., Haidich, A.B., Hovorka, R. and Tsapas, A.,2018. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. *bmj*, *361*.

mmol/L), and a decrease in HbA1c % showing superiority of HCL in comparison to other treatments.

Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families. People seem to report a better quality of life, diabetes burden and quality of sleep and less anxiety with technologies[3]. The study by Wheeler showed no significant improvements in the anticipated worry of hypoglycaemia in children, parents and adults. Studies included in this review used various tools to assess technology satisfaction. Only one study (Benhamou), that compared an open loop and closed loop system, found that user satisfaction had increased. In the other studies, the difference between the HCL group and comparator was not statistically significance. RCTs included in this review reported a low number of adverse events for both treatment groups. Although some reports of hypoglyceamia were identfied in the included studies, we did not identfify any clear trends and differences between HCL vs comparator. It is worth noting that the studies included in this review are of short duration. The REPOSE study assessed the relative effetivenss of CSII therapy in comparison to MDI over 24 months. Adverse events (such as DKA) were higher at the initiation of therpay and reduced over time. Therefore, it is important to assess the long term adverse events to allow for an adjustment period in people with type 1 diabetes.

6 Systematic review of existing cost-effectiveness evidence

6.1 Methods for assessing cost effectiveness evidence: Key questions

What is the cost effectiveness of hybrid closed loop systems (HCL) for managing glucose in people who have type 1 diabetes mellitus (T1DM), and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-

[3] Boughton, C.K. and Hovorka, R., 2021. New closed-loop insulin systems. *Diabetologia*, *64*(5), pp.1007-1015.

monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

Other questions:

1. What is the cost effectiveness of hybrid closed loop systems for managing glucose in pregnant women who have T1DM?

2. What is the cost effectiveness of hybrid closed loop systems for managing glucose in children who have T1DM and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

3. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, an extreme fear of hypoglycaemia, and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

4. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, with diabetes related comorbidities that are at risk of deterioration, and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

6.2 Systematic review of existing cost-effectiveness evidence

As per protocol, a systematic review of existing cost-effectiveness evidence surrounding HCL was commenced using the following methods.

6.2.1 Study identification

A comprehensive search of the literature for published economic evaluations was performed in a range of relevant bibliographic databases in April 2021, and updated in April 2022. The database searches were developed using search strings applied in the previous technology assessment on integrated sensor-augmented pump therapy systems

(DG21)[35] as the basis for selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections, and other systematic reviews for lines relating to pregnancy.[36-38] The search was informed by the strategy developed for the clinical effectiveness review (see section 4.1.2) and established economic terms based on the CRD NHS EED filter.[92] A date limit in 2014 was applied for each database, based on the search dates for DG21.[35] The search was limited to English language to reflect the inclusion criteria. Full details of the search strategies are provided in Appendix 1 (see section 10.1).

The following databases were searched, from 2014: MEDLINE ALL (via Ovid); Embase (Ovid); EconLit (EBSCO); HTA database (CRD); International HTA database (INAHTA); EconPapers (RePEc); AHRQ website; CADTH website; SBU website; Cost-Effectiveness Analysis (CEA) registry; and School of Health and Related Research Health Utilities Database (ScHARRHUD).

The reference lists of included studies and results of the clinical effectiveness search were also checked.

Records were exported to EndNote X9, where duplicates were systematically identified and removed.

An additional, scoping search for hypoglycaemia and health-related quality of life (HRQoL) in MEDLINE ALL (via Ovid) was conducted from 1st January 2020 to 10th June 2022 for studies on hypoglycaemia and quality of life in people with diabetes. The search was limited to 2020 onwards because searches for a recent economic report for NG17,[93] were undertaken in May 2020.[94] The targeted search included terms for hypoglycaemia and HRQoL, and used a recognised search filter (Arber 2017 FSF1 - sensitivity maximising health utilities search filter [95]). The full search strategy is provided in Appendix 1: Record of searches – Cost effectiveness (see section 10.1.2).

Additionally, the Hypo RESOLVE website was checked.[96]

Potentially relevant literature identified during the systematic review of economic evaluations and sent by topic experts was also examined for relevance.

127 records were retrieved and sifted by the health economists.

6.2.1.1 Inclusion and exclusion of relevant studies

Studies that satisfied the following criteria were included in the review:

Population:

People who have T1DM who are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections.ab

T1DM subpopulations included within:

- Pregnant women and those planning pregnancies (excluding gestational diabetes).
- Children (5 years and under, 6 – 11 years, 12 - 19 years).
- People with extreme fear of hypoglycaemia.
- People with diabetes related complications that are at risk of deterioration.

For the purpose of this review, difficulty refers to not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below, not maintaining at least 70% time in range of 3.9 -10 mmol/l, or repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life.

Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.

Intervention:

Hybrid closed loop systems

Comparators:

- Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated).
- Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.

For women with type 1 diabetes who are pregnant/planning pregnancy comparators also included:

- Real time continuous glucose monitoring with multiple daily insulin injections.
- Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections.
- Self-blood glucose monitoring with continuous subcutaneous insulin infusion.

Outcome measures:

- Cost and cost-effectiveness outcomes (costs for each treatment technology, direct medical care costs, incremental cost-effectiveness ratios (ICER) e.g. cost per quality-adjusted life year (QALY) gained).

Study design:

- Studies comprising an economic evaluation (cost analysis, cost-consequence analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis), and any model-based economic evaluation involving direct comparison between HCL and non-integrated CGM and CSII therapy in T1DM.

Other inclusion criteria:

- Full text reports published in English Language
- Abstracts (only if they are companion publications to full text included studies or contain extractable numerical data)

Papers that fulfilled the following criteria were excluded:

Studies evaluating automated insulin delivery systems which only suspend insulin delivery when glucose levels are low/ are predicted to get low.

Non-human studies, letters editorials and communications, and articles not available in the English language.

Methods

The searches were developed and run by our information specialists (Anna Brown and Rachel Court). Sifting was undertaken by 2 reviewers. Mary Jordan lead the review sifting abstract and titles of all identified studies while Felix Achana and Lena Al-Khudairy acted jointly as second reviewer. Results between 1st and respective 2nd reviewer were then compared and anomalies resolved through discussion or where this

was not possible by recourse to the full team of reviewers. Full text of the result of the first sift were obtained and screened using the same process.

Data extraction and quality assessment

As per the protocol, it was intended that information was extracted by one reviewer (MJ) using a pre-piloted data extraction form for full economic evaluation studies, and reporting quality of studies included in the systematic review would be assessed against the Consolidated Health Economic Reporting Standards (CHEERS)[97] and the Philips' checklist,[98] respectively. Where search results rendered this process unnecessary, quality appraisal was undertaken narratively guided by the criteria detailed in these checklists.[97, 98]

Data synthesis

Narrative synthesis of findings and assessment of study quality is presented, with recommendations for future economic models discussed.

Results

The literature search identified 745 records through electronic database searches and other sources. After removing duplicates, 516 records were screened for inclusion. On the basis of title and abstract, 497 records were excluded. The remaining 19 records were included for full-text screening. A further 13 articles were excluded at the full-text stage mainly due to incorrect intervention/comparator,[99-103] incorrect study design,[104] abstract/poster presentation only,[105-107] or further duplication identified.[108-110]

The literature search (Figure 19) identified six studies which were included in the review.[25, 111-115]

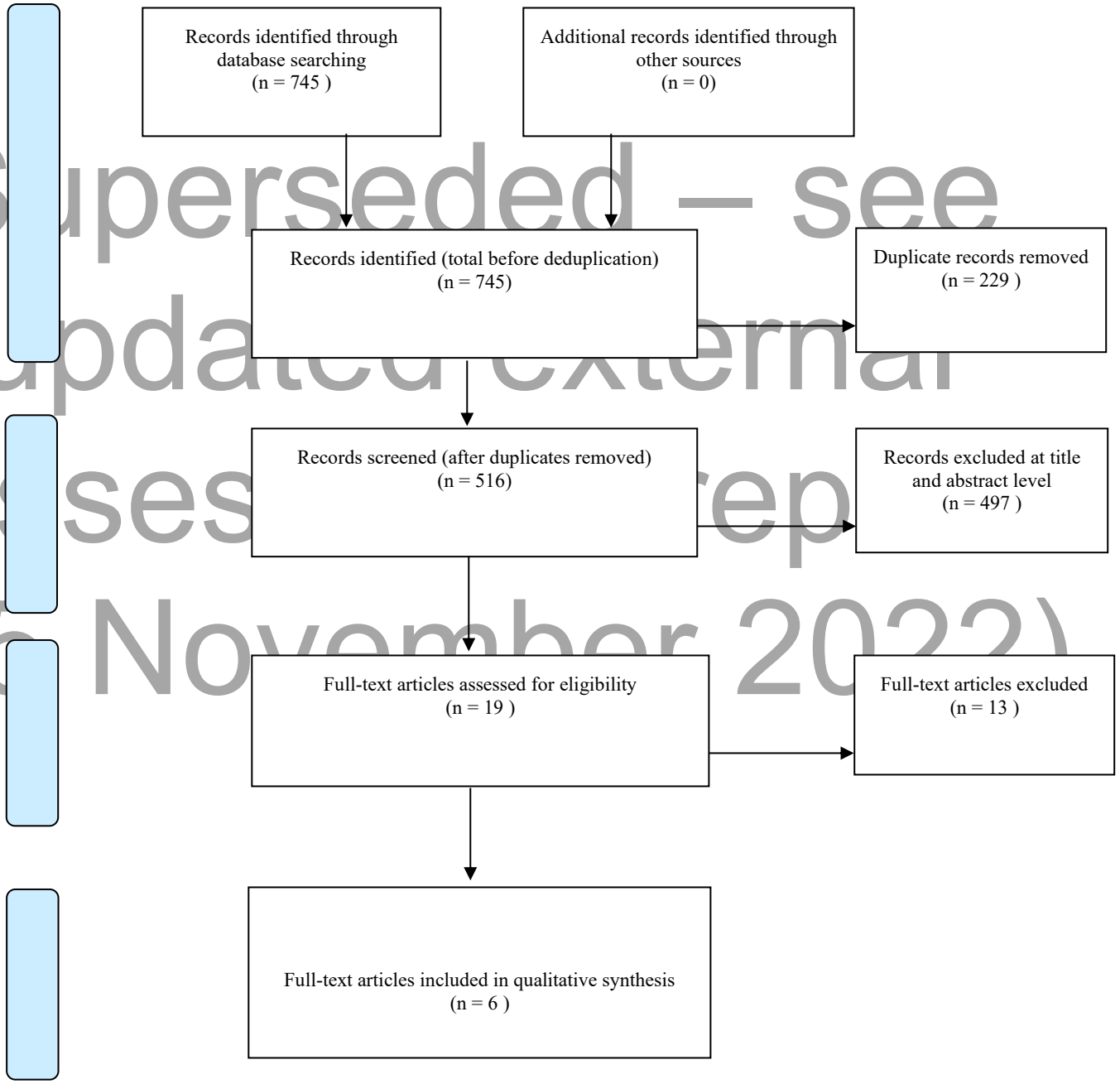


Figure 19. Search strategy flow diagram

6.2.1.2 Summary of the economic analyses undertaken

In this section, we summarise the economic analyses retained and discuss the approach taken and relevance in assessing HCL compared with CGM/FGM and CSII in adults with type 1 diabetes.

The first four studies use the IQVIA CORE Diabetes Model (CDM) to conduct their economic evaluations, whereas the study in the SHTG report [25] uses the Sheffield type 1 diabetes model. Both the IQVIA CORE Diabetes Model and the Sheffield type 1 diabetes model are validated models that employ Monte Carlo methods to estimate the cost effectiveness of diabetes related technologies including HCL systems. The study presented in the CADTH report [111] is a budget impact analysis and was conducted using a customized Microsoft Excel tool.

Jendle et al., 2019 [112]

Jendle et al., 2019[112] used the CDM to assess the cost effectiveness of the MiniMed™ 670G HCL system versus CSII in people with T1DM in Sweden.

Baseline cohort characteristics, and both treatment effect on HbA1c and rate of SHEs for the HCL system, were taken from a single arm before/after clinical study.[116, 117] Other clinical inputs were either assumed or derived from the literature and costs obtained from a variety of published sources.

All costs included in the model were reported in 2018 Swedish krona (SEK). The analysis was conducted from a Swedish societal perspective, over a lifetime horizon, with future clinical and economic costs discounted at a rate of 3% per annum. A human capital approach to costing lost productivity was used. Results were presented in terms of an incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life year (QALY) gained. Authors undertook scenario analyses around the costs of HCL, costs of comparator, rate of SHEs, impact of fear of hypoglycaemia (FoH) and cost effectiveness in poorly controlled patients (HbA1c ≥7.5%).

The base-case deterministic results showed that the MiniMed 670G HCL system when compared with CSII had an ICER of SEK 164,236 (1 SEK = £0.082) per QALY gained. This resulted from an increase of 1.90 QALYs but higher overall costs despite lower cumulative incidence of diabetes-related complications and reduced productivity losses.

The results of the scenario analyses showed that the ICER was most sensitive to assumptions relating to the impact of FoH on quality of life, treatment comparator costs, and reductions in SHE rates.

While the study added to the literature on the cost effectiveness of HCL systems by conducting a cost effectiveness analysis of the MiniMed 670G system in Sweden, the authors acknowledged and discussed the limitations associated with the analysis.

Roze et al., 2021 [114]

Roze et al., 2021[114] used the CDM to assess the cost effectiveness of the MiniMed™ 670G HCL system versus CSII in people with T1DM in the UK.

Baseline cohort characteristics, and both treatment effect on HbA1c and rate of SHEs for the HCL system, were taken from a single arm before/after clinical study.[116, 117] Other clinical inputs were either assumed or derived from the literature and costs obtained from a variety of published sources.

All costs included in the model were reported in 2018 British pound sterling (GBP). The analysis was conducted from a UK health care system perspective, over a lifetime horizon, with future clinical and economic costs discounted at a rate of 3.5% per annum. Results were presented in terms of an ICER expressed as cost per QALY gained.

Base-case deterministic results showed use of the MiniMed™ 670G HCL system led to an increase of 1.73 QALYs compared to CSII, with higher total lifetime direct costs of GBP 35,425. This resulted in an ICER of GBP 20,421 per QALY gained.

Sensitivity analyses showed sensitivity of the ICER to assumptions surrounding glycemic control and quality of life benefits associated with reduction in FoH.

Authors ultimately concluded that in the UK, over patient lifetimes, use of the MiniMed™ 670G HCL system is likely to be cost-effective relative to the continued use of CSII in people with T1D, particularly those with fear of hypoglycemia and poor glycaemic control at baseline. The main contribution to knowledge was that unlike the previous analysis of the MiniMed 670G in Sweden [112] that considered a societal perspective, Roze et al., 2021 adopted a UK health care system perspective.

Serne et al., 2022 [115]

Serne et al., 2022[115] used the CDM to determine the cost effectiveness of the MiniMed™ 670G HCL system versus IS-CGM with MDI or CSII in people with T1DM. The study extended the evidence base on the cost effectiveness of the MiniMed 670G HCL system by conducting a study in Netherlands.

Baseline cohort characteristics, and treatment effect data for the IS-CGM with MDI/CSII, were taken from a prospective observational real-world cohort study (FUTURE) in Belgium.[118] Treatment effect for the HCL cohort was sourced from a retrospective analysis of patients transitioning from SAP to the MiniMed 670G in the US.[119]

A societal perspective was taken for the analysis, over a lifetime time horizon, with future costs specific to the Netherlands discounted at 4% and clinical outcomes at 1.5% per annum. All direct and indirect costs included were reported in 2020 Euros, with a human capital approach taken to calculate cost of lost productivity.

Use of the MiniMed 670G HCL system increased mean QALYs by 2.231 versus IS-CGM in the deterministic base-case. Total mean lifetime costs were also higher in the HCL cohort, at EUR 13,683, resulting in an ICER of EUR 6133 per QALY gained.

Sensitivity analyses highlighted ICER results were sensitive to assumptions around SHE rates and the quality of life benefit associated with reduced FoH.

Some discussion of the limitations of data sources for this economic analysis was provided by authors. They concluded that use of the MiniMed 670G system is likely to be cost-effective relative to IS-CGM plus MDI or CSII for adults with long-standing T1DM based in the Netherlands.

Jendle 2021 [113]

Jendle 2021 [113] use the CDM (version 9.0) to evaluate the long-term cost-effectiveness of the MiniMed 780G advanced hybrid closed-loop (AHCL) system against isCGM plus MDI CSII in people with T1D in Sweden.

Baseline characteristics and treatment effect data for the IS-CGM with MDI/CSII cohort were taken from a the FUTURE clinical trial in Belgium,[118] with an assumed treatment effect applied for the HCL cohort based on Collyns et al., 2021.

The cost effectiveness analysis was conducted from a societal perspective projected over patients' lifetimes with results presented in Swedish Kroner (SEK), although no cost year was explicitly stated. Future clinical and cost benefits were discounted at 3.0% per annum and results presented in terms of an ICER expressed as cost per QALY gained.

Use of the MiniMed 780G system was associated with an improvement of 1.95 QALYs versus isCGM plus MDI or CSII. Clinical benefits accrued due to reduced incidence and delayed time to onset of diabetes-related complications. Total costs were estimated to be SEK 727,408 producing an ICER of SEK 373,700 per QALY gained.

Jendle et al. (2021) contributed to the literature by showing that the MiniMed 780G system is expected to be cost-effective versus isCGM plus MDI or CSII for the treatment of T1D in Sweden, at a willingness to pay threshold of SEK 500,000 per QALY gained.

SHTG (2022) [25]

The study in the 2022 Scottish Health Technologies Group (SHTG) report used the Sheffield type 1 diabetes model to examine the clinical and cost effectiveness of closed loop systems and the artificial pancreas for the management of type 1 diabetes. In particular, the study compared closed loop systems with five comparator interventions i.e. SMBG + MDI, CGM + MDI, isCGM + MDI, CSII+MDI and CSII + CGM.

The baseline characteristics and treatment effects for the simulation cohort were obtained from a 2017 Scottish type 1 diabetes cohort study and a network meta-analysis (NMA) of the published literature. The cohort study was a nationally representative sample of individuals living with type 1 diabetes in Scotland.

The analysis adopted a healthcare payer perspective with patients' lifetimes as the time horizon. The indirect costs associated with lost work productivity due to diabetes morbidity were not included and all the other costs were expressed in GBP. The costs and

utilities were discounted at 3.5% p.a. following the NICE methods of technology appraisal guidance.

The base case results showed that the ICERs of closed loop systems vs SMBG+MDI, CGM+MDI and isCGM + MDI were £44,920, £58,996 and £79,664 per QALY gained respectively. In all these pairwise comparisons, closed loop systems had the highest costs and QALYs compared with the comparators. It was, however, also noted that closed loop systems had lower costs and higher QALYs than CSII + MDI and were thus cost effective in this group. The deterministic sensitivity analyses showed that the findings were sensitive to changes in the assumed effects on hypoglycaemia and the per event disutility value associated with non-severe hypoglycaemic events, whereas the results of the probability sensitivity analysis were very similar to the base case results.

The main limitation of the study was that it relied on an algorithm to convert improvements in percentage time in range to measures of reduction in HbA1c which potentially resulted in inaccurate estimates. Nevertheless, the fact that the study used a nationally representative simulation cohort for Scotland meant that the findings were generalisable to the population unlike the results of the other identified economic studies that used baseline data for different countries. Furthermore, unlike the previous analyses in the literature that considered either the MiniMed 670G or the MiniMed 780G compared with isCGM+CSII or CSII alone, the study provided a more comprehensive analysis of closed loop systems in general compared with multiple configurations of the comparator technologies.

CADTH 2021 [111]

The study in the 2021 Canadian Agency for Drugs and Technology in Health (CADTH) report had three objectives. First, it extended the evidence base by estimated the financial impact of introducing HCL systems for individuals with type 1 diabetes using a budget impact analysis. Second, it assessed the perspectives, experiences and expectations of individuals living with type 1 diabetes as well as their carers. Third, it assessed the ethical aspects associated with the use of HCL systems.

The analysis was conducted from the perspective of the Canadian publicly funded healthcare system with a time horizon of 3 years. The base case results of the budget impact analysis showed that an additional $823 million would be needed to reimburse HCL systems for the eligible population. In particular, an additional $131 million would be needed in year 1, an additional $271 million in year 2 and an additional $421 million in year 3. The scenario analyses showed that the results were sensitive to changes in the population of eligible individuals. In particular, increasing the HCL coverage levels to 100% translated to an increase of $916 million needed to finance the provision of HCL systems. The results were also sensitive to changes in the price of CGM and the uptake of HCL systems among the users of MDI.

The main limitation of the analysis was that the epidemiological measures used to inform the budget impact analysis i.e. the prevalence of type 1 diabetes, the annual incidence of type 1 diabetes and the population growth rate were proximate measures derived from the literature and may thus not have been accurate. These measures were obtained from a 2014 report but the cost estimates for the base case were for 2020. The study also made several assumptions on the coverage levels of insulin-pump use, glucometers, CGM and SMBG test strips which had an impact on the accuracy of the results.

6.2.1.3 Characteristics of retained studies

The characteristics of the six retained studies are summarised in following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Five of these studies were economic evaluations of hybrid closed loop systems, whereas one was a budget impact analysis that aimed at estimating the financial impact of reimbursing HCL systems for individuals with type 1 diabetes. The economic evaluation studies compared the cost effectiveness of hybrid closed loop systems with various diabetes management technologies such as isCGM+MDI, CSII and SMBG among others. Four studies used the IQVIA CORE Diabetes Model to conduct their analyses (Jendle et al., 2019;[112] Jendle et al., 2021;[113] Roze et al., 2021;[114] Serne et al., 2022 [115]), while the study in the SHTG report [25] used the Sheffield type 1 diabetes model. Of the six studies, two

were conducted in Sweden (Jendle et al., 2021; Jendle et al., 2019) and one each in the UK (Roze et al., 2021), Netherlands (Serne et al., 2022), Scotland (SHTG, 2022 [25]) and Canada (CADTH, 2021).

The studies modelled their outcomes over patients' lifetimes and reported their outcomes as cost per QALY gained except from Roze et al., 2021 and the study in the CADTH report that considered a healthcare payer perspective.[111] All the studies discounted their costs and outcomes in line with their national guidelines. An interesting point to note, however, is that there was substantial heterogeneity in the choice of baseline cohort data as well as the data for the treatment effects. For instance, Serne et al., 2022 used different data sources for both the treatment effects and the simulation cohort. Moreover, the data was not for Netherlands. Similarly, the studies by Roze et al., 2021 and Jendle et al., 2019 used a baseline simulation cohort comprising individuals from the USA yet the studies aimed at informing long-term cost effectiveness for the UK and Swedish populations respectively. Jendle et al., 2021 despite being conducted in Sweden used simulation cohort data sourced from a Belgium study. It is only the Study in the SHTG report [25] that used baseline data for its population of interest.

In order to characterise uncertainty in the base case results, all the included studies performed several one-way sensitivity/scenario analyses. The studies that employed the IQVIA CORE Diabetes Model and the study in the SHTG report that used the Sheffield type 1 diabetes model further conducted probabilistic sensitivity analyses and presented the results in the form of cost effectiveness acceptability curves (CEAC). An interesting point to note is that the base case results were found to be very sensitive to the severe hypoglycaemic rates (SHE) and changes in the assumptions relating to the quality-of-life benefit associated with reduced fear of hypoglycaemia (FOH) in four out of the five cost effectiveness studies.[25, 113-115] Furthermore, the CEAC showed that HCL systems are expected to be cost effective compared with the comparator technologies at various hypothetical willingness-to-pay thresholds.

6.2.1.4 Quality assessment of the modelling methods and economic analyses

Structure

The budget impact analysis contained in the CADTH report [111] was conducted using a customised Microsoft Excel tool and it utilised several epidemiological measures obtained from the literature such as the prevalence of type 1 diabetes, incidence rates and population growth rates to estimate the market size and coverage levels of HCL systems in Canada. Financial projections were then made using these measures by adjusting the base year HCL costs over a 3-year time horizon.

The structure of the models used in the cost effectiveness studies was judged to be of good quality. The studies clearly stated their decision problem/research question, the viewpoint of their analyses and their modelling objectives, which were coherent with the decision problem. Both the IQVIA CORE Diabetes Model and the Sheffield type 1 diabetes model are validated models for evaluating diabetes technologies. The studies that used the IQVIA CORE diabetes Model described the model as one with a complex semi-Markov model structure with interdependent sub-models, so more thorough, easier access to its reported features would be of benefit to the intended audience. None of the studies clearly showed the illustrative model structure, which depicted the clinical pathway for T1DM, although references were given to previous publications which outline this. The model is capable of capturing both long- and short-term clinical complications and costs associated with T1DM and has been extensively validated for use in this condition since inception.[120, 121]

The Sheffield type 1 diabetes model is discussed more extensively by the study in the SHTG report [25] unlike the IQVIA CORE Diabetes Model studies that merely provide brief descriptions. The model also has a Markov model structure with several sub-models. The first Markov model predicts mortality in each cycle and is characterised by two states i.e. alive or dead. If a particular individual is alive, then the individual can develop microvascular complications or cardiovascular disease and can experience severe or non-severe hypoglycaemic events. A five-state model for nephropathy (i.e. no nephropathy, microalbuminuria, macroalbuminuria, end stage renal disease and death from end stage renal disease), a three-state neuropathy model (no neuropathy, neuropathy

and amputation) and a five-state model for retinopathy (i.e. no retinopathy, background retinopathy, proliferative retinopathy, macular oedema and blindness) is used to capture the progression of microvascular complications. A key difference between the STHG study that used the Sheffield type 1 diabetes model and the studies that used the IQVIA CORE Diabetes Model is that the SHTG study used a published algorithm to model cardiovascular disease and convert improvements in time in range to reductions in HbA1c, which was deemed to be a more relevant outcome measure. The algorithm assumed the form of a multivariable model where the 5-year risk of cardiovascular disease was dependent on several individual characteristics including duration of diabetes, age, systolic blood pressure, HbA1c levels, previous cardiovascular disease, presence of macroalbuminuria and cholesterol levels.

Data

All the studies required data to undertake the economic analyses. For the cost effectiveness studies to be conducted, both clinical and cost information as well as baseline characteristics for the simulation cohorts had to be inputted into the analytical models prior to the simulation process. The cost effectiveness analyses also required data on the disutilities associated with diabetes related complications as well as data on the utility benefits due to the reduction in the fear of hypoglycaemia (FOH), which were largely obtained from the published literature. The budget impact analysis in the CADTH report [111] used national statistics to inform the key epidemiological measures (i.e. the prevalence of type 1 diabetes, the annual incidence of type 1 diabetes and the population growth rate) and cost data required to estimate the market size and the amount of money needed to reimburse HCL systems.

Two studies i.e. Serne et al., 2022 [115] and Jendle et al., 2021[113] obtained their baseline data and data for the treatment effect of their comparators from a prospective cohort study conducted in Belgium [118] but used different data sources for their intervention treatment effects. The study by Serne et al., 2022 obtained the treatment effect for the intervention from a retrospective US based study of patients transitioning from SAP to the MiniMed 670G HCL system,[119] whereas the study by Jendle et al., 2021 obtained the intervention treatment effect from a randomised crossover trial conducted in New

Zeeland that comprised type 1 diabetes patients using the MiniMed 780G HCL system (Collyns et al., 2021 [49]). It is, however, not clear how the treatment effect was elicited as this is not explicitly stated in the text. Furthermore, the New Zealand study reported the treatment effects of the MiniMed 780G system on time in range. Yet time in range was not one of the outcomes of interest in Jendle et al., 2021.

The study by Roze et al., 2021 [114] and that by Jendle et al., 2019 [112] obtained their baseline data from a study similar to the one used by the Serne et al., 2022 for the intervention treatment effect,[116, 117] but Roze et al., 2021 used a network meta-analysis of the literature to obtain the treatment effects, whereas Jendle et al., 2019 sourced the treatment effects from the simulation cohort. Similar to Roze et al., 2021, the study in the SHTG report conducted a network meta-analysis of the published literature so as to get estimates of the treatment effects but unlike Roze et al., 2021, the baseline characteristics were sourced from a 2017 Scottish type 1 diabetes cohort study.

The relevant cost inputs were obtained from the published literature, and they reflected the perspective of each study as reported. Where suitable resource use data were not available e.g. for treatment mix of the comparator, limitations were acknowledged and authors justified the assumption of using a more conservative approach to costing. An important point to note is that the methods used to identify the relevant information sources were not clearly stated although justifications for the chosen data sources were made and appropriate references provided. It was not clear if quality appraisal of the studies serving as data sources was undertaken and to the best of our knowledge, the studies did not undertake systematic reviews to identify the studies reporting key inputs. With respect to the risk equations underlying clinical progression within the validated models (i.e. the IQVIA CORE Diabetes model and the Sheffield type 1 diabetes model), the sources and choice of source where multiple options were available were not provided or justified. Appropriateness of these sources for use within the specific decision problem cannot, therefore, be assessed.

Uncertainty

The budget impact analysis presented in the CADTH report [111] included scenario analyses where universal HCL coverage was assumed. All the five cost effectiveness studies also conducted several deterministic analyses by varying key input parameters to reflect lower and upper limits, or by making changes to input parameters if multiple sources of information were available to assess the impact on the base-case ICER, and/or to determine the key drivers of the economic model. It was unclear in some analyses whether the sensitivity analyses were exhaustive as no tornado plots were reported. However, results were presented for all sensitivity and scenario analyses.

Four out of the five cost effectiveness studies i.e. Serne et al., 2022,[115] Roze et al., 2021,[114] SHTG, 2022,[25] and Jendle et al., 2019 [112] noted that there was a substantial negative relationship between reducing the utility benefit for the HCL users due to an expected relatively lower FOH compared with the users of the comparator technologies and the incremental QALY gain. To the best of our knowledge, however, 'best-case' and 'worst-case' analyses were not undertaken. It appears that probabilistic sensitivity analyses were performed as CEAC were presented showing the probabilities at which the HCL systems under investigation were likely to be cost effective at various willingness-to-pay thresholds. This was, however, not explicitly stated in the texts.

Assumptions

The studies made several assumptions depending on the type of economic analysis being undertaken. There was significant overlap between studies about the assumptions made, likely due to the homogeneous nature of the economic analyses. For instance, the budget impact analysis in the CADTH report assumed particular figures for the epidemiological measures needed to estimate the market size and financial impact of reimbursing HCL systems. The study also assumed that the reimbursement would be limited to the eligible population but explored this assumption in a scenario analysis by varying the population coverage levels.

All the cost effectiveness analyses except from the study in the SHTG report [25] assumed that their findings were generalisable to their target populations despite using baseline data for other countries. The studies also used short-term simulation data to make long-

term projections over patients' lifetimes. The study in the SHTG report used an algorithm to convert improvements in time in range to reductions in HbA1c and assumed that the converted measures compared favourably with their actual estimates. In order to show that HCL systems were cost effective compared with their comparator technologies, the majority of the cost effectiveness analyses assumed a utility benefit to the HCL users due to the expected greater reduction in diabetes related complications for this group compared with the other technologies.

Discussion

The systematic review identified six studies containing economic analyses of HCL systems. Of the six studies, five were cost effectiveness analyses comparing HCL systems with various diabetes management technologies, whereas one was a budget impact analysis that estimated the financial impact of reimbursing HCL systems over a three-year time horizon. There were two studies conducted in Sweden [112, 113] and one study each in the United Kingdom,[114], Netherlands,[115] Scotland,[25] and Canada.[111] These studies were assessed using the CHEERS and Phillips checklists where applicable.

According to the assessment, four studies were identified as cost effectiveness analyses in their titles i.e. Jendle et al., 2021,[113] Serne et al., 2022,[115] Roze et al., 2021,[114] and Jendle et al., 2019.[112] The other two studies i.e. the study in the SHTG report [25] and the one in the CADTH report [111] did not have the phrase, 'cost effectiveness analysis' or other similar terminology in their titles that would have identified them as economic evaluations but upon further scrutiny of the studies, however, we noted that the SHTG report contained a cost effectiveness analysis in addition to a systematic review and network meta-analysis, while the CADTH report contained a budget impact analysis in addition to a review of the perspectives of HCL users and their carers as well as the ethical considerations of using HCL systems.

All the studies except from the one in the SHTG report [25] had structured abstracts containing information on the background, methods, study perspective, results and conclusions. Although the study in the SHTG 2022 report did not contain an abstract, it had several sections with the relevant information that would normally be found in an

abstract. The overall objective of Jendle et al., 2021 was to evaluate the long-term cost effectiveness of the MiniMed 780G HCL system (i.e. Advanced Hybrid Closed Loop System) compared with isCGM+MDI or CSII. The study in the SHTG report examined the clinical and cost effectiveness of closed loop systems and the artificial pancreas for the management of type 1 diabetes compared with the current diabetes management options. Serne et al., 2022, Roze et al., 2021 and Jendle et al., 2019 assessed the cost effectiveness of the MiniMed 670G HCL system compared with CSII but differed in the way the comparator intervention was configured. Serne et al., 2022 considered the users of isCGM+MDI or CSII, whereas Roze et al., 2021 and Jendle et al., 2019 considered only CSII users.

All the cost effectiveness studies noted that hybrid closed loop systems were cost effective over the lifetime compared with their comparator interventions. This inference was, however, subjective as the studies chose arbitrary willingness to pay thresholds. For instance, despite both Jendle et al., 2021 and Jendle et al., 2019 being conducted in Sweden, Jendle et al., 2019 found the MiniMed 670G HCL system to be associated with an ICER of SEK 164,236 per QALY gained and was thus cost effective at a threshold of SEK 300,000 per QALY gained. Jendle et al., 2021, on the other hand, showed that the MiniMed 780G HCL system was associated with an ICER of 373,700 per QALY gained and was cost effective at a willingness to pay threshold of SEK 500,000 per QALY gained. If a threshold of SEK 300,000 per QALY gained had been used instead, then the MiniMed 780G HCL system would not have been cost effective. The results in Serne et al., 2022 showed that the MiniMed 670G HCL system had an ICER of EUR 6133 per QALY gained compared with the comparator technology and was thus cost effective at willingness to pay thresholds of EUR 20,000, EUR 50,000 and EUR 80,000 per QALY gained. Roze et al., 2021 noted that the MiniMed 670G HCL systems had an ICER of GBP 20,421 per QALY gained which was below GBP 30,000 per QALY gained. The study in the SHTG report [25] noted that closed loop systems were not cost effective compared with CGM+MDI, SMBG+MDI and CGM+MDI since their ICERS were GBP 58,996, GBP 44,920 and GBP 79,604 per QALY gained respectively and they were all above a threshold of GBP 30,000 per QALY gained. If the study had considered a

willingness to pay threshold of GBP 80,000 per QALY gained, then closed loop systems would not have been found to be cost effective in all these pairwise comparisons. This therefore calls for economic evaluations to be undertaken with better justification for the chosen willingness to pay thresholds.

While the IQVIA CORE Diabetes model and the Sheffield type 1 diabetes model are both suited to conduct economic analyses of diabetes management technologies allowing for both deterministic and probabilistic sensitivity analyses to be undertaken; the four studies that use the IQVIA CORE Diabetes model [112-115] are limited in the sense that the model considers only life expectancy, quality adjusted life expectancy, cumulative incidence and time to onset of long-term complications as the outcomes of interest. These outcome measures are, however, sufficient in eliciting the population health gains (or health losses by extension) that are associated with the various diabetes management technologies. The IQVIA CORE Diabetes model uses time, time in state and diabetes dependent probabilities to simulate progression of diabetes and diabetes related complications with both diabetes and non-diabetes mortality accounted for. The model allows for both clinical and cost data to be inputted directly into the model or for the default parameters to be used instead. The studies identified in this review used the literature to obtain this information. The clinical data includes baseline characteristics such as age, sex, duration of diabetes, total daily insulin dose and HbA1c levels as well as data on the disutilities associated with diabetes related complications. The cost data includes the cost of insulin pumps and accessories e.g. infusion sets and reservoirs, sensors, transmitters, serters, batteries, self-monitored plasma glucose testing, the direct costs of diabetes related complications and the indirect costs if a societal perspective is adopted. The Sheffield type 1 diabetes model used by the study in the SHTG report [25] is also limited in the sense that it relies on published data from outside the United Kingdom to define risk of long-term complications. Furthermore, this risk largely depends on HbA1c ignoring the effects of the other risk factors and could thus introduce bias in the results when evaluating interventions that affect other factors besides HbA1c (Thokala et al., 2013). Given that our objective is to provide evidence to NICE on the cost effectiveness of hybrid closed loop systems in general and our scope is not limited to the interventions

that only affect HbA1c, we find the IQVIA CORE Diabetes model to be more appealing than the Sheffield type 1 diabetes model.

A major limitation of most of the cost effectiveness studies is that their findings might not be generalisable. This is because the studies did not use baseline characteristics and treatment effects data for their target populations. The studies relied on studies conducted in the USA for the treatment effects of the MiniMed 670G HCL system, a prospective cohort study conducted in Belgium for the simulation data and treatment effects of isCGM+MDI or CSII as well as a randomised crossover trial in New Zealand for the treatment effect of the MiniMed 780G HCL system despite some controversy around the elicitation of the treatment effect. It is only the SHTG study that used data for its study setting. The assumption made by these studies was that the simulation cohorts despite being for the USA, Belgium and New Zealand were representative of Netherlands, Sweden and the United Kingdom, which is a rather strong assumption. Furthermore, the chosen data sources had varying study designs with different identification assumptions which potentially affected the validity of the results. To extend these studies, therefore, cost effectiveness analyses with appropriate simulation cohorts are needed. Our study does this by using real world data for the United Kingdom to serve as the simulation cohort. We also extend the SHTG study that used the Sheffield type 1 diabetes model to simulate Scottish data by using the IQVIA CORE Diabetes model which obviates some of the limitations of the Sheffield type 1 diabetes model.

7 Companies' submissions of cost effectiveness evidence

7.1 Medtronic submission economics

The Medtronic submission used the iQVIA Core Diabetes Model, henceforth the iQVIA CDM and as described in more detail in section 7.2.1.4 below, to compare the AHCL 780G Minimed pump with the CSII using the 640G Minimed pump. Two comparisons were made with CSII+CGM, the first compared to rtCGM using the Guardian sensor and transmitter and the second compared to isCGM using the Freestyle Libre sensor.

HCL was associated with an HbA1c reduction of 0.8% and both CSII+rtCGM and CSII+isCGM with no change. Thereafter a common annual worsening of the iQVIA default of 0.045% was applied.

The change in HbA1c was derived from the Collyns et al [49] Medtronic funded open label RCT two sequence cross over study of HCL compared to SAP+PLGM. Collyns et al used the HCL 670G Minimed pump, revising the operational mode to implement SAP+PLGM. Collyns et al report a mean baseline of 9.3mmol/l with this improving to 8.5mmol/l in the AHCL arm and worsening slightly to 9.5mmol/l in the PLGS arm, equivalent to approximately a 7.5% HbA1c at baseline and 7.0% HbA1c for AHCL and 7.6% HbA1c for PLGS.

No difference in NSHE was assumed, though it can be noted that time below 3.9mmol/l improved from a baseline of 3.1% to 2.1% for HCL.

Both HCL and CSII+rtCGM were assumed to have no SHEs. For the comparison with CSII+isCGM annual rates of SHEs not requiring medical assistance and requiring medical assistance of 0.65 and 0.25 were stated as being sourced from Östenson et al [122].

Patient population characteristics at baseline were taken from Collyns et al, with a mean age of 23 years, a duration of diabetes of 13 years, a baseline HbA1c of 7.6% and 42% male.

Total annual technology costs were [redacted] for A/HCL 780G, [redacted] for CSII+rtCGM and £3,516 for CSII+isCGM. Other costs were largely sourced from NG17.

For the comparison of 780G with CSII+rtCGM the company estimated totals of 13.89 QALYs and 13.67 QALYs respectively yielding a net gain of 0.21 QALYs. Total costs of £253,583 and £259,400 were estimated, yielding a net cost saving of £5,816 hence dominance for HCL 780G over CSII+rtCGM. A scenario analysis using the net HbA1c gain of 0.3% from the Isganaitis study roughly halved the gain to 0.12 QALYs but net savings of £4,765 persisted so HCL 780G remained dominant over CSII+rtCGM.

For the comparison of HCL 780G with CSII+isCGM the company estimated totals of 13.89 QALYs and 13.19 QALYs respectively yielding a net gain of 0.69 QALYs. Total costs of £253,583 and £240,526 were estimated, suggesting a net cost of £13,057 and an

ICER of £18,672 per QALY. The scenario analysis using the net HbA1c gain of 0.3% from the Isganaitis study slightly reduced the estimated gain to 0.61 QALYs and net costs increased to £14,758 resulting in an ICER of £23,873 per QALY.

The EAG makes the following observations.

- The results of Collyns et al are for AHCL compared to PLGS rather than for HCL compared to CSII+CGM.
- Östenson et al [122], the reference for SHE rates for CSII+CGM, does not specify that patients with T1DM were on CSII+isCGM. The only treatment information that is available is the types of insulin that were received, with 8% receiving only long acting insulin, 65% both short and long acting insulin and 27% receiving other types of insulin. There is no obvious reason why the SHE rates are specific to CSII+isCGM and do not include other regimens such as MDI.
- The ERG is unable to source the annual SHE rates not requiring medical assistance and requiring medical assistance of 0.65 and 0.25 from Östenson et al who reported a mean annual SHE rate of 0.7 among those with T1DM.
- It appears that the iQVIA CDM default quality of life values were used throughout. These relate to T2DM patients with a quality of life value of 0.752 when having no complications, rather than the 0.839 for T1DM patients. Additional survival may have been undervalued.
- The sensors and transmitters for the Guardian system within the costing of the 780G system and CSII+rtCGM were costed at the anticipated April 2023 list price rather than the current list price.
- Both CSII+rtCGM and CSII+isCGM were costed as using the Medtronic 640G pump. There may be a range of other pumps that can be used within both CSII+rtCGM and CSII+isCGM, the costs of which may differ from the Medtronic 640G.
- The sensors and transmitters for a CSII+rtCGM assumed the Guardian system. There may be a range of other sensors and transmitters that can be used, the costs of which may differ.

7.1.1 Dexcom submission economics

[redacted]

The ERG makes the following observations.

[redacted]

Table 10: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

7.1.2 Tandem submission economics

The Tandem submission referenced the Dexcom submission economics, and provides no additional cost effectiveness estimates.

7.1.3 Camdiab submission economics

Camdiab presented two cost effectiveness modelling exercises, one based upon the Dan05 study among patients aged 6 to 18 years using the [redacted] and the other based upon the KidsAP02 study among patients aged 1 to 7 years using [redacted]

7.1.3.1 Camdiab Dan05 study economics

The Dan05 trial, reported in greater detail in Ware et al [57], compared HCL using the CamDiab algorithm with usual care, 3 months prior pump use being an inclusion criterion. It recruited 133 children with a mean age of 13 years, a mean duration of diabetes of 6.3 years, 43% male and a mean baseline HbA1c of 8.2% in the HCL arm and 8.3% in the control arm.

At 6 months HbA1c had fallen to 7.6% and 8.1% respectively, with an adjusted net effect of -0.32%. Time below 3.9mmol/l remained the same in the HCL arm at 6.1% but increased from 4.9% to 5.4% in the control group. Ware et al note that there were seven SHEs, four of which were in the HCL arm and 3 in the control arm, and 2 DKA events, all in the HCL arm.

The Dan05 study was complicated by the HCL arm being split between FlorenceM using the Medtronic 640G pump and CamAPS FX using the Dana RS pump. Due to problems

with the FlorenceM, HbA1c results were based upon the CamAPS FX subset of the HCL arm.

In a post hoc analysis of the HCL CamAPS FX group (N=21) against its control (N=25) baseline HbA1c was 7.9% for CamAPS FX compared to 8.0% for control. At 6 months this had fallen to 6.8% and 7.9% respectively, with an adjusted net effect of -1.05%. Time below 3.9mmol/l rose from 8.6% to 10.8% for CamAPS FX compared to falling from 8.7% to 6.3% for control, with an adjusted net effect of +3.13%.

[redacted]

The ERG makes the following observations:

[redacted]

Table 11: Dan05 EQ-5D values

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 12: Dan05 severe hypoglycaemic events

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n.r.: not reported				

[redacted]

[4] [redacted].

[redacted]

Table 13: Dan05 unscheduled contacts and visits

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.1.3.2 Camdiab KidsAP02 study economics

The KidsAP02 cross-over trial, reported in greater detail in Ware et al [56], compared HCL using the CamDiab algorithm and DanaRS pump and Dexcom transmitter with SAP. It recruited 74 children with a mean age of 5.6 years, a mean duration of diabetes of 2.6 years, 58% male and a mean baseline HbA1c of 7.3%. During the closed loop period HbA1c fell to 6.6% in the treatment arm compared to 7.0% in the control arm, a mean adjusted difference of 0.4%. Median time below 3.5 mmol/l was 2.6% and 2.4% respectively, with a mean adjusted difference of +0.04%, while median time below 3.0 mmol/l was 1.0% and 0.9% respectively, with a mean adjusted difference of +0.02%. There was one SHE in the CamDiab arm and none in the SAP arm.

[redacted]

[redacted]

The ERG makes the following observation.

- [redacted]

7.1.4 Summary of companies' economic modelling

The inputs and outputs of the companies' economic modelling are summarised below.

Table 14: Company submission economics summary: Baseline characteristics and inputs common to both arms

	Medtronic	DexCom/Tandem	CamDiab Dan05	CamDiab KidsAP02
Baseline characteristics				
Mean age	23.5 (7.0)	[redacted]	[redacted]	[redacted]
Male %	42%	[redacted]	[redacted]	[redacted]
Duration diabetes	13 (10.2)	[redacted]	[redacted]	[redacted]
HbA1c	7.6% (0.9)	[redacted]	[redacted]	[redacted]
Costs of hypoglycaemic events				
NSHE	£0	[redacted]	[redacted]	[redacted]
SHE non-medical	£489	[redacted]	[redacted]	[redacted]
SHE medical	£2,358	[redacted]	[redacted]	[redacted]
Disutilities hypoglycaemic events				
NSHE daytime	..	[redacted]	[redacted]	[redacted]
NSHE night time	..	[redacted]	[redacted]	[redacted]
SHE non medical	-0.0137	[redacted]	[redacted]	[redacted]
SHE medical	-0.0578	[redacted]	[redacted]	[redacted]
SHE any daytime	..	[redacted]	[redacted]	[redacted]
SHE any night time	..	[redacted]	[redacted]	[redacted]

Table 15: Company submission economics summary: Model clinical inputs and outputs

Company	Medtronic	DexCom/Tandem	CamDiab Dan05	CamDiab KidsAP02
Model	iQVIA CDM	[redacted]	[redacted]	[redacted]

Regime	HCL	CSIIrtCGM	CSIIisCGM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pump	780G	640G	n.r.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical effects									
HbA1c	-0.8%	0.0%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSHE	..	..	..	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SHE non-medical	0	0	0.65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SHE medical	0	0	0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SHE total	0	0	0.90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QoL direct effect	..	..	..	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual cost	[redacted]	[redacted]	£3,516	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Results									
LY undiscounted	42.79	41.67	41.67	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LY discounted	20.57	20.34	20.34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.89	13.67	13.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net vs comp.		0.21	0.70		[redacted]		[redacted]		[redacted]
Costs	£253,583	£259,400	£240,526	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net vs comp.		-£5,816	£13,057		[redacted]		[redacted]		[redacted]
ICER vs comp.		Dominant	£18,672		[redacted]		[redacted]		[redacted]

[redacted]

n.r.: not reported

Superseded – see updated external assessment report (15 November 2022)

7.2 Independent economic assessment

7.2.1 Methods

7.2.1.1 Patient population

The key baseline characteristics are drawn from the 2019-20 National Diabetes Audit subgroup of those on pump therapy. For the scenario analyses that uses the adult NHSE pilot data, the baseline characteristics are taken from the pilot.

Table 16: Baseline characteristics

	National Diabetes Audit		NHSE adult pilot	
	Mean	s.d.	Mean	s.d.
Age	43.4	17.8	[redacted]	[redacted]
Duration diabetes	24.8	15.6	[redacted]	[redacted]
HbA1c	8.0	1.1	[redacted]	[redacted]
Male	42%	n.a.	[redacted]	[redacted]
Race				
White	97%	n.a.	[redacted]	[redacted]
Black	1%	n.a.	[redacted]	[redacted]
Asian	2%	n.a.	[redacted]	[redacted]

Other baseline characteristics needed as inputs to the iQVIA CDM are taken from NG17, these largely being derived from the Repose trial of pumps against MDI as reported in Heller et al [123]. It can be noted that these characteristics relate to a slightly more poorly controlled group of patients, their baseline HbA1c being 9.1% at baseline. Patients were excluded if they had used a pump in the last three years, and among those randomised to pump therapy a 0.85% improvement was observed which brings it into line with that of the National Diabetes Audit pump subgroup. Unfortunately, in common with the HCL trials the Repose trial did not report changes in other baseline characteristics that might have been affected by pump adoption, such as SBP. The other baseline characteristics are reported in appendix 10.2.

7.2.1.2 Treatment options to be evaluated

The cost effectiveness analysis considers the three comparators within the EAG NMA:

- CSII+CGM non-integrated
- LGS/PLGS
- HCL

CSII+CGM is not separately evaluated as CSII+rtCGM and CSII+isCGM. Based upon feedback from the Diabetes Technical Network the balance is assumed to be 10% CSII+rtCGM and 90% CSII+isCGM for adult patients[5], though this may underestimate CSII+isCGM use. The EAG scenario analysis that applies the NHSE adult pilot data CSII+CGM applies 100% CSII+isCGM due to prior use of CSII+isCGM being reported as a requirement.

7.2.1.3 Framework: methods of synthesis

HbA1c effects

The EAG base case applies the results of the NMA. The EAG also presents scenarios restricting the NMA evidence base to adult trials and applying the mean change of the NHSE adult pilot.

Table 17: EAG HbA1c (s.e) changes

	NMA	NMA adult	NHSE pilot adult
HCL	-0.28% (0.033%)	-0.24% (0.043%)	[redacted]
PLGS	-0.06% (0.079%)	-0.01% (0.115%)	[redacted]
CSII+CGM	0.00%	0.00%	[redacted]

The base case assumes that the HbA1c effect endures for the model time horizon of 50 years. Scenarios of durations of 5 years, 10 years and 20 years are presented.

[5] Paediatric patients may have a higher rtCGM proportion of around 25%, in part due to higher Omnipod use.

NSHE and SHE rates

NSHE rates were not reported in the trials. As reviewed in more detail below, where they were reported they were typically based upon proxies such as the number of periods of 20 minutes or more spent below 3.0mmol/l. The EAG presents a brief review of the literature on NSHE and SHE rates before presenting scenario analyses that estimate NSHE and SHE rates based upon estimates in the literature coupled to the EAG NMA results for time below range.

The SHTG report estimated NSHEs from Donnelly et al [124]: a randomly drawn sample of 267 T1DM and T2DM insulin treated patients in Tayside during 2001. These patients were asked to record their hypoglycaemic events for one month. Among the T1DM patients (N=94), who had a mean age 41 years, a mean duration of diabetes 10 years, were 49% male and had a mean HbA1c of 8.5%, the numbers of NSHEs and SHEs were 327 and 9 respectively, suggesting per patient average annual rates of 42 for NSHEs and 1.15 for SHEs. The SHTG assumed that these rates apply to MDI+SMBG as is reasonable given the 2001 data and that patients were advised to check their blood glucose 2-4 times daily with a portable glucose meter. The SHTG coupled these with reductions of 50% for HCL from [125], 35% for MDI+rtCGM from Beck et al [126], 25% for MDI+isCGM from Bolinder et al [127] and an assumption of 30%, the midpoint of the MDI+rtCGM and MDI+isCGM values, for CSII+CGM. This implies annual NSHE rates of 21 for HCL and 29 for CSII+CGM.

Note in passing that the 1.15 annual average for SHEs of Donnelly et al is an order of magnitude greater than the 0.115 annual rate for SHEs requiring NHS resource use that Leese et al [4] estimated across all T1DM patients in Tayside (N=977), average age 33, average duration diabetes 17 years, 57% males and a mean 7.92% HbA1c. These estimates if taken together suggest that only 10% of SHEs require NHS attention which is somewhat less than the EAG base case of 37.9% as summarised in section 120335920.499.120335920.499 below.

McAuley et al [125], sponsored by JDRF Australia, compared HCL using the Medtronic 670G with MDI+SMBG or CSII+SMBG over six months among 120 T1DM patients, mean age 44 years, mean duration diabetes 24 years, 47% male and a mean of 7.4%

HbA1c. In the HCL group (N=61) there were 8 SHEs, of which 4 were attributed to the study device, while in the control group (N=59) there were 7 SHEs. These correspond to annual SHE rates of 0.26 and 0.24 respectively, a ratio of 111%, but when only including SHEs attributable to HCL annual SHE rates of 0.13 and 0.24 respectively, a ratio of 55%. Unfortunately, McAuley et al do not specify how SHEs were attributed to device or other causes. Turning to the time below range, both HCL and control showed improvements over the course of the trial. The net effects favoured HCL with the percentage time below range improving by 2.0%, 0.8%, 0.6% and 0.4% for 3.9 mmol/l, 3.3 mmol/l, 3.0 mmol/l and 2.8 mmol/l respectively. Applying these net changes to the end of trial control arm time below ranges of 3.8%, 1.4% 0.9% and 0.6%, the ratios of time below range[6] that result are 47%, 43%, 33% and 33%. These ratios may be subject to quite considerable rounding error but show some alignment with the 55% SHE ratio that excludes SHEs not attributable to HCL. But it must be acknowledged that this in turn begs the question of how to handle SHEs not attributable to HCL in the HCL arm for any comparison with the control arm.

In a similar vein the RCTs of HCLs that reported SHEs and ratios of time below range are presented below. Few papers reported NSHEs and those that did used proxies:

- Kariyawasam et al [128] used the number of events below 3.9mmol/l
- Brown et al (Brown, 2019 #132} and Breton et al [69] used the median numbers of events of at least 15 minutes ≤ 3.0 mmol/l
- Abraham et al [67] used the median numbers of events of at least 20 minutes ≤ 3.0 mmol/l

The median weekly NSHE rates at end of trial reported by Abraham et al of 2.1 for control and 1.1 for HCL are notably different from the numbers of moderate hypoglycaemia events reported in the supplementary appendix of 7 and 13 respectively. The former imply annual event rates of 57 for HCL and 109 for control, while the latter imply annual event rates of 0.21 and 0.38. But the ratios of these events are similar at

[6] While a percentage of e.g. 0.9% may at first sight seem small it corresponds with an hourly 1.5 per week.

53% and 55%, which are also quite similar to the ratios of the time below range as reported below.

Table 18: RCTs NSHE and SHE rates and ratios and time below range ratios

Lead author	Abraham	Brown	McAuley	Ware	Boughton	Breton	Ware	Benhamou	Tauschmann	Thabit	Thabit	Kariyawasam
Published	2021	2019	2020	2022	2019	2022	2022	2019	2018	2015a	2015b	2021
Study wks	26	26	26	26	16	16	16	12	12	12	12	6
Comparator	Mixed	CSII*	Mixed	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*
Age	15	33	44	13	68	11	5.6	48	22	40	12	8.2
Dur. diabetes	7.7	17	24	6.5	38	5.2	2.6	28	12	21	4.7	5.5
Male	44%	50%	46%	43%	57%	50%	58%	38%	49%	55%	56%	47%
HbA1c base	7.75%	7.40%	7.80%	8.25%	7.45%	7.7	7.35%	7.60%	7.90%	7.60%	7.80%	7.25%
NSHEs annual												
Comparator	109.2	26.0	n.r.	n.r.	n.r.	31.2	n.r.	n.r.	n.r.	n.r.	n.r.	24.5
HCL	57.2	20.8	n.r.	n.r.	n.r.	20.8	n.r.	n.r.	n.r.	n.r.	n.r.	13.0
Ratio	52%	80%	..	..	..	67%	..	..	..	..	..	53%
SHEs annualised												
Comparator	0.00	0.00	0.24	0.00	0.38	0.00	0.00	0.19	0.20	0.00	0.00	0.00
HCL	0.00	0.00	0.26	0.06	0.00	0.00	0.04	0.32	0.17	0.13	0.35	0.00
Ratio	100%	100%	111%	..	0%	100%	..	167%	86%	..	..	100%
Excl. non attr.			0.13									
Ratio			55%									
Time ratios												

≤ 3.9 mmol/l	54%	61%	47%	110%	94%	78%	102%	44%	79%	81%	83%	50%
≤ 3.5 mmol/l	n.r.	n.r.	n.r.	n.r.	100%	n.r.	102%	n.r.	84%	n.r.	n.r.	n.r.
≤ 3.3 mmol/l	44%	n.r.	43%	n.r.	n.r.	n.r.	n.r.	35%	n.r.	n.r.	n.r.	n.r.
≤ 3.0 mmol/l	50%	97%	33%	n.r.	100%	77%	102%	n.r.	n.r.	n.r.	n.r.	56%
≤ 2.8 mmol/l	50%	n.r.	33%	n.r.	n.r.	n.r.	n.r.	29%	118%	45%	47%	n.r.
Mixed comparators: Abraham: CSII+CGM and MDI+CGM, McAuley: CSII+SMBG and MDI+SMBG. Others CSII* was in conjunction with CGM												

For individual studies, the reductions in time below range tend to be similar across the thresholds though Brown et al and Thabit et al do not follow this pattern.

Among the papers that report NSHEs there is a reasonable if imperfect correspondence between the reduction in NSHEs and the reduction in time below range. But there is a degree of circularity in this due to the definition of NSHEs not being symptomatic events but the number of times patients fell below a mmol/l threshold for at least a given amount of time.

Rates of SHEs are low but vary between the papers even for just their HCL arms. There is no obvious pattern between comparator and HCL, or with the time below range ratios.

Turning to rates of NSHEs within the two main quality of life studies reviewed in more detail in section 120335920.499.120335920.499 below, Gordon et al [129] and Currie et al [23], NSHEs were defined symptomatically with Gordon et al relying upon trial data and Currie et al relying upon postal questionnaire 3 month recall data with a 31% response rate. Gordon et al did not report NSHE rates. Currie et al reported an annualised symptomatic NSHE rate for the T1DM subset of 37.6 which given that the surveys were in 2000 and 2006 probably related mainly to MDI. This needs to be read in conjunction with the reported annual SHE rate of 1.47 and the 31% response rate. But the 37.6 annual NSHE rate corresponds quite closely to the 42 annual NSHE rate reported in Donnelly et al [124] from which the SHTG inferred annual NSHE rates of 21 for HCL and 29 for CSII+CGM. This in turn corresponds quite closely with the common 20.8 annual NSHE rate for HCL reported in Brown et al and Breton et al.

Due to there being no direct RCT evidence of the effects of HCL upon NSHEs the EAG does not include NSHE effects in its base case. Given the range of reported SHE rates the EAG also does not include SHE effects in its base case.

For NSHEs the EAG presents a scenario analysis that couples the 20.8 annual NSHE rate for HCL of Brown et al and Breton et al with the EAG NMA time below 3.0 mmol/l net effect estimates, the weighted mean of the end of trials' time below 3.0 mmol/l for the

CSII+CGM and the assumption that the number of NHSEs is proportionate to the time below 3.0 mmol/l. Scenarios of annual NSHE rates of 57.2 and 13.0 for HCL are presented.

For SHEs the EAG adopts the same approach in exploratory scenarios that assumes SHE rates are proportionate to time below 3.0 mmol/l. Note that this is not saying that the threshold for SHEs is 3.0mmol/l, only that the best measure of whatever is the appropriate threshold for SHEs is likely to be itself proportionate to time below 3.0mmol/l. Coupled with the annual SHE rate for HCL of 0.26[‡‡] as reported in McAuley et al, chosen due to it being a 26 week study and a reasonable midpoint, results in the following estimates.

Table 19: EAG base case average annual NHSEs and SHEs

	Time below 3.0mmol/l				
	NMA net	Absolute	Ratio	NSHEs	SHEs
HCL	-0.14%	0.46%	100%	20.8	0.26
PLGS	-0.16%	0.44%	96%	19.9	0.25
CSII	Reference	0.60%	130%	25.9	0.32

The annual SHE rates correspond reasonably closely with the [redacted]

[redacted]

[‡‡] These are reasonably similar to the 0.20 annual SHE rate for CSII+CGM that was applied in the DG21 assessment of sensor augmented pump therapy for T1DM patients. The mean annual SHEs of 0.1855 for rtCGM and 0.1358 for isCGM of NG17 suggest an annual rate of around 0.14. The second year annual SHE rate of 0.30 for those on pumps in the Repose trial is also reasonably aligned with this, bearing in mind that CGM was not a requirement.

7.2.1.4 Treatment pathways and modelling

Treatment pathway

The treatment pathway assumes that patients remain on a single treatment option throughout: CSII+CGM, PLGS or HCL.

Modelling of HbA1c effects: iQVIA Core Diabetes Model summary

In line with DG21 and NG17 the EAG uses the iQVIA CDM to model the micro and macro vascular complications of diabetes and patients' overall survival. This decision is in part due to its availability to the EAG at the start of the DAR process, but is mainly due to precedents with NG17 noting:

"*The previously published IQVIA CDM (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*."

There is also the benefit of a direct comparability with most of the industry submissions' economic modelling. But it should be borne in mind that the SHTG modelling used the Sheffield model.

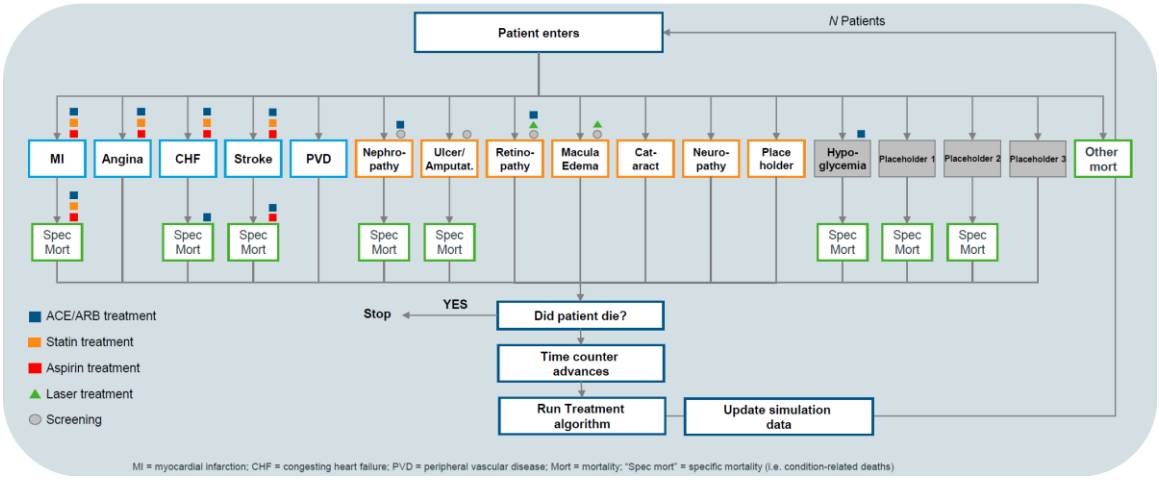


Figure 20: iQVIA CDM structure[§§]

In brief, as shown in the model diagram above, the iQVIA CDM predicts the progress of patients with T1DM over their lifetime, modelling the incidences of the 11 macro and micro vascular complications the likelihoods of which are affected by T1DM. The default and recommended setting are to sample 1,000 patients from the patient characteristics and run each of these patients through the model 1,000 times.

The iQVIA team has advised the EAG that for modelling a T1DM cohort only the non-specific mortality approach should be use as per the diagram above, and not the combined approach of the T2DM UKPDS 62 and UKPDS 82 studies. Given the event specific mortality, to estimate the non-specific mortality by age, "Other Mort" in the diagram, the EAG adjusts UK life table data to remove deaths due to the ICD10 codes for CVD, cerebrovascular disease and renal failure as presented in appendix **Error! Reference source not found.**. The iQVIA modelling team have indicated that removal of deaths due to the ICD10 codes for hypertension may also be reasonable and the EAG presents this in a scenario analysis. The iQVIA CDM team indicate that for T1DM this approach requires that the non-combined modelling of mortality be selected.

Modelling of HbA1c effects: iQVIA Core Diabetes Model validation work

Both Palmer et al [120] and McEwan et al [121] presented model validation work for previous versions of what was then the IMS CDM. McEwan et al is the more recent paper, probably used a more recent version of the CDM and with the DCCT/EDIC study has a study with a large number of patients and a long follow up and is consequently preferred by the EAG. But only Palmer et al reported validation work around overall survival, and the EAG turns to this at the end of the review.

[§§] Diagram courtesy of the iQVIA CDM team

McEwan et al modelled the internal validity of what was then the CDM version 8.5 in predicting events for the DCCT cohort with follow-up of 5.0 to 6.5 years and the EDIC cohort with follow-up of 17 to 30 years.

Table 20: DCCT and EDIC events: Observed vs modelled

		Trial observed			CDM v8.5 modelled		
Study	Event	Treat.	Control	Net	Treat.	Control	Net
DCCT	Retinopathy	23	91	-68	18	91	-73
N=1,441	Neuropathy	7	28	-21	8	30	-22
5.0-6.5 yrs FU	Microalb.	55	103	-48	72	105	-33
	Albuminuria	9	9	0	6	10	-4
DCCT/EDIC	CV events	25	38	-13	38	43	-5
N=1,226	Retinopathy	153	356	-203	200	211	-11
17-30 yrs FU	Neuropathy	66	178	-112	101	83	18
	CVD	66	100	-34	115	118	-3
	ESRD	7	14	-7	26	23	3

Validation is reasonable for the DCCT study, suggesting that the CDM is relatively good at modelling events over a medium time horizon. But given the lifetime modelling of most cost effectiveness analyses the validation for the DCCT/EDIC study is the more relevant. McEwan et al reported the relative risks of events for the CDM compared to the trial, but for cost effectiveness modelling the differences in the absolute numbers of events are the more relevant metric. It is not reported why McEwan et al group CV events given the CDM model structure, but this may have been due to trial reporting necessitating this.

The control arm of the DCCT/EDIC is now obsolete. Concentrating upon the DCCT/EDIC intensive treatment arm, the iQVIA CDM overestimated all events for the treatment arm, this being most serious for ESRD for which the model estimate was 26 compared to the observed 7: more than triple the observed at 371%. But CV events, retinopathy, neuropathy and CVD were also overestimated, the modelled incidences being 152%, 131%, 153% and 174% respectively of those observed in the trial. The EAG

presents a scenario analysis that reduces these costs proportionately to their overestimation as reported in McEwan et al. This mainly affects the costs of eye and renal complications due to their high annual costs. This scenario does not address the effects of any possible overestimation of eye and renal complications upon quality of life and overall survival.

It can be noted that Palmer et al also examined the observed versus the modelled incidences of ESRD over time and found a very good correspondence with data from 1,075 US T1DM patients recruited prior to the age of 18 years, a 25 year cumulative incidence of 9.1% observed compared to 8.9% modelled. It is unclear whether this model validation was internal, using a study used to construct the CDM, or external, trying to model the outcomes of a study not used in the construction of the CDM.

It is particularly important to model ESRD correctly within the CDM due to its large effect upon quality of life, a disutility of 0.164 for haemodialysis and 0.204 for peritoneal dialysis compared to a patient with no complications, and its very large ongoing annual cost of £34,613 for haemodialysis and £31,139 for peritoneal dialysis. The effects of the modelled ESRD upon QALYs, costs and the ICER bear particular scrutiny.

Unfortunately, McEwan et al did not report the corresponding survival percentages. Any modelled differences in overall survival may drive the ICER to a somewhat greater extent than the modelled differences in vascular events and albuminuria. This somewhat limits the usefulness of the validation exercise for assessing the reasonableness of using the CDM for economic assessments. This may also be the reason for the incidence of ESRD being modelled as higher in the treatment arm than in the control arm, the reverse of that observed. Time spent with ESRD would have been a better comparison, but data for this comparison may not have been available for the trial.

Turning back to Palmer et al, they reported the observed overall proportion surviving compared to that modelled for a cohort of 142 US T1DM patients in the Joslin clinic who were all recruited prior to the age of 21 years.

Table 21: Joslin clinic survival: Observed vs modelled

	Observed	Modelled
At 4 years	99%	99%
At 10 years	97%	95%
At 15 years	96%	87%
At 20 years	88%	79%
At 25 years	81%	70%

Again, the observed values and the CDM modelled values were reasonably aligned in the medium term but diverged somewhat in the longer term. This may argue for exploring the effect that shorter time horizons have upon the ICER, and if modelling children or adolescents keeping a weather eye on the considerably longer time horizons that have to be modelled to effect a lifetime time horizon.

The Mount Hood challenges invite diabetes modellers to test their models against long term follow up data in competition with other modellers. The EAG has identified the 1st, 4th, 5th, 8th and 9th challenges as being published in peer reviewed journals, but of these only the 4th held in 2004 reported validation data on model performance for T1DM patients.

The Mount Hood 4 Modelling Group [130] reported the results for two models that attempted to replicate the DCCT for the primary prevention cohort at 9 years, CORE and Archimedes[***]. Only the micro-vascular complications that could be compared with published DCCT data were presented, results for the Archimedes model being very similar to those of the CORE model.

Table 22: 4th Mount Hood Challenge: CORE model T1DM results

	DCCT			CORE		
Arm	Control	Intense	Net	Control	Intense	Net

[***] A third model, EAGLE, attempted to reproduce results for the secondary prevention cohort.

Microalbuminuria	27.3%	16.0%	-11.3%	27.7%	14.9%	-12.8%
Back. retinopathy	52.2%	14.3%	-37.9%	39.4%	14.4%	-25.0%
Periph. neuropathy	63.2%	27.7%	-35.5%	64.0%	25.0%	-39.0%

The CORE model estimated 9 year cumulative incidences for the intensive care arm quite well, but estimates for the control arm were more variable. This caused the net estimates of microalbuminuria to be closely aligned, peripheral neuropathy to be reasonably aligned and background retinopathy to be poorly aligned with those of the DCCT. Within the above it should be borne in mind that the control arm of the DCCT is obsolete and that only the intensive treatment arm has any relevant today.

The above may appear critical of the validity of the iQVIA CDM as longer time horizons are modelled. It is almost inevitable that uncertainty around modelled outputs will increase as the time horizon extends and that observed values will diverge to some extent from that modelled. While the validation work suggests a less than perfect correspondence between the model and real life, the availability of the validation work is a strength. Much of the economic modelling presented to NICE within other workstreams such as STAs relies upon short term trials extrapolated to lifetime horizons for which no parallel validation work is possible. It should also be borne in mind that the iQVIA CDM continues to evolve.

The ability of the iQVIA CDM to reliably simulate a T1DM paediatric population is an open question, being affected by both the longer duration that is required for a lifetime horizon and the degree to which the risk equations of the model relate to a paediatric population. A key source for T1DM model inputs appears to be the DCCT/EDIC trial which recruited patients between 13 and 39 years, with a mean baseline age of 27 years and a standard deviation of 7.1 years. If normally distributed this would imply that of the 1,441 recruited at baseline around 24 (2%) would have been up to 12 years, 40 (3%) between 13 and 15 years and 80 (6%) between 16 and 18 years: a total of 144 (10%) being up to 18 years of age at baseline. At close of the DCCT the mean age had increased to 33 years while at EDIC 18 years follow up it had risen to 52 years meaning that the

great majority of the DCCT/EDIC data will relate to an adult population. An alternative to the EDIC CVD model in the iQVIA CDM is the Pittsburg CVD model, this being based upon Epidemiology of Diabetes Complications Study (EDC) which recruited 658 subjects with childhood onset of diabetes before the age of 17 years and has followed them up for 22 years. If modelling a younger population this suggests at a minimum exploring the effect of the Pittsburg CVD model. The EAG remains uncomfortable simulating a paediatric population using the iQVIA CDM but presents a scenario of this in appendix **Error! Reference source not found.**.

Modelling of HbA1c effects: HbA1c progression

The iQVIA CDM default for HbA1c progression is an annual 0.045% worsening. This is drawn from the DCCT/EDIC trial as reported in Nathan et al [131]. The DCCT trial compared intensive therapy with conventional therapy among 1,441 patients with T1DM. A primary prevention cohort with a duration of diabetes of 1-5 years had to have no history of hypertension, cardiovascular disease, neuropathy requiring treatment or retinopathy. A secondary intervention cohort could have a duration of diabetes of 1-15 years had to have at least one microaneurysm on one eye. Intensive therapy included MDI with a minimum of three daily injections or CSII with patient specific HbA1c goals. Conventional therapy was standard of care in the 1980s, typically one or two daily injections and SMBG or urine testing, with the only HbA1c goal being the avoidance of values over 13.5%. EDIC provided long term follow up to the DCCT. After DCCT and prior to enrolment in EDIC all in the conventional therapy arm were offered training in intensive therapy. The DCCT was a controlled trial, the EDIC observational.

Tabulated data suggests that at the end of the DCCT for the intensive therapy arm the median HbA1c was 7.2%. Figure 1 of Nathan et al is reproduced below, the values being taken from the graph.

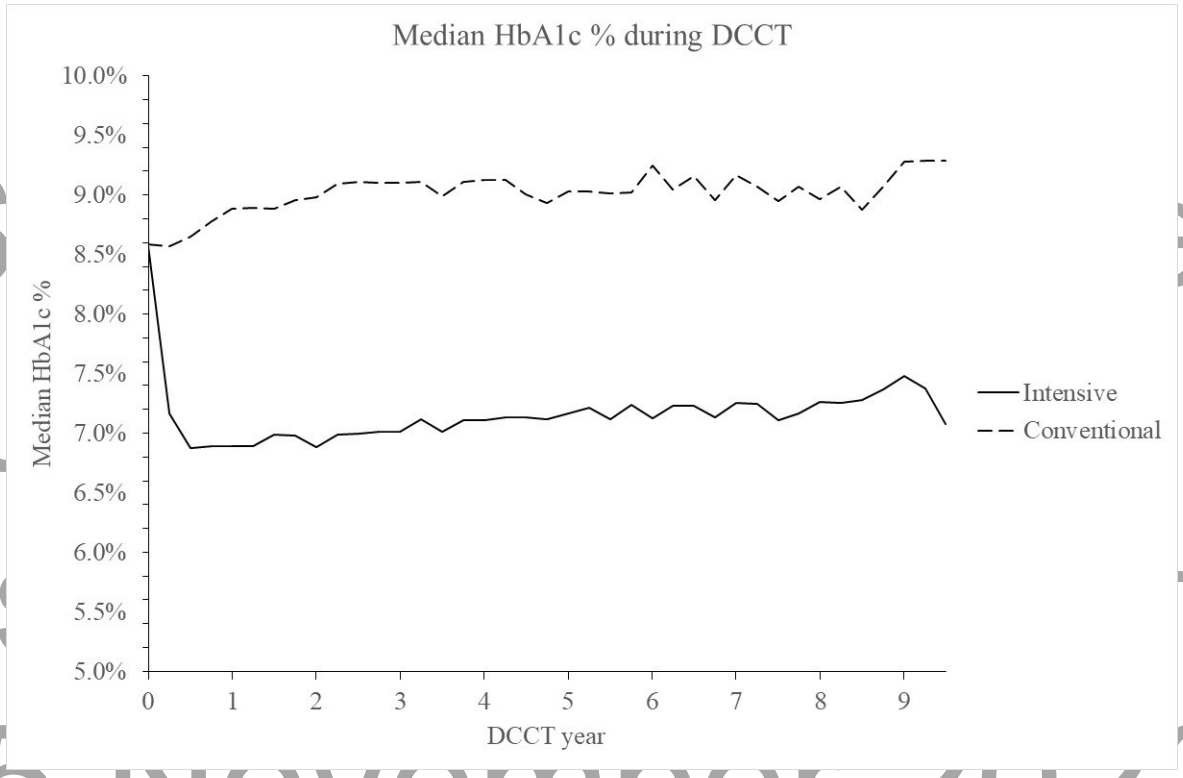


Figure 21: Median HbA1c during the DCCT trial

The reasons for downturn at the end of intensive therapy are unclear, the graphed value appearing to be below the reported 7.2% for the end of the DCCT phase. Values prior to this also appear slightly higher than 7.2%.

The EAG estimates that in the intensive therapy arm median HbA1c at 6 months was 6.88% while at 9 years it was 7.48% which suggests an annual worsening of 0.07%. Applying the stated end of DCCT value of 7.2% suggests and annual worsening of 0.04% which is reasonably aligned with 0.045% default of the iQVIA CDM. But this ignores the long term EDIC follow up as graphed below.

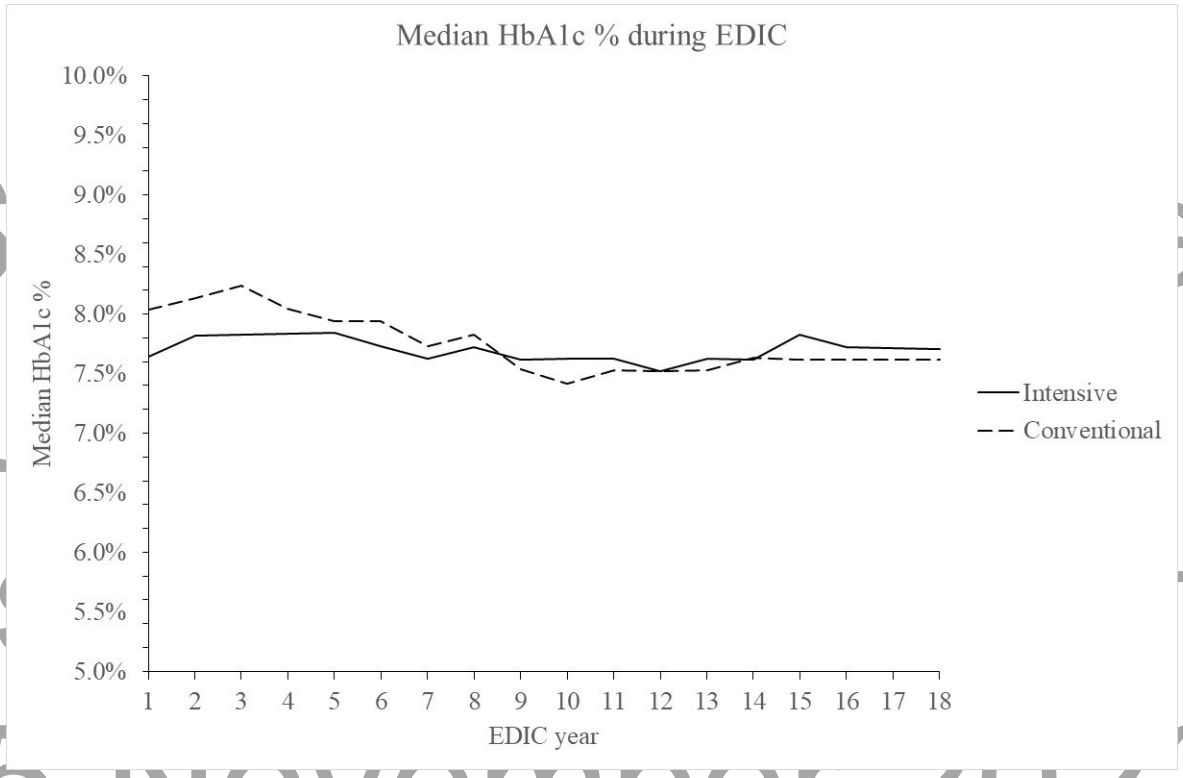


Figure 22: Median HbA1c during the EDIC extension trial

The EAG estimates that for those initially on intensive therapy who continued on it during EDIC at EDIC baseline the median HbA1c was 7.64% and at 18 years was 7.71% which suggests little to no annual worsening during EDIC. Nathan et al tabulate an end of EDIC value of 8.0%. which over the course of EDIC might suggest an annual worsening of 0.02% in the intensive care arm.

Combining the tabulated 8.0% end of EDIC value with the EAG estimates of a 6 month DCCT of 6.88% suggests an annual worsening over the 26.5 years[†††] of 0.042% which is aligned with the iQVIA CDM value of 0.045%.

It should be noted that both the DCCT and the EDIC are relatively old and of questionable relevance to the current appraisal. The DCCT control arm is obsolete. There

[†††] Ignoring the intervening training period.

was a slight upwards trend among the intensive care arm during the DCCT but this may have reflected "trial fatigue", or the incidence of hypos, or in the early years concern about retinopathy and "glycaemic re-entry". Follow-up in the DCCT intensive care arm was intensive with frequent visits. This intensity of follow-up was not carried through to EDIC which could account for any general worsening during EDIC rather than it being due to any underlying disease progression. It can also be noted that when the DCCT control group moved to EDIC and transferred to the intensified insulin regime they saw an initial fall in their HbA1c but no general upwards trend thereafter.

Turning to the UK National Diabetes Audit 2019-20 the median HbA1c by age among those with T1DM is shown below.

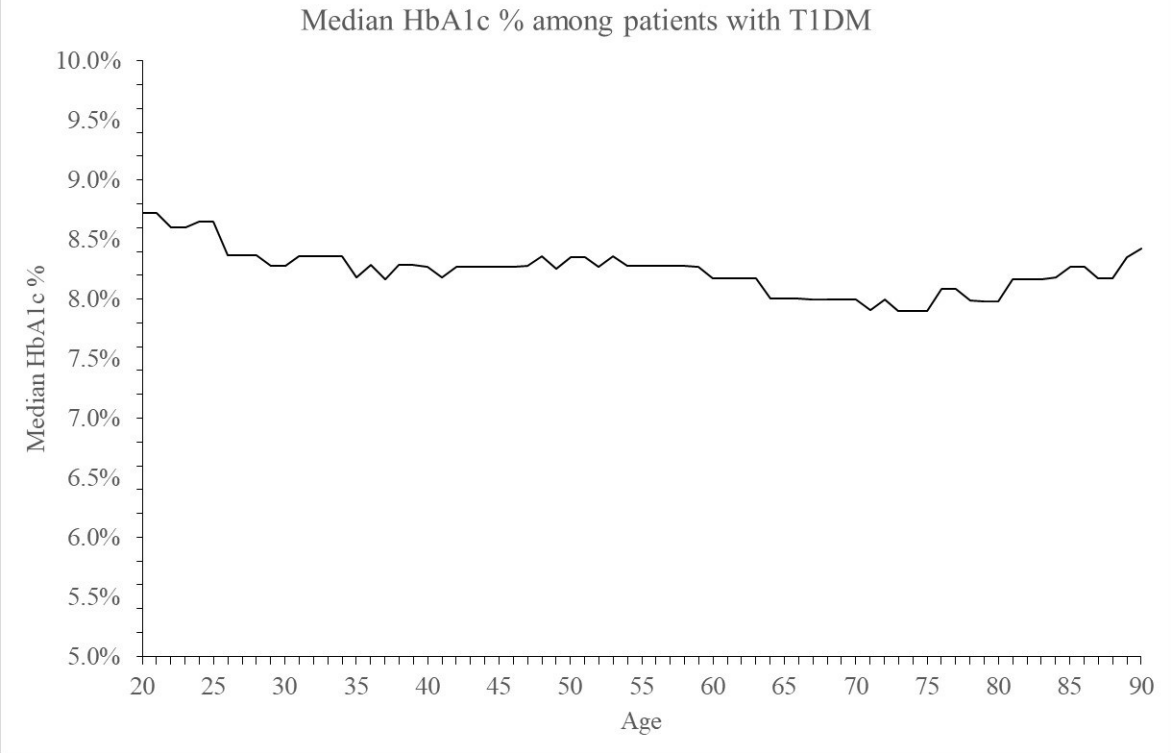


Figure 23: UK Diabetes Audit: Median HbA1c by age

While this does not follow individual patients through time, there is no obvious worsening of the median HbA1c with age. HbA1c appears to become better controlled in early adulthood. This is mirrored in Acharya et al [132] who in a cross sectional study of

255 young Scottish diabetics with T1DM found that those in the youngest age group had statistically significantly higher mean HbA1c than those in the eldest age group, with means of 9.9% for those age 15-18 years, 9.4% for those age 18-22 years and 8.8% for those age 22-25 years. Turning back to the National Audit data, HbA1c remains reasonably constant throughout middle age, possibly showing slight further improvement above the age of 60, though this might be the result of survivor bias, it not rising above the values of middle age until patients are in their 80s.

In the light of the above, for the base case the EAG will assume no annual worsening of HbA1c over time as would be expected in a disease where beta cell capacity is mostly lost by diagnosis. A scenario analyses of an annual worsening of 0.045% will be presented, in part to aid comparison with other modelling efforts.

Modelling of other clinical effects: NSHEs and SHEs

There is some lack of clarity around the iQVIA CDM implementation of the quality of life decrements for NSHEs, as reviewed in greater detail in section 120335920.499.120335920.499 below.Coupled with a wish to simplify the implementation of scenario analyses, the EAG uses the iQVIA CDM to model the effects of HbA1c upon survival and the micro and macro vascular complications of diabetes. The iQVIA CDM overall survival curve for each comparator is then coupled with comparator specific treatment costs and in scenario analyses with the comparator specific NSHE rate and SHE rate. With the addition of the events' unit costs and disutilities this enables technologies' other effects to be incorporated into the cost effectiveness analysis.

Note that this assumes that there are no deaths from SHEs, in common with iQVIA CDM defaults and the NG17 model inputs.

7.2.1.5 Perspective, discount rates and time horizon

As per the NICE methods guide, the perspective for costs is the NHS and PSS, the perspective for benefits is that of the patient, and costs and benefits are discounted at 3.5%.

The base case assumes a 50 year time horizon which is effectively a lifetime horizon for all but an insignificant proportion of patients.

Given the uncertainty around the iQVIA CDM outputs for longer time horizons as reviewed in section 120335920.499.120335920.499 above time horizons of 8, 12 and 24 years will also be explored. Multiples of 4 years correspond with pumps' lifespans.

7.2.1.6 Health valuation

Quality of life without complications and disutilities of micro and macro vascular complications

The 0.839 values for quality of life without complications for patients with T1DM, based upon Peasgood et al [133], and the disutilities of micro and macro vascular complications are taken from the default values of the iQVIA CDM[‡‡‡]. This is in line with NG17.

Table 23: Disutilities of micro and macro vascular complications

Complication	Disutility
MI event	-0.055
MI subsequent	-0.055
Angina	-0.090
CHF	-0.108
Stroke event	-0.164
Stroke subsequent	-0.164
PVD	-0.061
Gross proteinuria	-0.048
Haemodialysis	-0.164
Peritoneal dialysis	-0.204
Renal transplant	-0.023
Background diabetic retinopathy (BDR)	-0.040

‡‡‡ The iQVIA CMD team stated that the default utilities for complications relate to T2DM patients and that to derive utilities for T1DM patients the T2DM disutilities should be calculated and applied to the T1DM quality of life value for no complications.

BDR wrongly treated	-0.040
Proliferative diabetic retinopathy (PDR)	-0.070
PDR lasered	-0.070
Macular oedema	-0.040
Severe vision loss	-0.074
Cataract	-0.016
Neuropathy	-0.084
Ulcer	-0.170
Amputation	-0.280
Post amputation	-0.280

Disutilities of hypoglycaemia events

Given previous reviews of the effects of hypoglycaemia upon quality of life, the ERG largely relies upon NG17 coupled with the systematic reviews of Chatwin et al [134], Coolen et al [135], Jensen et al [136] and Matlock et al [137] to extract and review papers that may report values compatible with the NICE reference case. The ERG augments this with a systematic literature search from 2020 to find papers that may have been published subsequent to previous reviews' date cut-offs.

The EAG first summarises the papers underlying the iQVIA defaults, with the range of these estimates being subsequently graphed in **Figure 24**, appending the review of Gordon et al [129] to this due to the similarity of its method to that of Currie et al [23]. It then turns to other papers in the literature, these mostly being more recent publications.

If a constant disutility per NSHE is applied the iQVIA CDM default is 0.00335 per event as drawn from the poorly reported US data of Foos & McEwan [138]. But the preference appears to be for non-linear models and diminishing marginal disutilities, in which case the iQVIA CDM defaults for the effect of NSHEs on QoL are to choose either the analyses of Lauridsen et al,[19] based upon the TTO data of Evans et al [139], or the analyses of Currie et al [23].

Foos & McEwan [138] is only available in abstract with minimal information, other than it being a US based survey that collected 6 month data about mild, moderate, severe and very severe hypoglycaemia events. No information about how quality of life was calculated or measured is provided, but this coupled with mean event rates within the categories resulted in annual disutility scores of -0.0011, -0.0062, -0.0148 and -0.0586 for mild, moderate, severe and very severe hypoglycaemia events, the weighted average for mild and moderate events of -0.00340 being essentially the same as the -0.00335 iQVIA CDM default if a linear disutility is selected.

Evans et al [139], sponsored by Novo Nordisk, undertook an internet based time trade-off (TTO) exercise among three samples from the general population, patients with T1DM and patients with T2DM from an existing panel in Canada, the US, Germany, Sweden and the UK. Evans et al did not state how many of those in the existing general population panel chose not to start the questionnaire, but of the 11,196 who did, 90% completed it, among whom a further 17% were excluded leaving 8,286 or 82%.

The central estimates suggested that respondents were willing to sacrifice 3.8% of their future survival to go from one quarterly daytime NSHE to none, and to sacrifice 4.1% to go from one quarterly nocturnal NSHE; i.e. sacrifices of around 2 weeks survival per year. Similarly, to go from none to one annual SHE respondents were willing to sacrifice around 10% of future survival, around 5 weeks per year. The decrements for going from some to no events seem quite high and may not be reasonable. If so, this also carries through to the functions of Lauridsen et al.[19]

Evans et al report mean decrements[§§§] per event among the T1DM subgroup of 0.004 for a daytime NSHE, 0.008 for nocturnal NSHE, 0.047 for a daytime SHE and 0.051 for a

[§§§] Evans et al imply that their TTO study does not take into account discounting. Given T1DM respondents' mean age of 39 they might reasonably expect to live for at least another 30 years. Time preferences among respondents of the NICE reference case discount rate of 3.5% would reduce e.g. the disutility for one annual SHE from 0.082 to 0.049, a 40% reduction. But it can be noted that Dolan and Gudex 10. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQoL: results from a UK General Population Survey*. University of York; 1995. URL: https://www.york.ac.uk/che/pdf/DP138.pdf (Accessed 9 February 2021). in a study of 39 members of the general public estimated individual discount

nocturnal SHE, the values for severe events being slightly less than those reported for the general population of 0.057 and 0.062. The ERG assumes that these are disutilities per annual event and include the step going from none to some NSHEs.

Lauridsen et al,[19] sponsored by Novo Nordisk, used the TTO values for NSHEs of Evans et al [139] to estimate the quality of life impact of NSHEs recognising the apparent diminishing marginal disutilities as graphed below in **Figure 24**. The non-linearity appears to be mainly driven by the step going from none to some NSHEs. A two stage estimation procedure that modelled this step separately from subsequent increases in the NSHE rate might result in a smaller and more linear effect for the subsequent increases after the initial step.

Currie et al et al [23], sponsored by Novo Nordisk, used the results of postal questionnaires mailed to UK patients, average age 63 years, identified as having either T1DM, 34%, or T2DM, 66%, in two surveys of N=1,500 and N=3,200 with some overlap between the surveys. The overall response rate across the two surveys was 31% which is quite low and may reflect self-selection bias; those responding may tend to have been those whose NSHEs and SHEs had a greater impact upon their quality of life.

They collected data on patient characteristics, comorbidities, the number of NSHEs and the presence of SHEs during a 3-month recall period, the HFS version 1 worry subscale (HFS1-ws) and the EQ-5D. For patients who responded to both surveys their second response was chosen. The effect of this choice was not explored, but it can be noted that the mean HFS score for the first survey of 6.76 was somewhat lower than the 9.39 of the second survey.

Reported rates of SHEs among those experiencing them, 10.3% of T1DM patients, 8.3% of T2DM patients in insulin and 1.8% of T2DM patients on oral antidiabetes drugs

rates scattered around 0%, and it appears standard in TTO to not estimate individuals' time preferences alongside their quality of life estimates.

(OADs) , were quite high[****]: annualised rates of 14.3, 22.3 and 7.6 respectively yielding an overall sample mean of 14.9 among those experiencing SHEs. This contrasts with annual rates from the UK hypoglycaemia study group among those experiencing SHEs of 5.1 and 6.9 for T1DM patients of less than 5 years and more than 15 years duration, and 1.5, 1.4 and 2.8 for T2DM patients on OADs, insulin for less than 2 years and insulin for more than 5 years.

Among the 84.7%, 78.0% and 49.5% of patients reporting symptomatic NSHEs the corresponding annual rates are 44.4, 31.2, and 48.7 with an average of 45.5. Nocturnal NSHEs were reported by fewer patients, 30.1%, 25.6% and 4.2% respectively, these patients reporting annual event rates of 21.3, 17.7 and 30.6 yielding an overall average of 21.7. While only a relatively small proportion of patients reported SHEs their average number of SHEs may be a concern, particularly when interpreting their estimated effect upon the HFS1-ws due to this being the presence or absence of SHEs rather than their number.

In a two-stage analysis, the HFS1-ws was modelled as a function of the age, insulin use, the logarithm of the number of NSHEs and the presence or absence of SHEs. Two separate HFS1-ws regressions were undertaken, one for symptomatic NSHEs and one for nocturnal NSHEs. Unfortunately, Currie et al were not explicit about the time period that should be used when calculating the number of NSHEs but it can be noted that the presence or absence of SHEs can only have been calculated based upon the 3-month recall period of the questionnaires[††††]. The EQ-5D was modelled as a function of the HFS1-ws, age, BMI and the presence or absence of a range of comorbidities.

[****] Table 3 is poorly labelled but states the total number of patients, the proportion of patients experiencing SHEs and an annualised SHE rate. For it to be possible for the annualised rate to apply only to those experiencing an SHE during the 3 month recall period the minimum possible annualised rate would be 4. Table 3 gives annualised rates of 1.47, 1.86 and 0.14. The EAG concludes that these annualised rates must be across the entire patient number and not the subgroup who experienced SHEs.

[††††] The EAG contacted Currie as the corresponding author about this but did not receive a reply. It appears that the iQVIA CDM may input an annual rate of NSHEs to the HFS1-ws function(s) of Currie et al when

Currie et al report disutilities for symptomatic and nocturnal NSHEs of 0.0142 (1.42%) and 0.0084 (0.84%), implicitly suggesting that these are additive. Given the regression analyses and probability of positive covariance between symptomatic and nocturnal NSHEs the EAG thinks that only one of the HFS1-ws regressions should be applied, this also avoiding double counting the effects of SHEs. The stated disutility values also only apply when patients are moving from experiencing no NSHEs to a small number of NSHEs. The functions are non-linear and have a quite rapidly declining marginal disutility for NSHEs.

The more recent paper by Gordon et al [129], sponsored by AstraZeneca, very closely mirrors the analysis of Currie et al, both being co-authored by McEwan. As with Currie et al, Gordon et al used the EQ-5D and did not specify that the UK social tariff was used though this seems likely.

Gordon et al were explicit about the time period that should be used when calculating the NSHE event rate and the presence or absence of SHE events within their functions: a common 4-week period for both. In the light of the common co-authorship and similarity of analyses of Gordon et al and Currie et al, the EAG thinks that the most reasonable assumption about the time period that should be used when calculating the NSHE event rate and the presence or absence of SHE events for the functions of Currie et al should be a common 3-month period in line with the recall period of the questionnaires‡‡‡‡.

calculating their effect. The EAG contacted the iQVIA about this but did not receive a reply. Partly because of the uncertainty about its implementation in the iQVIA CDM, the EAG estimates the effects of NSHEs separately from the modelling that uses the iQVIA CDM through application of the modelled overall survival curve to event rates, disutilities and costs. The EAG adopts a parallel approach for estimating the treatment costs and the costs and quality of life effects of NSHEs and SHEs.

‡‡‡‡ Currie et al noted that the more numerous second questionnaire recall period was 3 months. The EAG assumes that this also applies to the first questionnaire.

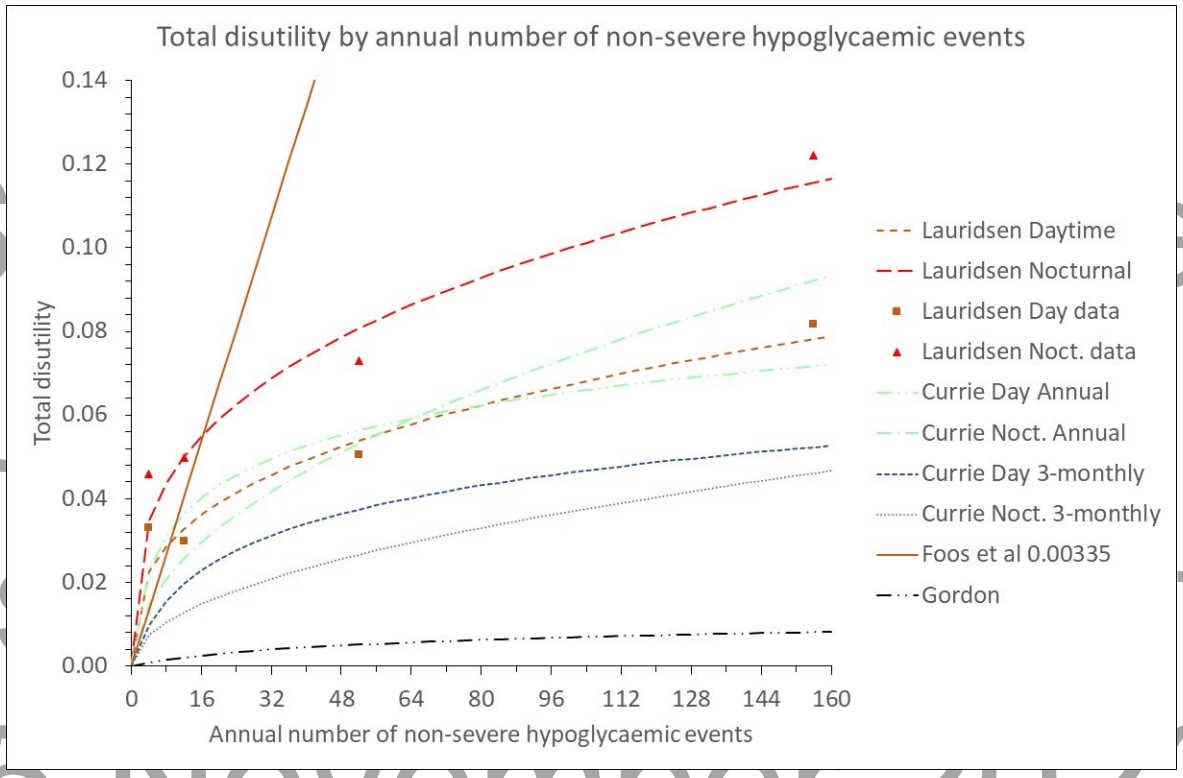


Figure 24: NSHE disutilities for the iQVIA CDM defaults and Gordon et al

Turning to other papers in the literature, Yfantopoulos et al [140] recruited 938 adult subjects with T2DM who were receiving insulin with an average age of 67 years, these being split into an estimation sample of 489 and a validation sample of 449. EQ-5D data was valued using the UK social tariff. Within a multivariate analysis the presence of severe hypoglycaemia was estimated to reduce the EQ-5D by a disutility of -0.050, this being statistically significant. Unfortunately, the period over which SHEs were recorded is not reported.

Zhang et al [141] analysed the records of 7,081 Chinese patients with T2DM receiving oral agents, with an average age of 60 years. EQ-5D data was collected and valued using a Chinese tariff. Unfortunately, the paper does not report the data period or recall period for the hypoglycaemia event rates. An OLS regression that controlled for various patient characteristics and comorbidities estimated that an "additional" NHSE relative to none had a disutility of -0.007 while SHEs has a disutility of -0.008, both being statistically

significant. The similarity of disutilities for NSHEs and SHEs suggests that they relate to the presence or absence of events, rather than a disutility per event.

Nauck et al [142], sponsored by Novo Nordisk, analysed the LEADER cardiovascular outcomes trial among patients with T2DM who had a high risk of cardio-vascular disease, patients being randomised to liraglutide (N=4,668) or placebo (N=4,672). This followed patients for 3.5 to 5.0 years and collected the EQ-5D at baseline, 12 months, 24 months and study completion, it being valued using the UK social tariff. A linear mixed repeated measurements model estimated that severe hypoglycaemia had a disutility of -0.029 but that this did not quite reach statistically significant with a p-value of 0.073 due to the small number of events. The text does not specify whether this related to any severe hypoglycaemia events during follow-up or was e.g. an annualised event rate, but it appears to be the former.

Levy et al [21], sponsored by Novo Nordisk, elicited quality of life values using the TTO for quarterly, monthly and weekly NSHEs from 51 Canadian diabetics, and from 79 and 75 members of the Canadian and UK general population. For those with diabetes the central TTO values reported for annualised NSHE rates of 0, 4, 12 and 52 were 0.92, 0.91, 0.87 and 0.75, which suggests a more linear relationship than the TTO values of Evans et al. An OLS regression estimated that the number of NSHEs had a coefficient of -0.0033 while within a Flogit analysis it was -0.0247, both being statistically significant. They conclude that an NSHE is associated with a -0.0033 disutility for those with diabetes compared to an estimate of -0.0032 from the general public, these estimates being aligned with the -0.00335 that the iQVIA CDM estimates from Foos & McEwan.

Briggs et al [143], sponsored by BMS, analysed the 2 year data from the SAVOR-TIMI 53 trial of saxagliptin against placebo among 16,488 patients with T2DM. Patients were followed for 2 years with the EQ-5D being collected alongside event rates and valued using the UK social tariff. This was focussed upon the impact of cardiovascular events but also included a dichotomous variable for whether the patient had a history of on-trial hypoglycaemic events, which the EAG assumes were SHEs. This estimated a decrement of -0.027 with a p-value of 0.157, this being similar to the -0.029 estimate of Nauck et al.

Pratipanawatr et al [144], sponsored by MSD, analysed EQ-5D data valued using the UK social tariff from a Thai cross-sectional study of sulfonylurea compared to sulfonylurea with metformin among 659 patients with T2DM. Data on hypoglycaemia events was collected using 6 month recall data with patients being classified as to their most severe hypoglycaemia event: none, mild, moderate, severe with 202 (31%) patients having experienced some hypoglycaemia during the preceding 6 months. A multivariate regression that controlled for age, sex, vascular complication, treatment, weight, medication adherence, worry about hypoglycaemia, worry about weight gain and overall satisfaction found that the presence of hypoglycaemia during the preceding 6 months was statistically significantly associated with reduction in quality of life: a worst experienced hypoglycaemia event of mild, moderate or severe reduced quality of life by 0.156, 0.096 or 0.198 respectively.

Peasgood et al [133] analysed data from 2,469 UK patients with T1DM taking part in a DAFNE course who were followed up for 2 years. Quality of life data was collected using the EQ-5D, SF-36 and the EQ-5D VAS. They imply that the EQ-5D was valued using the UK social tariff with a baseline average of 0.839 among a patient group with an average age of 39 years and duration of diabetes of 16 years. Questionnaires were administered at baseline, 1 year and 2 years, with follow-up rates of 58% and 24% respectively, the mean EQ-5D remaining reasonably constant at 0.851 and 0.840 respectively.

Peasgood et al report the distribution of the number of SHEs during the preceding year.

Table 24: Peasgood distribution of the annual number of SHEs

	Baseline	Year 1	Year 2
0	78.4%	89.9%	90.5%
1	9.4%	5.0%	5.4%
2	4.4%	2.0%	1.8%
3	2.2%	1.0%	1.0%
4	1.4%	0.7%	0.8%
5+	4.2%	1.4%	0.6%

While an underestimate, if those experiencing 5+ SHEs are assumed to have experienced 5 SHEs the above suggests annual event rates per patient of 0.51, 0.22 and 0.18 for baseline, year 1 and year 2. It can also be noted that in years 1 and 2 the proportion reporting SHEs is reasonably similar to the 10.3% 3-monthly proportion reported in Currie et al.

Table 25: Peasgood distribution of the annual number of SHEs among those experiencing

	Baseline	Year 1	Year 2
1	43.5%	49.5%	56.5%
2	20.4%	19.8%	18.7%
3	10.2%	9.9%	10.4%
4	6.5%	6.9%	8.3%
5+	19.4%	13.9%	6.3%

Around half of those experiencing SHEs only experienced 1 during the preceding year. The vast majority, over 80% at all time points, experienced at most 4 per year. If it is assumed that those experiencing 5+ experienced only 5 SHEs, among those having had an SHE during the preceding year these correspond to annual rates of 2.38, 2.16 and 1.90 at baseline, year 1 and year 2 respectively. These contrast with the EAG inferred annual rate among the T1DM patients who experienced an SHE of 14.3 for Currie et al.

Peasgood et al undertook linear modelling of the EQ-5D that controlled for a large number of the complications of diabetes. This estimated a -0.0020 fixed effects coefficient and a -0.0022 random effects coefficient for the number of SHEs in the preceding year, though only the random effects coefficient was statistically significant. There may be the possibility of confounding variables or multicollinearity with HbA1c having a statistically significant negative coefficient and the HADS depression score also having a statistically significant coefficient. These might artificially reduce the estimated effect of SHEs upon quality of life.

For the disutility of NSHEs Gordon et al and Currie et al are the papers which provide estimates that conform most closely to the NICE reference case. The key differences between Gordon et al and Currie et al are:

- Gordon et al was specific to T1DM patients receiving insulin while Currie et al had a majority of T2DM patients.
- Gordon et al used data from the RCT of dapagliflozin against placebo within which the trial data definitions, interpretation and collection seem likely to have been more stringently defined and consistently applied than within the postal recall questionnaires of Currie et al.
- The response rate of Gordon et al was high at around 80% of the baseline population and more relevantly at around 90% of those remaining in the trial at the 52 week data analysis point, compared to only 31% for Currie et al.

This leads the EAG to prefer the estimates of Gordon et al over those of Currie et al. The EAG provides a scenario analyse of the estimates of Currie et al assuming that the NSHE rate should be 3-monthly and that the 69% non-responders had the preferences as the 31% responders.

For the disutility of SHEs most papers provide estimates for the presence of SHEs rather than the disutility per annual SHE. If annual SHE rates are of the order reported in Currie et al this is problematic. But if annual SHE rates are more in line with those reported in Peasgood et al this may be less problematic. Subsequent to DAFNE over half of those reporting SHEs only had one SHEs during the preceding year. In this situation any treatment effects upon SHE event rates are more likely to be determining their presence or absence; i.e. going from one to none or none to one SHE.

The EAG adopts the estimates of Gordon et al for SHE disutilities and applies this to the SHE event rate. For relatively rare events like SHEs the short DEPICT-2 4 week window of Gordon et al may be a concern. The EAG supplies a scenario analysis that applies the coefficient of Nauck et al.

Hypoglycaemia events and carer disutilities

Parents are affected by their children having hypoglycaemia events and are fearful of them occurring. Friends and relatives caring for people with T1DM may be similarly affected. The EAG has not identified any research that quantifies these disutilities.

A reasonable upper limit for the effect upon carers might be to assume that they have the same disutility as the patient with T1DM that they are caring for.

The EAG will provide a scenario analysis that simply doubles the disutilities associated with hypoglycaemia events; i.e. that relates to the subset of patients being cared for and that assumes carers experience the same disutility as the patient.

7.2.1.7 Costs

Training costs

The Diabetes Technical Network has provided estimates of the number of OP visits and nursing time required to move from MDI+CGM to CSII+CGM and from MDI+CGM to HCL. There is no difference between these estimates; i.e. going onto a pump using CSII+CGM involves much the same visits and staff time as going onto a pump using HCL. As a consequence, the EAG base case ignores training costs.

This does not cover the situation of moving from CSII+CGM to HCL, with most patients moving from isCGM to rtCGM and with some further training required for changing to HCL pump use. The Diabetes Technical Network indicates that pre-fitment, fitment and additional post fitment vists would total 3 consultant led OP visits, 3 nurse led OP visits, 3 nurse follow up calls or e-mails plus an additional nurse hour for a fitment visit. Costing these at £208 and £144 of the Diabetic Medicine WF01A NHS 2020/21 NHS Schedule of Costs and £51 per hour for Band 5 nursing time spent on patient activities from the 2021 PSSRU Unit costs of Health and Social Care, with an assumption of an average 10 minutes per phone call or e-mail, this results in an additional cost of £1,132.

Treatment costs

To cost the technologies the EAG uses current list prices supplied by the NHS Supply Chain. While the costs of HCL pumps and consumables differ slightly between systems the total 4 year costs are similar, with the exception of one system which is around an annual average of £500 more than the unweighted average. This also applies to the LGS/PLGS systems. The ERG applies the unweighted averages for year1 and years 2, 3 and 4 and provides a scenario analysis which increases these by £500 for both HCL and LGS/PLGS.

In response to EAG clarification questions Dexcom provided data suggesting that the average G6 sensor duration was slightly less than the maximum 10 days, with around 87% lasting for 10 days and a mean duration of 9.5 days or 95% of maximum duration. Medtronic also provided median durations of GS3 of [redacted] and G4S of [redacted]. [redacted] This is reasonably aligned with the 95% mean of Dexcom. The EAG inflates the cost of all CGM sensors by 5% to account for this.

The EAG assumes that only 10% of Dexcom users require a dedicated receiver due to the near ubiquity of smartphones.

Table 26: Pump and consumable costs

	Year 1	Years 2-4	4 yr Total	Average
HCL	£7,931	£5,015	£22,975	£5,744
LGS/PLGS	£7,135	£4,455	£20,498	£5,125
CSII+CGM	£5,480	£3,751	£16,734	£4,184

The EAG adds an additional annual average £315 insulin cost to all regimes, based upon a daily average of 50IU.

Companies have indicated that prices will change for the next financial year and some products have confidential volume discounts. The EAG addresses these aspects in the cPAS appendix.

Ongoing visits and the costs of micro and macro vascular complications

It is assumed that without complications the average patient once established on treatment is seen in outpatient clinic once per quarter. This is costed at the NHS reference cost for consultant led non-admitted face to face follow-up appointment for diabetic medicine. This cost is reasonably different for 2019-20, £154, compared to 2020-21, £208. The proportion of follow-up visits that were not face to face also differed, 9.6% compared to 49.6%. It seems reasonable to assume that the 2020-21 costs were in part driven by Covid with only the more serious cases being seen in clinic. For this reason the EAG will apply the 2019-20 of £154 uprated by the NHSCII pay and prices index 3.08% to £160 in 2020-21 prices resulting in an annual routine OP cost of £640.

The costs of other routine management for e.g. ACE inhibitors and the proportion in receipt of these and the costs of micro and macro vascular complications are taken from NG17, inflated to 2019-20 prices. All patients are assumed to receive screening.

Table 27: Costs of ongoing management and proportion receiving

		In receipt	
Complication	Cost	Primary prevention	Secondary prevention
Statins	£28.42	47%	84%
Aspirin	£16.96	59%	88%
ACE-I/ARB	£23.71	21%	76%
Stopping ACE-I/ARB due to AEs	£40.72		
Microalbuminuria screening	£4.41		
Gross proteinuria screening	£4.41		
Eye screening	£56.44		

Table 28: Costs of micro and macro vascular complications

Complication	Cost
MI 1st year	£4,231
MI subsequent years	£894
Angina 1st year	£7,265

Angina subsequent years	£327
CHF 1st year	£4,077
CHF subsequent years	£2,945
Stroke 1st year	£4,728
Stroke subsequent years	£175
Stroke death within 30 days	£1,332
PVD 1st year	£1,380
PVD subsequent years	£600
Haemodialysis 1st year	£34,855
Peritoneal dialysis	£31,357
Renal transplant (1st year)	£21,810
Renal transplant (2nd year)	£8,649
Laser treatment	£151
Cataract operation	£962
Following cataract operation	£211
Blindness 1st year	£7,858
Blindness subsequent years	£7,592
Neuropathy 1st year	£39
Neuropathy subsequent years	£39
Active ulcer	£3,654
Amputation event	£8,761
Post amputation	£26,653

NSHE costs

It is assumed that there are no costs to the NHS or PSS from NSHEs.

SHE costs

A number of previous NICE assessments have applied the resource use estimates of Leese et al [4] to estimate the cost per SHE that requires medical attention. Leese et al identified 244 hypoglycaemia events requiring medical attention in Tayside during the year from June 1997, the balance between these being roughly equally split between

T1DM and T2DM[§§§§]. These were estimated to cost £141,120 when uprated from 2002 prices to 2021 prices, equivalent to an average of £578 per event requiring outside medical assistance.

NG17 used Heller et al [123] to cost severe SHEs, separately for those with T1DM, those with T2DM on insulin and those with T2DM on OADs. They analysed 15 trials, the mean ages being around 42 years for T1DM, 58 years for T2DM on insulin and 57 years for T2DM on OADs. The trials yielded 536 severe glycaemia events for analysis, the proportion of T1DM patients with severe hypoglycaemia being around 11% for the two 26 weeks trials, and 12% and 15% for the two 52 week trials. The majority of events, 78% (N=420) occurred among the T1DM patients. The use of medical services for T1DM patients was slightly lower at 37.9% of events than the 47.4% of T2DM patients but given that most SHEs were among T1DM patients this was little different from the overall average of 39.9%. Across all events 29.3% required an ambulance or emergency room team, 11.9% led to hospital or emergency room assistance and 6.7% required hospital admission for at least 24 hours, these averages being only slightly different for T1DM patients at 31.0%, 9.5% and 5.0% respectively.

NG17 also cited Hammer et al 2009, sponsored by Novo Nordisk, who used resource use questionnaire data from 201 UK T1DM and T2DM patients, all of whom were using insulin and had experienced at least one SHE in the last year. The mean direct costs per SHE, inflated to 2021 prices using the HCHS to 2015 and the NHSCII thereafter, were estimated as £36 for those not requiring external medical assistance, these costs being mostly due to follow-up contacts, £327 for those requiring medical treatment in the community and £1,113 for those requiring hospital treatment. The weighted average of these was £374 which is aligned with the £370 of NG17.

[§§§§] Even rates of 11% for T1DM and 1.7% for T2DM patients were balanced out by the higher number of T2DM patients.

Applying the weights of Heller et al for T1DM patients results in a lower cost of £260, this being £36 for those with no outside medical assistance and £628 for those requiring outside medical assistance. It is uncertain how accurately subsequent follow-up contacts and visits can be ascribed exclusively to preceding SHEs given that these patients will be receiving ongoing care. Excluding these costs and using the T1DM weights of Heller et al for T1DM patients results in a lower average cost of £206, this being £1.83 for those with no outside medical assistance and £542 for those requiring outside medical assistance. The cost of between £542 and £628 for events requiring outside medical assistance is quite well aligned with the £578 cost of Leese et al, though it should be borne in mind that the latter is a roughly equal mix between events among T1DM patients and T2DM patients.

In the light of the above, for its base case the EAG will apply a cost of £1.83 for SHEs not requiring outside medical attention and of £542 for those requiring medical attention, with it being assumed that 37.9% of SHEs require medical attention. A scenario analysis that applies £36 for SHEs not requiring outside medical attention and of £628 for those requiring medical attention will be supplied. A scenario that costs all SHEs at the 2021 updated £381 of NG17 will also be supplied, somewhat higher than the base case average of £207 despite the same sources being cited.

7.2.2 EAG cost effectiveness modelling results

7.2.2.1 EAG base case

The base case modelling provides the following disaggregate estimates.

Table 29: EAG base case disaggregate results

		PLGS		HCL	
	CSII	Value	net vs CSII	Value	net vs CSII
LYs Undiscounted	32.499	32.685	0.186	32.957	0.458
QALYs					
iQVIA CDM modelled	14.232	14.291	0.059	14.392	0.160
NHSEs	0.000	0.000	0.000	0.000	0.000

SHEs	0.000	0.000	0.000	0.000	0.000
Total QALYs	14.232	14.291	0.059	14.392	0.160
Costs					
Treatment	£86,564	£105,258	£18,694	£117,749	£31,185
Routine OP	£12,182	£12,222	£40	£12,279	£97
SHEs	£0	£0	£0	£0	£0
Other management	£1,700	£1,708	£8	£1,721	£21
CVD	£4,691	£4,649	-£42	£4,531	-£160
Renal	£10,365	£10,367	£3	£9,943	-£421
Ulcer/Amp./Neuropathy	£889	£898	£9	£880	-£9
Eye	£18,270	£17,604	-£666	£16,185	-£2,085
Total Costs	£134,661	£152,706	£18,045	£163,289	£28,628

Undiscounted survival is estimated to increase by 0.458 years through the use of HCL compared to CSII+CGM. But in part due to discounting which reduces the net survival gain to 0.149, the patient gain is only 0.160 QALYs. The net treatment cost of £31,185 is partly offset by renal savings of £421 and eye savings of £3,085, resulting in a net cost of £28,628. This results in the following cost effectiveness estimates.

Table 30: EAG base case cost effectiveness estimates

	CSII	PLGS	HCL
LYs Undiscounted	32.499	32.685	32.957
Total QALYs	14.232	14.291	14.392
Total Costs	£134,661	£152,706	£163,289
ICER vs CSII	..	£305,852	£178,925

The results suggest that PLGS is extendedly dominated by HCL, but that HCL has a poor cost effectiveness estimate of £179k per QALY.

The iQVIA CDM does not permit periodic capital costs to be modelled, so for the deterministic modelling the EAG uses the modelled OS curves to estimate treatment costs. This approach cannot be adapted to the probabilistic modelling so the EAG

approximates these costs within the iQVIA CDM by applying the four yearly annual average costs for CSII+CGM and HCL respectively, the iQVIA CDM only permitting pairwise comparisons. This results in a central cost effectiveness estimate of £186k per QALY for HCL compared to CSII+CGM which is similar to the deterministic estimate, and probabilities of HCL being cost effective at thresholds of £20k, £30k, £50k and £100k per QALY of 21%, 31%, 39% and 47% respectively.

8.2.2.2 EAG scenario analyses

The EAG presents the following scenario analyses.

- SA01: Revising the NMA to [66](a) be restricted to only adult studies and (b) exclude Banhamou [66].
- SA02: Application of the NHSE adult pilot (a) patients baseline characteristics and (b) patients baseline characteristics and HbA1c change of [redacted] for HCL with an assumption of no change for CSII+CGM and (c) SA02b with the costs of complications reduced by their possible overestimation as identified in McEwan et al [121]
- SA03: Time horizons of 8, 12 and 24 years.
- SA04: Durations of HbA1c effect of 5, 10 and 20 years.
- SA05: Inclusion of NSHEs, based upon an HCL annual rate of (a) 20.8, (b) 57.2 and (c) 13.0 with comparator rates based upon the ratio of time below 3 mmol/l, valued using Gordon et al [129]
- SA06: Inclusion of NSHEs as per SA05a and SHEs, valued using Gordon et al
- SA07: Inclusion of NSHEs as per SA05a valued using Currie et al [23] and SHEs valued using (a) Currie et al and (b) Nauck et al [142]
- SA08: SA06 with SHEs costed at (a) £36 for no medical attention and £628 for medical attention, and (b) £381 for all SHEs
- SA09: SA06 with a doubling of the NSHE and SHE quality of life effects to reflect possible carer effects

- SA10: CSII is (a) 85% isCGM and 15% rtCGM and (b) 95% isCGM and 5% rtCGM
- SA11: HCL and PLGS average annual cost being £500 higher
- SA12: Additional £1,132 training cost for transferring from CSII+CGM to either PLGS[*****] or HCL
- SA13: Revising non-specific mortality to (a) all-cause mortality and (b) non-specific mortality that also excludes all deaths associated with hypertension.
- SA14: Annual 0.045% HbA1c worsening

Within these results PLGS is extendedly dominated throughout, and for reasons of space the EAG does not consider it further.

Table 31: EAG scenario analyses' ICERs: HCL vs CSII+CGM

	Δ Costs	Δ QALYs	ICER
Base case	£28,628	0.160	£179k
SA01a: Only adult studies	£28,734	0.141	£204k
SA01b: Benhamou excluded	£28,096	0.169	£166k
SA02a: NHS adult pilot baseline characteristics	£25,775	0.205	£126k
SA02b: NHS adult pilot characteristics and effect	£12,447	1.004	£12,398
SA02c: SA02b + reduced complication costs	£21,669	1.004	£21,583
SA03a: 8 year time horizon	£12,740	0.014	£910k
SA03b: 12 year time horizon	£16,601	0.025	£664k
SA03c: 24 year time horizon	£23,975	0.073	£328k
SA04a: 5 year HbA1c effect	£29,571	0.045	£657k
SA04b: 10 year HbA1c effect	£28,887	0.068	£425k
SA04c: 20 year HbA1c effect	£28,369	0.115	£247k

[*****] The EAG did not ask the Diabetes Technical Network about transferring from CSII+CGM to PLGS. But since the main issue identified for transferring to HCL was the move from isCGM to rtCGM the EAG assumes that the same costs will be incurred transferring to PLGS.

SA05a: NSHEs with HCL 20.8 annual	£28,628	0.170	£169k
SA05b: NSHEs with HCL 57.2 annual	£28,628	0.173	£166k
SA05c: NSHEs with HCL 13.0 annual	£28,628	0.168	£170k
SA06: HEs: NSHEs and SHEs	£28,325	0.174	£163k
SA07a: SA06 + HEs Currie values	£28,325	0.235	£121k
SA07b: SA06 + HEs Currie and Nauck values	£28,325	0.260	£109k
SA08a: SA06 + £36/£628 SHE cost	£28,246	0.174	£162k
SA08b: SA06 + £381 SHE cost	£28,069	0.174	£161k
SA09: SA06 + HEs double quality of life effect	£28,325	0.188	£151k
SA10a: CSII 85% isCGM 15% rtCGM	£27,117	0.160	£169k
SA10b: CSII 95% isCGM 5% rtCGM	£30,139	0.160	£188k
SA11: HCL/PLGS annual cost £500 more	£38,244	0.160	£239k
SA12: CSII to HCL training cost £1,132	£29,760	0.160	£186k
SA13a: All-cause mortality	£27,846	0.139	£200k
SA13b: Non-specific mortality excl. H.T.	£28,556	0.171	£167k
SA14: Annual 0.045% HbA1c worsening	£27,694	0.181	£153k

8 Discussion

8.1 Summary of key results

The aim of the RCTs was generally to demonstrate improvement of glycaemic control with use of HCL. We identified one study by Stewart of pregnant women included only 16 participants followed for 4 weeks; the population, study design and outcomes in this study were clearly different from other studies so that transitivity in NMA including Stewart is threatened. This was addressed by conducting a sensitivity analysis (see Results of the subgroup and sensitivity analyses compared to the overall NMA results)

There were relatively few studies, they were of small size encompassing a total of ~450 HCL recipients followed for between 4 and 26 weeks accumulating approximately 110 person years of observation. Inclusion criteria applied for the studies were relatively narrow and most participants had reasonably good glycaemic control at entry, as indicated in most of those studies reporting baseline TIR (3.9 to 10 mmol/L) at greater than 50% (range 47% to 62%), and baseline HbA1c at between 7% and 8%. There was considerable heterogeneity across studies regarding the age of participants, some studies presented results stratified by age groups. The relevance of the RCT populations and outcome measure results for the decision problem is debatable and not easy to judge. The quality of studies assessed according to Cochrane criteria was associated with either low risk of bias or some concern.

In the HCL arm of RCTs the intervention achieved a statistically significant improvement in HbA1c % that decreased mean difference 0.28 (-0.34 to -0.21), in TIR between 3.9 to 10 mmol/L significantly increased % TIR (between 3.9 – 10.0 mmol/L) mean difference 8.6 (7.03 to 10.22), and in hyperglycaemic levels (significantly decreased TIR (% above 10.0 mmol/L), with a mean difference of -7.2 (-8.89 to -5.51). Control arms also showed improvement but this was less than that seen with HCL. Irrespective of type of intervention used in the control arms these outcomes were statistically superior in the HCL arm vs. control arm. Available evidence from the RCTs suggests that these gains in

glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration. Adverse events were reported in some studies and were mainly low. Patient reported outcomes were assessed using various methods and did not result in clear trends.

The estimated cost effectiveness of PLGS compared to CSII+CGM is consistently worse than that of HCL compared to CSII+CGM, for both the base case and the scenario analyses. PLGS is extendedly dominated by HCL and the EAG does not consider it further

Given the NMA estimated effect upon HbA1c of -0.29% for HCL compared to CSII+CGM the cost effectiveness of HCL is poor. Net treatment costs are estimated to be £31,185, cost offsets from fewer complications and in particular -£2,085 from reduced eye complications, probably mostly severe visual loss, and -£421 from reduced renal complications, probably mostly ESRD, reduce the net total cost to £28,628. The net undiscounted survival gain is 0.458 years, this contributing to a patient gain of 0.160 QALYs. This results in a base case deterministic cost effectiveness estimate of £179k per QALY, a probabilistic central estimate of £186 per QALY and probabilities of HCL being cost effective at £20k per QALY and £30k per QALY thresholds of 21% and 31% respectively.

The NHS adult pilot baseline patient characteristics result in a reasonable improvement to £126k per QALY. Assuming that the pilot's [redacted] in HbA1c is the net effect for HCL over CSII+CGM results in net treatment costs of £35,912. Cost offsets from reduced eye complications of -£16,442 and from reduced renal complications of -£6,731 help reduce the net total cost to £12,447. The net undiscounted survival gain increases to 3.1 years, this contributing to the increased patient gain of 1.004 QALYs. The resulting cost effectiveness estimate of £12,398 per QALY is an order of magnitude better than the EAG base case. The EAG review of the published model validation work highlights that incidences of renal and eye complications may be overestimated.

Adjusting the costs of these roughly doubles the NHS pilot scenario cost effectiveness estimate to £21,583 per QALY. Note that this does not take into account any possible effects upon quality of life or life expectancy.

The EAG review of the published model validation work also highlights that modelling of longer term effects is more uncertain. Time horizons of 8, 12 and 24 years worsen the cost effectiveness estimate to £910k, £664k and £328k per QALY respectively.

The duration of the HbA1c effect is also uncertain. Limiting this to 5, 10 and 20 years while retaining a time horizon of 60 years worsens the cost effectiveness estimate to £657k, £425k and £247 per QALY respectively.

The EAG base case does not include the effects of symptomatic or severe hypoglycaemia events due to the high uncertainty around annual event rates and the lack of direct evidence that HCL has an effect upon these. Incorporating non-severe symptomatic hypoglycaemia event rates, inferred from an annual rate of 20.8 for HCL with an annual rate of 27.1 for CSII+CGM based upon the ratio of times below 3.0 mmol/l, improves the cost effectiveness estimate to £169k per QALY. Annual rates of 57.1 and 13.0 for HCL result in cost effectiveness estimates of £166k and £170k per QALY. Including severe hypoglycaemia events improves the cost effectiveness to £163k per QALY.

If both non-severe and severe hypoglycaemia events are included and are valued using the same source as NG17 the cost effectiveness improves £121k per QALY, while if severe events are valued using another reasonable source within the literature the cost effectiveness improves further to £109k.

Doubling the quality of life effect of hypoglycaemia events to reflect possible carer effects improves the cost effectiveness estimate from £169k to £151k per QALY. Increasing the costs of severe hypoglycaemia events has relatively little effect upon the cost effectiveness estimate.

Reducing the proportion of CSII+CGM that is isCGM from 90% to 85% improves the cost effectiveness to £169k per QALY while increasing it to 95% worsens it to £188k per QALY. Additional annual HCL costs of £500, as may apply to some HCL systems,

worsen the cost effectiveness to £239k per QALY, while training costs for cross over from CSII+CGM to HCL of £1,132 worsen it to £186k per QALY.

The EAG non-specific mortality estimates may be too low if there are competing risks. All-cause mortality is too high but it forms an upper bound. Its application results in a cost effectiveness estimate of £200k per QALY. There may be an argument for removing deaths associated with hypertension from the non-specific mortality. This improves the cost effectiveness estimate to £167k per QALY.

If T1DM is associated with an annual worsening of 0.045% in HbA1c this improves the cost effectiveness estimate by a reasonable amount to £153k per QALY.

The key model inputs are:

- The net effect upon HbA1c.
- The duration of the net effect upon HbA1c.
- The model time horizon.
- Treatment costs.

Other important model inputs are:

- Hypoglycaemia event rates.
- What source is used to value the disutilities of hypoglycaemia event rates.
- What non-specific mortality is applied.
- Whether HbA1c worsens annually among T1DM patients and if so by how much.

The key modelling uncertainties are around:

- Overall survival gains.
- Severe visual loss and its effects upon survival, quality of life and costs.
- ESRD and its effects upon survival, quality of life and cost.

8.2 Generalisability of results

The modelled cost effectiveness of HCL is driven by the change in HbA1c and how long that change persists, the latter depending upon modelling assumptions and the baseline patient age. The larger is the HbA1c effect and the longer it persists, the greater is the difference in the modelled proportions having serious visual loss and ESRD. Assuming an annual worsening of HbA1c compounds this effect. If it is assumed that the HbA1c effect persists for the patient lifetime, the baseline age determines the duration of the HbA1c effect. The EAG base case applies the national diabetes audit mean age of those on pumps, sampling this using the standard deviation.

Exploratory modelling of a paediatric population as presented in appendix **Error! Reference source not found.** very broadly mirrors the adult results, but the EAG has reservations about the reliability the iQVIA CDM for modelling a paediatric population. It also raises questions about durations of effects and how the transition from childhood to adulthood may affect these.

The EAG has not considered the cost effectiveness of HCL for pregnant women due to the lack of evidence. It notes the relationship between HbA1c and birth defects. If HCL reduces HbA1c in pregnant women to the same extent as in the adult population the short term additional costs of HCL will have some immediate cost offsets from reduced birth defects, with the potential for additional benefits to the child at no additional cost. It also seems likely that the baseline age of pregnant women is below the national diabetes audit mean age which is likely to further improve cost effectiveness. If after giving birth women remain on HCL into the long term the cost effectiveness estimate of HCL will trend towards that of the adult female T1DM population of the same age, but will remain superior to it.

8.3 Strengths and limitations of analysis

The clinical analysis prioritised randomised controlled evidence that provides superior evidence to other study designs. The clinical evidence also provided additional observational evidence to compare to the NHS audit studies. The analysis was conducted

following Cochrane Handbook for Systematic Reviews of Interventions. Forest plots and network-meta analysis results were presented. Transitivity of the network is threatened because the RCTs were heterogeneous in multiple respects including trial design (parallel groups or cross over design with wash-out phase between different treatments), participants' age, number of participants, and other demographics including run-in times, duration of observation periods, and number and types of previous treatments. Studies screened relatively small numbers of patients. The number of participants randomised ranged from < 20 to 135. However, sensitivity and subgroup analysis were performed and provided some reassurance in our findings. The quality of observational studies is generally poor. Nevertheless, the outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Half of the included studies included UK centres therefore represents some relevance to UK settings. There was very limited evidence on pregnancy and the effectiveness of HCL in pregnant women remains unclear.

A strength and a weakness of the analysis is the availability of published iQVIA CDM validation data against long terms observational studies. This validation data relates at least in part to earlier model iterations of the iQVIA CDM than that used by the EAG. The strength is its availability, it often being absent from other NICE assessments. But it highlights some uncertainty about the reliability of the modelling of the incidence of retinopathy, in one validation exercise this having been overestimated by around 30% for the intervention arm of the EDIC trial, and of the incidence of ESRD, this having been overestimated by around 250% for the intervention arm of the EDIC trial. Modelling of survival appears reasonable in the medium term but the longer term modelling of survival is subject to more uncertainty.

The net HbA1c effect, its duration and the resulting costs offsets from reduced eye and renal complications determine whether HCL is likely to be estimated to be cost effective at conventional thresholds. The trials were of relatively short duration which argues for consideration of shorter effect durations.

There is an argument for reducing the eye and renal cost offsets proportionately to their possible overestimation. Uncertainty around the modelled overall survival argues for consideration of shorter time horizons.

The uncertainty around the modelled long term survival coupled with uncertainty about how much of the clinical data underlying model construction was drawn from a paediatric population causes the EAG to view paediatric modelling using the iQVIA CDM with some caution.

A weakness of the analysis is the lack of data on the effect of HCL upon symptomatic and severe hypoglycaemia events. The EAG has inferred these from the ratio of time below 3.0mmol/l for HCL compared to that of the other comparators, coupled with event rates for HCL. There is considerable uncertainty around these and the EAG only presents the possible effects of hypoglycaemic events within scenario analyses. It should also be noted that the EAG preferred quality of life function for hypoglycaemia events differs from that of NG17 and suggests a somewhat smaller effect.

8.4 Conclusions

RCTs of HCL interventions in comparison CSII+CGM or sensor augmented pump therapy achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10 mmol/L, and in hyperglycaemic levels. The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range (3.9 to 10 mmol/L), and % time above range >10 mmol/L all improved on transfer to HCL.

Well-designed RCTs are needed to explore the effectiveness of hybrid closed loop systems in larger samples of people, with longer follow-ups, and in in pregnant women. Trials that include a wider variety of participants, for example people with poor glycaemic control, or who live in remote or rural areas, would be helpful. Trials that collect data to support economic modelling of hybrid closed loop systems, such as quality of life and adverse events would be very beneficial. Studies are required to clearly describe comparators and should ideally use real time GM+CSII or FGM+CSII as the

control group, as these are the most relevant comparators. There is a lack of evidence on the long term effect of the hybrid closed loop system and especially on clinical outcomes such as cardiovascular disease. Carer outcomes and patient reported outcomes are not systematically captured or reported.

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10 APPENDICES

10.1 Appendix 1: Literature Search Strategies

10.1.1 Record of searches – Clinical effectiveness

Overview:

Database / website	Date searched (date updated)	Number of records + update number of records = TOTAL
MEDLINE ALL (Ovid)	31/03/21 (11/04/22)	1,914 + 789 = 2703
Embase (Ovid)	31/03/21 (11/04/22)	4,267 + 1210 = 5477
Science Citation Index & Conference Proceedings - Science (Web of Science)	31/03/21 (12/04/22)	2,190 + 514 = 2704
Cochrane Library (Wiley)	31/03/21 (12/04/22)	1,327 [all CENTRAL, 0 CDSR] + 159 [all CENTRAL, 0 CDSR] = 1486
Clinicaltrials.gov	12/04/21 (12/04/22)	392 + 57 = 449
HTA database (CRD)	07/04/21	16*
International HTA database (INAHTA)	07/04/21 (06/04/22)	22 + 10 = 32
NIHR Journals Library	12/04/21 (12/04/22)	5 + 1 = 6
AHRQ website	12/04/21 (06/04/22)	1 + 0 + 1
CADTH website	12/04/21 (07/04/22)	14 + 2 = 16
SBU website	12/04/21 (07/04/22)	0 + 0 = 0

* No new records in database so search did not require updating

Note: The WHO International Clinical Trials Registry Platform (ICTRP) was not searched due to being unavailable between 12/4/21 and 22/4/21.

Total results: 10,148 + 2742 from update = 12,890
Total after 4,211 duplicates removed + 1005 duplicates within update results + 382 duplicates with original results removed = 7292

Also searched for background information about hybrid closed loop technologies:

Website	Date searched	Number of records
FDA devices databases	21/04/21	12
MHRA (via www.gov.uk)	22/04/21	7

Search strategies:

Note: See below each database strategy for details of update searches

Medline (via Ovid)

Date searched: 31/03/21
Database: Ovid MEDLINE(R) ALL <1946 to March 30, 2021>
Search Strategy:
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1 Diabetes Mellitus, Type 1/ (77349)
2 Diabetic Ketoacidosis/ (6613)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kf,ti. (56549)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kf,ti. (28252)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kf,ti. (33812)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kf,ti. (23572)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kf,ti. (11574)
8 Hyperglycemia/ (28751)
9 Hypoglycemia/ (27924)
10 (hyperglyc?em$ or hypoglyc?em$).ab,kf,ti. (116536)
11 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kf,ti. (151415)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 [population: T1DM] (365002)
13 Pancreas, Artificial/ (816)
14 closed loop.ab,kf,ti. (10516)
15 (artificial adj2 (pancreas or beta cell$)).ab,kf,ti. (1729)
16 (bionic adj2 pancreas).ab,kf,ti. (25)
17 (Automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kf,ti. (285)
18 ((minimed or medtronic) and (670G or 780G)).ab,kf,ti. (57)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,kf,ti. (175)
20 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (12163)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kf,ti. (7798)
22 SAPT.ab,kf,ti. (533)
23 predictive low glucose.ab,kf,ti. (95)
24 basal iq.ab,kf,ti. (9)
25 ((minimed or medtronic) and 640G).ab,kf,ti. (33)
26 (paradigm$ adj3 (veo or pump$)).ab,kf,ti. (57)
27 (veo adj3 pump$).ab,kf,ti. (9)
28 (g4 adj3 platinum).ab,kf,ti. (58)

29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,kf,ti. (14)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (8467)
31 Insulin Infusion Systems/ (5477)
32 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kf,ti. (14806)
33 (pump$ adj2 (therap$ or treatment$)).ab,kf,ti. (3223)
34 ((subcutaneous adj2 insulin$) or CSII).ab,kf,ti. (3863)
35 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,kf,ti. (376)
36 (medtronic adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (719)
37 (tandem adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (925)
38 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,kf,ti. (34)
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 [insulin pumps/CSII] (20952)
40 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kf,ti. (5859)
41 (glucose adj (sensor$ or sensing)).ab,kf,ti. (4186)
42 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kf,ti. (4526)
43 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,kf,ti. (2410)
44 40 or 41 or 42 or 43 [continuous or flash glucose monitors] (13031)
45 (2014082* or 2014083* or 201409* or 201410* or 201411* or 201412* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).dt,ez,da. [added to database since search for previous DAR in 2014] (8960844)
46 12 and 20 and 45 [T1DM and closed loop + date limit] (1134)
47 12 and 30 and 45 [T1DM and SAPT + date limit] (498)
48 12 and 39 and 44 and 45 [T1DM and pumps and GMs + date limit] (1090)
49 46 or 47 or 48 (1951)
50 limit 49 to english language (1903)
51 exp Pregnancy/ (912957)
52 exp Pregnancy Complications/ (435723)
53 Perinatal Care/ or Preconception Care/ or Prenatal Care/ (35143)
54 exp Cesarean Section/ (46694)
55 Pregnant Women/ (9180)
56 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kf,ti. (1208728)
57 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kf,ti. (352238)
58 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kf,ti. (364876)
59 apgar.ab,kf,ti. (12586)
60 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 [pregnancy, planning pregnancy, pregnancy complications; broad] (1735176)
61 exp Insulin/ and Injections, Subcutaneous/ (2455)

62 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (1309)
63 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (563)
64 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (10207)
65 MDI.ti,ab,kf. (3832)
66 (injection adj3 therapy).ti,ab,kf. (4196)
67 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,kf. (1376)
68 (short acting adj3 insulin).ti,ab,kf. (576)
69 (rapid acting adj3 insulin).ti,ab,kf. (799)
70 or/61-69 [insulin injections] (21919)
71 Blood Glucose Self-Monitoring/ (7126)
72 Blood Glucose/ (167907)
73 (blood glucos$ or blood sugar$).ab,kf,ti. (87354)
74 72 or 73 (210595)
75 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kf,ti. (43222)
76 (capillary adj4 (test$ or measur$)).ab,kf,ti. (5082)
77 75 or 76 (47993)
78 74 and 77 (5789)
79 SMBG.ab,kf,ti. (1195)
80 glucometer$.ab,kf,ti. (1146)
81 71 or 78 or 79 or 80 [self monitoring of blood glucose] (11381)
82 44 and 70 [continuous or flash GMs AND MDI] (488)
83 81 and 39 [SMBG AND CSII] (1709)
84 82 or 83 (2022)
85 12 and 60 and 84 and 45 [T1DM and pregnancy and any of the comparator groups specific to this population + date limit] (55)
86 limit 85 to english language (54)
87 50 or 86 (1914)

Update
Date searched: 11/04/22
Re-ran above search with search line 45 altered to:
45 ("20210331" or 202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022*).dt,ez,da. [added to database since original MTA search in March 2021]
Total:
87 50 or 86 (789)

Search strings used in the previous technology assessment on integrated sensor-augmented pump therapy systems were used as the basis for developing selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections:

Appendix 1: Literature search strategies. In: Riemsma R, Corro Ramos I, Birnie R, Büyükkaramikli N, Armstrong N, Ryder S, et al. Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation. Health Technol Assess 2016;20(17):v-xxxi, 1-251. http://dx.doi.org/10.3310/hta20170

The following were used as sources of search terms for pregnancy and related concepts:

Tessier V. Périnatalité: Perinatality: Rappel favorisé sur la précision. Canadian Health Libraries Association - Association des bibliothèques de la santé du Canada; 2017. URL: https://extranet.santecom.qc.ca/wiki/!biblio3s/doku.php?id=concepts:perinatalite (Accessed 26 April 2021).

Kyrgiou M, Mitra A, Arbyn M, Paraskevaidi M, Athanasiou A, Martin-Hirsch PPL, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2015. http://dx.doi.org/10.1002/14651858.CD008478.pub2

Cochrane Pregnancy and Childbirth's Trials Register: Detailed search methods used to maintain and update the Specialised Register. 2018. URL: https://pregnancy.cochrane.org/sites/pregnancy.cochrane.org/files/public/uploads/cochrane_pregnancy_and_childbirth_search_methods_2018_1.docx (Accessed 26 April 2021).

Embase (via Ovid)

Date searched: 31/03/21
Database: Embase <1974 to 2021 March 30>
Search Strategy:
---

1 insulin dependent diabetes mellitus/ (120636)
2 diabetic ketoacidosis/ (13211)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kw,ti. (89362)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kw,ti. (39641)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kw,ti. (42438)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kw,ti. (41350)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kw,ti. (17665)
8 hypoglycemia/ or insulin hypoglycemia/ or nocturnal hypoglycemia/ or hyperglycemia/ (169981)
9 (hyperglyc?em$ or hypoglyc?em$).ab,kw,ti. (171413)
10 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kw,ti. (219463)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 [population: T1DM] (552812)
12 exp artificial pancreas/ (2518)
13 "glucose monitoring/insulin pump system"/ (19)
14 closed loop.ab,kw,ti. (13542)
15 (artificial adj2 (pancreas or beta cell$)).ab,kw,ti. (2728)
16 (bionic adj2 pancreas).ab,kw,ti. (84)
17 (automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kw,ti. (501)
18 ((minimed or medtronic) and (670G or 780G)).ab,dm,dv,kw,ti. (204)

19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,dm,dv,kw,ti. (452)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (16556)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kw,ti. (9751)
22 SAPT.ab,kw,ti. (498)
23 predictive low glucose.ab,kw,ti. (216)
24 basal iq.ab,dm,dv,kw,ti. (35)
25 ((minimed or medtronic) and 640G).ab,dm,dv,kw,ti. (162)
26 (paradigm$ adj3 (veo or pump$)).ab,dm,dv,kw,ti. (251)
27 (veo adj3 pump$).ab,dm,dv,kw,ti. (63)
28 (g4 adj3 platinum).ab,dm,dv,kw,ti. (215)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,dm,dv,kw,ti. (56)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (10819)
31 insulin infusion/ (8355)
32 insulin pump/ or implantable insulin pump/ (7934)
33 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kw,ti. (23686)
34 (pump$ adj2 (therap$ or treatment$)).ab,kw,ti. (6128)
35 ((subcutaneous adj2 insulin$) or CSII).ab,kw,ti. (7275)
36 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,dm,dv,kw,ti. (1653)
37 (medtronic adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (3028)
38 (tandem adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (1170)
39 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,dm,dv,kw,ti. (174)
40 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 [insulin pumps/CSII] (36787)
41 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kw,ti. (10566)
42 (glucose adj (sensor$ or sensing)).ab,kw,ti. (5539)
43 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kw,ti. (8864)
44 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,dm,dv,kw,ti. (4605)
45 41 or 42 or 43 or 44 [continuous or flash glucose monitors] (20571)
46 11 and 20 [T1DM and closed loop] (4001)
47 11 and 30 [T1DM and SAPT] (1703)
48 11 and 40 and 45 [T1DM and pumps and GMs] (4215)
49 46 or 47 or 48 (7448)
50 limit 49 to dc=20140825-20210331 (4300)
51 limit 50 to english language (4177)
52 exp pregnancy/ (688558)
53 exp pregnancy disorder/ (555248)
54 exp cesarean section/ (101840)
55 pregnant woman/ (87032)
56 pregnancy outcome/ (63986)
57 perinatal care/ or prepregnancy care/ or prenatal care/ (57151)

58 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kw,ti. (1447977)
59 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kw,ti. (455281)
60 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kw,ti. (465863)
61 apgar.ab,kw,ti. (19929)
62 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 [pregnancy, planning pregnancy, pregnancy complications; broad] (1956753)
63 blood glucose monitoring/ (28256)
64 glucose blood level/ (263683)
65 (blood glucos$ or blood sugar$).ab,kw,ti. (130425)
66 64 or 65 (300041)
67 self monitoring/ (8173)
68 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kw,ti. (67932)
69 (capillary adj4 (test$ or measur$)).ab,kw,ti. (6773)
70 67 or 68 or 69 (76712)
71 66 and 70 (9965)
72 SMBG.ab,kw,ti. (2497)
73 glucometer$.ab,kw,ti. (2300)
74 63 or 71 or 72 or 73 [self monitoring of blood glucose] (35552)
75 insulin/ and exp injection/ (5679)
76 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (2612)
77 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (783)
78 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (15088)
79 MDI.ab,kw,ti. (6716)
80 (injection adj3 therapy).ab,kw,ti. (6291)
81 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ab,kw,ti. (2369)
82 (short acting adj3 insulin).ab,kw,ti. (969)
83 (rapid acting adj3 insulin).ab,kw,ti. (1412)
84 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 [insulin injections / MDI] (34854)
85 45 and 84 [continuous or flash GMs AND MDI] (1390)
86 74 and 40 [SMBG AND CSII] (5410)
87 85 or 86 (6238)
88 11 and 62 and 87 [T1DM and pregnancy and any comparator group specific to the pregnancy population] (443)
89 limit 88 to dc=20140825-20210331 (240)
90 limit 89 to english language (233)
91 51 or 90 (4267)

Update
Date searched: 11/04/22
Re-ran above search with search lines 50 and 89 altered to:

50 limit 49 to dc=20210331-20220411
89 limit 88 to dc=20210331-20220411
Total:
91 51 or 90 (1210)

Science Citation Index – Expanded & Conference Proceedings Citation Index - Science (via Web of Science)

Date searched: 31/03/21

# 69	2,190	#68 OR #43 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 68	43	(#66 AND #48 AND #8) *AND* **LANGUAGE:** (English) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 67	47	#66 AND #48 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 66	605	#65 OR #64 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 65	248	#55 AND #33 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 64	400	#63 AND #38 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 63	6,208	#62 OR #61 OR #60 OR #59 OR #58 OR #57 OR #56 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 62	1,189	TS=(insulin* NEAR/0 inject*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 61	338	TS=("rapid acting" NEAR/3 insulin) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 60	137	TS=("short acting" NEAR/3 insulin) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 59	1,994	TS=(injection NEAR/3 therapy) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 58	2,420	TS=MDI *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 57	109	TS=("multiple dose" NEAR/3 (inject* OR insulin* OR regime* OR routine*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 56	737	TS=("multiple daily" NEAR/3 (inject* OR insulin* OR regime* OR routine*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 55	2,407	#54 OR #53 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 54	1,088	TS=(SMBG OR glucometer*)

		Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021
# 53	1,823	#52 AND #49 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 52	57,400	#51 OR #50 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 51	2,658	TS=(capillary NEAR/4 (test* OR measur*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 50	54,859	TS=("self monitor*" OR "test* strip*" OR "finger prick*" OR fingerprick* OR "finger stick*" OR fingerstick* OR lancet* OR meter*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 49	32,964	TS=("blood glucos*" OR "blood sugar*") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 48	450,041	#47 OR #46 OR #45 OR #44 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 47	3,630	TS=apgar *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 46	103,621	TS=(perinatal OR "peri natal" OR fetal OR foetal OR intrauterine OR "intra uterine") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 45	124,549	TS=(miscarr* OR abort* OR cesarean OR caesarean OR "c section*" OR (prematur* AND (birth* OR rupture* OR infant*)) OR preterm OR "pre term" OR prematurity OR prom OR macrosomia* OR "birth weight*" OR birthweight* OR eclamp* OR preeclamp* OR stillbirth* OR "still birth*" OR stillborn* OR "still born*") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 44	379,961	TS=(pregnan* OR "ante natal*" OR antenatal* OR "pre natal*" OR prenatal * OR (expectant* NEAR/2 mother*) OR "mother* to be" OR matern* OR conception* OR preconception* OR "trying to conceive" OR prepregnan* OR periconception* OR "giving birth" OR childbirth* OR labo*r OR newborn* OR "new born*" OR neonat* OR "neo nat*" OR baby OR babies) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 43	2,175	(#41 OR #40 OR #39) *AND* **LANGUAGE:** (English) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 42	2,255	#41 OR #40 OR #39 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 41	983	#38 AND #33 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 40	593	#25 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 39	1,445	#15 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 38	14,694	#37 OR #36 OR #35 OR #34 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

# 37	1,701	TS=(dexcom OR freestyle OR libre OR enlite OR (guardian AND (medtronic OR sensor)) OR eversense OR "glucomen day") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 36	7,203	TS=(CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 35	4,043	TS=(glucose NEAR/0 (sensor* OR sensing)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 34	4,292	TS=((continu* OR flash OR intermittent* OR sensor OR sensors or "real time") NEAR/4 glucose NEAR/4 (monitor* OR measurement*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 33	9,131	#32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 32	26	TS=((accu-chek OR accuchek) NEAR/3 (pump* OR system* OR deliver* OR combo OR insight OR solo)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 31	1,121	TS=(tandem NEAR/3 (pump* OR system* OR deliver*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 30	310	TS=(medtronic NEAR/3 (pump* OR system* OR deliver*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 29	232	TS=(minimed OR "dana diabecare" OR "dana R" OR "dana RS" OR kaleido OR omnipod OR medtrum OR touchcare OR ypsopump OR cellnovo) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 28	1,748	TS=((subcutaneous NEAR/2 insulin*) OR CSII) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 27	2,715	TS=(pump* NEAR/2 (therap* OR treatment*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 26	5,555	TS=(insulin* NEAR/3 (pump* OR infus* OR deliver* OR catheter*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 25	14,388	#24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 24	12	TS=((animas OR vibe) NEAR/3 (pump* OR infus* OR system*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 23	53	TS=(g4 NEAR/3 platinum) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 22	7	TS=(veo NEAR/3 pump*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 21	40	TS=(paradigm* NEAR/3 (veo OR pump*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 20	45	TS=((minimed OR medtronic) AND 640G) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 19	12	TS="basal iq" *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

# 18	115	TS="predictive low glucose" *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 17	440	TS=SAPT *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 16	13,776	TS=(sensor$ NEAR/3 (augment* OR integrat* OR pump$ OR insulin)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 15	42,226	#14 OR #13 OR #12 OR #11 OR #10 OR #9 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 14	177	TS=(tslim OR "t slim" OR "control iq" OR camAPS OR camdiab OR "dexc om G6" OR "dexcom G7" OR smartguard OR "smart guard" OR diabeloop OR dblg1 OR ilet OR "beta bionics" OR (omnipod AND horizon) OR (mylife AND loop) OR (tidepool AND loop) OR bigfoot OR "anydana loop") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 13	88	TS=((minimed OR medtronic) AND (670G OR 780G)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 12	258	TS=(automat* NEAR/2 ("insulin deliver*" OR "insulin dosing" OR "glucose control*" OR "glyc$emic control*")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 11	124	TS=(bionic NEAR/2 pancreas) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 10	1,299	TS=(artificial NEAR/2 (pancreas OR "beta cell*")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 9	41,216	TS="closed loop" *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 8	146,413	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 7	78,894	TS=((high OR higher OR low OR lower OR increas* OR decreas* OR defic ien* OR sufficien* OR insufficien* OR reduce* OR reduction* OR fluctuat * OR fallen OR falling OR threshold OR safe) NEAR/3 (glucose* OR sugar* OR hba1c OR "hb a1" OR hba1 OR a1c OR h$emoglob* OR glycoh$emoglob*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 6	47,313	TS=(hyperglyc$em* OR hypoglyc$em*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 5	4,801	TS=(ketoacidosis OR acidoketosis OR "keto acidosis" OR ketoacidemia OR ketosis OR dka) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 4	11,210	TS=(dm1 OR "dm 1" OR dmt1 OR "dm t1" OR t1dm OR "t1 dm" OR t1d O R iddm) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 3	3,716	TS=((insulin* NEAR/2 depend*) OR insulindepend*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

# 2	11,031	TS=(diabet* NEAR/3 (britt* OR juvenil* OR pediatric OR paediatric OR early OR keto* OR labil* OR acidos* OR autoimmun* OR "auto immun*" OR "sudden onset")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 1	27,913	TS=(diabet* NEAR/3 ("typ* 1" OR "typ* i" OR type1 OR typei OR "typ* one")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

Update
Date searched: 12/04/22
Original search above not fully saved in WoS because it is over 40 lines so strategy re-entered using fewer lines (one line for each concept), combined as above and run with Timespan altered to:
Timespan: 2021-03-31 to 2022-04-12 (Index Date)
Total: 514

The Ovid Medline search strategy was translated for use in Web of Science with the aid of the Polyglot Search Translator:
Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc 2020;108(2):195-207. http://dx.doi.org/10.5195/jmla.2020.834

Cochrane Database of Systematic Reviews (CDSR) & Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Cochrane Library)

Date searched: 31/03/21
Search interface: https://www.cochranelibrary.com/advanced-search/search-manager

#1	[mh ^"Diabetes Mellitus, Type 1"]	5614
#2	[mh ^"Diabetic Ketoacidosis"]	139
#3	(diabet* NEAR/3 ((typ* NEXT 1) OR (typ* NEXT i) OR type1 OR typei OR (typ* NEXT one))):ti,ab,kw	10200
#4	(diabet* NEAR/3 (britt* OR juvenil* OR pediatric OR paediatric OR early OR keto* OR labil* OR acidos* OR autoimmun* OR (auto NEXT immun*) OR "sudden onset")):ti,ab,kw	3429
#5	((insulin* NEAR/2 depend*) OR insulindepend*):ti,ab,kw	22663
#6	(dm1 OR (dm NEXT 1) OR dmt1 OR (dm NEXT t1) OR t1dm OR "t1 dm" OR t1d OR iddm):ti,ab,kw	3481
#7	(ketoacidosis OR acidoketosis OR "keto acidosis" OR ketoacidemia OR ketosis OR dka):ti,ab,kw	1174
#8	[mh ^Hyperglycemia]	1952
#9	[mh ^Hypoglycemia]	2258
#10	(hyperglyc?em* OR hypoglyc?em*):ti,ab,kw	24948

#11	((high OR higher OR low OR lower OR increase* OR decreas* OR deficien* OR sufficien* OR insufficien* OR reduce* OR reduction* OR fluctuat* OR fallen OR falling OR threshold OR safe) NEAR/3 (glucose* OR sugar* OR hba1c OR (hb NEXT a1) OR hba1 OR a1c OR h?emoglob* OR glycoh?emoglob*)):ti,ab,kw	23784
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	59772
#13	[mh ^"Pancreas, Artificial"]	73
#14	"closed loop":ti,ab,kw	1264
#15	(artificial NEAR/2 (pancreas OR (beta NEXT cell*))):ti,ab,kw	365
#16	(bionic NEAR/2 pancreas):ti,ab,kw	47
#17	(automat* NEAR/2 ((insulin NEXT deliver*) OR "insulin dosing" OR (glucose NEXT control*) OR (glyc?emic NEXT control*))):ti,ab,kw	117
#18	((minimed OR medtronic) AND (670G OR 780G)):ti,ab,kw	32
#19	(tslim OR "t slim" OR "control iq" OR camAPS OR camdiab OR "dexcom G6" OR “dexcom G7” OR smartguard OR "smart guard" OR diabeloop OR dblg1 OR ilet OR "beta bionics" OR (omnipod AND horizon) OR (mylife AND loop) OR (tidepool AND loop) OR bigfoot OR "anydana loop"):ti,ab,kw	152
#20	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	1564
#21	(sensor? NEAR/3 (augment* OR integrat* OR pump? OR insulin)):ti,ab,kw	838
#22	SAPT:ti,ab,kw	48
#23	"predictive low glucose":ti,ab,kw	63
#24	"basal iq":ti,ab,kw	11
#25	((minimed OR medtronic) AND 640G):ti,ab,kw	30
#26	(paradigm* NEAR/3 (veo OR pump*)):ti,ab,kw	42
#27	(veo NEAR/3 pump*):ti,ab,kw	24
#28	(g4 NEAR/3 platinum):ti,ab,kw	39
#29	((animas OR vibe) NEAR/3 (pump* OR infus* OR system*)):ti,ab,kw	17
#30	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	984
#31	[mh ^"Insulin Infusion Systems"]	669
#32	(insulin* NEAR/3 (pump* OR infus* OR deliver* OR catheter*)):ti,ab,kw	4129
#33	(pump* NEAR/2 (therap* OR treatment*)):ti,ab,kw	1666
#34	((subcutaneous NEAR/2 insulin*) OR CSII):ti,ab,kw	1528
#35	(minimed OR "dana diabecare" OR "dana R" OR "dana RS" OR kaleido OR omnipod OR medtrum OR touchcare OR ypsopump OR cellnovo):ti,ab,kw	203
#36	(medtronic NEAR/3 (pump* OR system* OR deliver*)):ti,ab,kw	214
#37	(tandem NEAR/3 (pump* OR system* OR deliver*)):ti,ab,kw	57
#38	((accu-chek OR accuchek) NEAR/3 (pump* OR system* OR deliver* OR combo OR insight OR solo)):ti,ab,kw	17
#39	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	5680

#40	((continu$ or flash or intermittent$ or sensor or sensors or real time) NEAR/4 glucose NEAR/4 (monitor* OR measurement*)):ti,ab,kw	625
#41	(glucose NEXT (sensor? OR sensing)):ti,ab,kw	348
#42	(CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS):ti,ab,kw	2033
#43	(dexcom OR freestyle OR libre OR enlite OR (guardian AND (medtronic OR sensor)) OR eversense OR "glucomen day"):ti,ab,kw	1563
#44	#40 OR #41 OR #42 OR #43	3621
#45	#12 AND #20	861
#46	#12 AND #30	556
#47	#12 AND #39 AND #44	853
#48	#45 OR #46 OR #47	1520
#49	#45 OR #46 OR #47 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021*	1319
#50	[mh Pregnancy]	22393
#51	[mh "Pregnancy Complications"]	12074
#52	[mh ^"Perinatal Care"] OR [mh ^"Preconception Care"] OR [mh ^"Prenatal Care"]	1792
#53	[mh "Cesarean Section"]	3153
#54	[mh ^"Pregnant Women"]	297
#55	(pregnan* OR (ante NEXT natal*) OR antenatal* OR (pre NEXT natal*) OR prenatal* OR (expectant* NEAR/2 mother*) OR (mother? NEAR/2 "to be") OR matern* OR conception* OR preconception* OR "trying to conceive" OR prepregnan* OR periconception* OR "giving birth" OR childbirth* OR labo?r OR newborn* OR (new NEXT born*) OR neonat* OR (neo NEXT nat*) OR baby OR babies):ti,ab,kw	107835
#56	(miscarr* OR abort* OR cesarean OR caesarean OR (c NEXT section*) OR (prematur* AND (birth* OR rupture* OR infant*)) OR preterm OR "pre term" OR prematurity OR prom OR macrosomia* OR (birth NEXT weight*) OR birthweight* OR eclamp* OR preeclamp* OR stillbirth* OR (still NEXT birth*) OR stillborn* OR (still NEXT born*)):ti,ab,kw	46780
#57	(perinatal OR "peri natal" OR fetal OR foetal OR intrauterine OR "intra uterine"):ti,ab,kw	21877
#58	apgar:ti,ab,kw	4463
#59	#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	122190
#60	[mh Insulin] AND [mh ^"Injections, Subcutaneous"]	454
#61	("multiple daily" NEAR/3 (inject* OR insulin* OR regime* OR routine*)):ti,ab,kw	714
#62	("multiple dose" NEAR/3 (inject* OR insulin* OR regime* OR routine*)):ti,ab,kw	249

#63	(multiple NEAR/3 (inject* OR insulin* OR regime* OR routine*)):ti,ab,kw	2186
#64	MDI:ti,ab,kw	2986
#65	(injection NEAR/3 therapy):ti,ab,kw	2610
#66	((basal* AND bolus) NEAR/3 (injection* OR regime* OR routine* OR system*)):ti,ab,kw	3745
#67	("short acting" NEAR/3 insulin):ti,ab,kw	363
#68	("rapid acting" NEAR/3 insulin):ti,ab,kw	417
#69	#60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68	11689
#70	[mh ^"Blood Glucose Self-Monitoring"]	805
#71	[mh ^"Blood Glucose"]	16258
#72	((blood NEXT glucose*) OR (blood NEXT sugar*)):ti,ab,kw	34151
#73	#71 OR #72	34151
#74	((self NEXT monitor*) OR (test* NEXT strip*) OR (finger NEXT prick*) OR fingerprick* OR (finger NEXT stick*) OR fingerstick* OR lancet? OR meter?):ti,ab,kw	14651
#75	(capillary NEAR/4 (test* OR measur*)):ti,ab,kw	600
#76	#74 OR #75	15159
#77	#73 AND #76	2965
#78	SMBG:ti,ab,kw	797
#79	glucometer*:ti,ab,kw	401
#80	#70 OR #77 OR #78 OR #79	3438
#81	#44 AND #69	400
#82	#39 AND #80	513
#83	#81 OR #82	822
#84	#12 AND #59 AND #83	52
#85	#12 AND #59 AND #83 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021*	44
#86	#49 OR #85	1327
#87	#49 OR #85 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021, in Cochrane Reviews and Cochrane Protocols*	0
#88	#49 OR #85 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021, in Trials*	1327

Update
Date searched: 12/04/22
Re-ran above search with limit for search lines 49, 85, 87 and 88 altered to:
Cochrane Library publication date from Apr 2021 to Apr 2022
Results:

#87	#49 OR #85	0

	with Limits: Cochrane Library publication date from Apr 2021 to Apr 2022*, in Cochrane Reviews and Cochrane Protocols*	
#88	#49 OR #85 *with Limits: Cochrane Library publication date from* Apr 2021 to Apr 2022*, in Trials*	159

The Ovid Medline search strategy was translated for use in the Cochrane Library with the aid of the Polyglot Search Translator:
Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc 2020;108(2):195-207. http://dx.doi.org/10.5195/jmla.2020.834

clinicaltrials.gov

Date searched: 12/04/21
Search interface: 'Advanced search' https://clinicaltrials.gov/ct2/search/advanced

Original search	Results	Update	Results
"closed loop" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021	190	"closed loop" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	29
"artificial pancreas" OR "artificial endocrine pancreas" OR "bionic pancreas" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021	158	"artificial pancreas" OR "artificial endocrine pancreas" OR "bionic pancreas" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	15
"minimed 670G" OR "minimed 780G" OR "control iq" OR camaps OR camdiab OR "dexcom G6" OR "dexcom G7" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021	83	"minimed 670G" OR "minimed 780G" OR "control iq" OR camaps OR camdiab OR "dexcom G6" OR "dexcom G7" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	30
"sensor augmented" OR SAPT OR "predictive low glucose" [other	79	"sensor augmented" OR SAPT OR "predictive low glucose"	1

terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021		[other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	
insulin AND infusion AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	95	insulin AND infusion AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	11
insulin AND infusion AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	107	insulin AND infusion AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	11
("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	197	("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	27
("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	210	("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	27
CSII AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	39	CSII AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	6

CSII AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	42	CSII AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	5
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	6	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	0
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	4	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	1
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	5	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	0
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	5	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	0
Total:	1220		163
Total after duplicate removal (using EndNote):	392		57

Update

Date searched: 12/04/22. For update search and numbers see right-hand columns in original strategy table above. 57 new.

Health Technology Assessment (HTA) database (via CRD website)

Date searched: 07/04/21

Search interface: https://www.crd.york.ac.uk/CRDWeb/

((closed loop) OR (artificial NEAR2 pancreas) OR (bionic NEAR2 pancreas)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	2
((minimed or control iq or camAPS or camdiab or dexcom)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((sensor augmented) OR (SAPT)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((automat* NEAR2 (insulin OR glucose OR glycemic OR glycaemic))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	0
((insulin NEAR2 (pump* OR infus*)) OR (subcutaneous NEAR2 insulin*) OR (CSII)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	10
((continu* or flash or intermittent* or sensor or sensors or real time) AND (glucose) AND (monitor* or measurement*)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	6
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	3
((diabet* or insulin*) AND (pregn*) AND (injection* or MDI or self monitoring or SMBG)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
Total unique records:	16

No new records so update search not needed.

International HTA database (via INAHTA website)

Date searched: 07/04/21
Search interface: Advanced search builder https://database.inahta.org/search/advanced

(closed loop) FROM 2014 TO 2021	0
(artificial pancreas) FROM 2014 TO 2021	2
(bionic pancreas) FROM 2014 TO 2021	0
(minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2021	2
("Pancreas, Artificial"[mh]) FROM 2014 TO 2021	2
("sensor augmented") FROM 2014 TO 2021	1
(SAPT) FROM 2014 TO 2021	0
("Insulin Infusion Systems"[mh]) FROM 2014 TO 2021	7
(insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2021	8
(CSII) FROM 2014 TO 2021	2
((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2021	15
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2021	7
((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2021	4
Total:	50
Total after duplicate removal (using EndNote):	22

Update

Date searched: 06/04/22
Re-ran search above search in one line with end date altered to 2022:

(((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2022) OR (((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2022) OR (((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2022) OR ((CSII) FROM 2014 TO 2022) OR ((insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2022) OR (("Insulin Infusion Systems"[mh]) FROM 2014 TO 2022) OR ((SAPT) FROM 2014 TO 2022) OR (("sensor augmented") FROM 2014 TO 2022) OR (("Pancreas, Artificial"[mh]) FROM 2014 TO 2022) OR ((minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2022) OR ((bionic pancreas) FROM 2014 TO 2022) OR ((artificial pancreas) FROM 2014 TO 2022) OR ((closed loop) FROM 2014 TO 2022)

Total: 32

Notes: After checking several lines from the original search above and finding some of the new records were for HTAs were published before 2021, it was decided that all 32 should be exported and de-duplicated with the previous results in EndNote.

Total after de-duplication in EndNote: 10

NIHR Journals Library

Date searched: 12/04/21
Search interface: Basic search https://www.journalslibrary.nihr.ac.uk/#/

Search terms	Total results	Total at update	Number of new (not in previous results or sets), possibly relevant results
"closed loop"	3	3	0
"closed-loop"	2	3	1
"artificial pancreas"	2	1	0
"bionic pancreas"	0	0	0
Minimed	5	5	0
"Control IQ"	0	0	0
"Control-IQ"	0	0	0
camAPS	0	1	0
Camdiab	0	0	0
dexcom	0	1	0
"automated insulin delivery"	0	0	0
Total unique results, added since 2014:	*5*		*1*

Update

Date searched: 12/04/22. For numbers see right-hand column in original strategy table above. 1 new, 1 potentially relevant.

Agency for Healthcare Research and Quality (AHRQ) website

Agency for Healthcare Research and Quality (AHRQ) website

Date searched: 12/04/21

Search Publications: https://www.ahrq.gov/research/publications/search.html

Search terms	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	0		0	
diabetes	6	0 relevant	6 (0 new)	
insulin	0		0	

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 0 new.

Search Evidence Based Reports: https://www.ahrq.gov/research/findings/evidence-based-reports/search.html

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	0 relevant; about pancreatic adeno-carcinoma	1 (0 new)	
Browsed Topic: Endocrine conditions	25 reports, of which 10 published 2014-present	0 relevant	26 reports, of which 11 published 2014-present (1 new)	0 relevant

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 1 new, 0 relevant.

Full Research Reports: https://www.ahrq.gov/research/findings/final-reports/index.html
Checked 10 reports listed; none relevant.

Update. Checked again 06/04/22. 0 new reports listed.

Technology Assessment Program: https://www.ahrq.gov/research/findings/ta/index.html
Checked all reports and projects listed; none relevant

Update. Checked again 06/04/22. 0 new published reports listed. 1 new revised report listed, but not relevant.

Technology Assessment Archive (up to 2016): https://archive.ahrq.gov/clinic/techarch.htm
Used ctrl + F to search webpage for:

diabet
closed
pancreas
insulin
glucose

- nothing relevant found

AHRQ Research Studies: https://www.ahrq.gov/research/findings/studies/index.html

Search term	Total results	Comments	Total at update 04/22	Comments at update 04/22
Closed loop	4	0 relevant (all about closed loop communi-cation systems; not diabetes)	5 (1 new)	0 relevant (all about closed loop communi-cation systems; not diabetes)
Artificial pancreas	0		0	
Bionic pancreas	0		0	
insulin delivery	3	0 relevant	0	
minimed	0		0	
control iq	0		527 (technical changes to search likely)	See new search in row below
control iq AND diabetes	-	-	58	Checked 2021 and 2022. None relevant
camAPS	0		0	
camdiab	0		0	

dexcom	0		0	
insulin pump	0		0	
insulin pumps	0		0	
insulin infusion	1	0 relevant	1 (0 new)	
insulin infusions	0		0	
CSII	0		0	
glucose monitoring	3	0 relevant (2 x type 2 diabetes, 1 about behaviour change)	6 (3 new)	0 relevant
glucose monitors	0		0	
glucose monitor	1	1 possibly relevant	1 (0 new)	
flash	0		0	
insulin AND injections	0		0	
daily injections	0		0	
blood glucose	13	0 relevant; either type 2 diabetes, or not about self-monitoring	15 (2 new)	0 relevant
smbg	0		0	
Total possibly relevant studies:		*1*		*0*

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 6 new, 0 relevant.

Canadian Agency for Drugs and Technologies in Health (CADTH) website

Date searched: 12/04/21
Search box on homepage https://www.cadth.ca/

Limit results by 'Result Type: Reports; Projects in Progress'.
Sort by Newest to Oldest (to enable easy exclusion of pre-2014 records)

Search terms	**Total results**	**Number of new (not in previous sets),**	**Total at update 04/22**	**Number of new (not in previous results or**

		possibly relevant results		**sets), possibly relevant results**
"closed loop"	34	5	19	1
artificial pancreas	22	2	9	0
bionic pancreas	5	0	2	0
automated insulin delivery	18	0	10	0
minimed	16	1	5	0
"control IQ"	2	0	1	0
camAPS	0	0	0	0
camdiab	0	0	0	0
Dexcom	10	1	2	0
"insulin pump"	41	1	12	0
"insulin infusion"	51	0	5	0
CSII	23	0	3	0
"glucose monitor"	25	0	10	0
"glucose monitoring"	80	4	29	1
"insulin injections"	41	0	3	0
"daily injections"	43	0	8	0
"self monitoring" AND glucose	124	0	0	0
SMBG	31	0	5	0
Total unique, possibly relevant results:		*14*		*2*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 2 new, 2 potentially relevant.

Note: Assume website has been restructured or search interface / system changed since original search. Searched for words without quotation marks in 'Contains all the words' and terms in quotation marks in 'Advanced Search'. Sorted by Last updated and checked records for 2021 and 2022.

Swedish Agency For Health Technology Assessment And Assessment Of Social Services (SBU) website

Date searched: 12/04/21
Search box on home page: https://www.sbu.se/en/

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	not relevant; 'dialysis for acute hepatic failure'	1 (0 new)	
bionic pancreas	0		0	
diabetes > Filter on subject and publication type > Publication year From 2014 to 2021	30	0 relevant	5 new	0 relevant
insulin > Filter on subject and publication type > Publication year From 2014 to 2021	5	0 relevant	1 new	0 relevant
Total possibly relevant studies, published since 2014:		*0*		*0*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 0 relevant.

U.S. Food & Drug Administration (FDA) Premarket Notification, Premarket Approval & De novo databases (via FDA website)

Date searched: 21/4/21
Search interfaces:

- devices@FDA (searches PMN-510(k) Premarket Notification and PMA-Premarket Approval databases) https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm
- De novo database, 'device name' field https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm

Search terms	devices@FDA results	De novo database results	**Documents downloaded** (judged to contain potentially useful/relevant information not already identified in previous sets)

dexcom	13	2	3 decision summaries, 1 classification order
control-IQ	4	1	2 decision summaries, 1 classification order
control iq	Same results as control-IQ		0
t:slim	0	1	1 decision summary, 1 classification order
t slim	3	1	0
tslim	1	0	0
camaps	0	0	0
camdiab	0	0	0
minimed 670G	7	0	2 summaries of safety & effectiveness data
minimed 780G	0	0	0
minimed		0	0
smartguard	8	0	0
smart guard	2	0	0
ilet	0	0	0
beta bionics	0	0 (also tried 'Requester name' field)	0
closed loop	13		1 summary of safety & effectiveness data
artificial pancreas	1		0
bionic pancreas	0		0

Medicines & Healthcare Products Regulatory Agency (MHRA) (via gov.uk website)

Date searched: 22/04/21
Search interface: https://www.gov.uk/

Filters selected:
About (Topic): Health and social care and Medicines, medical devices
Updated after: 1 January 2014

Search term	**Results**	**Documents downloaded** (judged to contain potentially useful/relevant information not already identified in previous sets)
dexcom	6	2 Field Safety Notices (FSNs), 1 gov.uk web page
"control-iq"	0	0
"control iq"	0	0
"t:slim"	2	1 FSN, 1 gov.uk web page

"t slim"	1	0
tslim	0	0
camaps	0	0
camdiab	0	0
“minimed 670G”	2	2 FSNs
minimed 780G	1	0
smartguard	0	0
“smart guard”	0	0
ilet	0	0
"beta bionics"	0	0
“closed loop”	3	0
“artificial pancreas”	0	0
“bionic pancreas”	0	0

10.1.2 Record of searches – Cost effectiveness

Overview:

Database / website	Date searched (date updated)	Number of records + update = TOTAL
MEDLINE ALL (Ovid)	07/04/21 (05/04/22)	162 + 56 = 218
Embase (Ovid)	07/04/21 (05/04/22)	312 + 91 = 403
EconLit (Ebsco)	07/04/21 (05/04/22)	7 + 1 = 8
HTA database (CRD)	07/04/21 *	16
International HTA database (INAHTA)	07/04/21 (06/04/22)	22 + 10 = 32
EconPapers (RePEc)	07/04/21 (06/04/22)	16 + 6 = 22
AHRQ website	12/04/21 (06/04/22)	1 + 0 = 1
CADTH website	12/04/21 (07/04/22)	14 + 2 = 16
SBU website	12/04/21 (07/04/22)	0 + 0 = 0
CEA registry	14/04/21 (07/04/22)	27 + 2 = 29
ScHARRHUD	14/04/21 *	0

* No new records in database so search did not require updating

Total results: 577 + 168 from update = 745
Total after 158 duplicates + 43 duplicates within update results + 28 duplicates with original results removed = 516

Additional targeted searches were made for other parameters later (see end)

Search strategies:

Note: See below each database strategy for details of update searches

MEDLINE (via Ovid)

Date searched: 07/04/21
Database: Ovid MEDLINE(R) ALL <1946 to April 06, 2021>

Search Strategy:
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1 Diabetes Mellitus, Type 1/ (77411)
2 Diabetic Ketoacidosis/ (6618)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kf,ti. (56642)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kf,ti. (28281)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kf,ti. (33825)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kf,ti. (23617)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kf,ti. (11593)
8 Hyperglycemia/ (28779)
9 Hypoglycemia/ (27948)
10 (hyperglyc?em$ or hypoglyc?em$).ab,kf,ti. (116710)
11 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kf,ti. (151670)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 [population: T1DM] (365496)
13 Pancreas, Artificial/ (816)
14 closed loop.ab,kf,ti. (10542)
15 (artificial adj2 (pancreas or beta cell$)).ab,kf,ti. (1730)
16 (bionic adj2 pancreas).ab,kf,ti. (25)
17 (Automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kf,ti. (287)
18 ((minimed or medtronic) and (670G or 780G)).ab,kf,ti. (58)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,kf,ti. (176)
20 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (12190)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kf,ti. (7831)
22 SAPT.ab,kf,ti. (536)
23 predictive low glucose.ab,kf,ti. (97)
24 basal iq.ab,kf,ti. (9)
25 ((minimed or medtronic) and 640G).ab,kf,ti. (33)
26 (paradigm$ adj3 (veo or pump$)).ab,kf,ti. (58)
27 (veo adj3 pump$).ab,kf,ti. (9)
28 (g4 adj3 platinum).ab,kf,ti. (58)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,kf,ti. (14)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (8503)
31 Insulin Infusion Systems/ (5481)

32 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kf,ti. (14832)
33 (pump$ adj2 (therap$ or treatment$)).ab,kf,ti. (3232)
34 ((subcutaneous adj2 insulin$) or CSII).ab,kf,ti. (3868)
35 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,kf,ti. (380)
36 (medtronic adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (720)
37 (tandem adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (926)
38 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,kf,ti. (34)
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 [insulin pumps/CSII] (20986)
40 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kf,ti. (5882)
41 (glucose adj (sensor$ or sensing)).ab,kf,ti. (4191)
42 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kf,ti. (4544)
43 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,kf,ti. (2422)
44 40 or 41 or 42 or 43 [continuous or flash glucose monitors] (13072)
45 (2014082* or 2014083* or 201409* or 201410* or 201411* or 201412* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).dt,ez,da. [added to database since search for previous DAR in 2014] (8999414)
46 12 and 20 and 45 [T1DM and closed loop + date limit] (1143)
47 12 and 30 and 45 [T1DM and SAPT + date limit] (505)
48 12 and 39 and 44 and 45 [T1DM and pumps and GMs + date limit] (1100)
49 46 or 47 or 48 (1967)
50 limit 49 to english language (1919)
51 exp Pregnancy/ (913489)
52 exp Pregnancy Complications/ (435971)
53 Perinatal Care/ or Preconception Care/ or Prenatal Care/ (35179)
54 exp Cesarean Section/ (46725)
55 Pregnant Women/ (9210)
56 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kf,ti. (1210177)
57 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kf,ti. (352725)
58 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kf,ti. (365250)
59 apgar.ab,kf,ti. (12609)
60 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 [pregnancy, planning pregnancy, pregnancy complications; broad] (1736892)
61 exp Insulin/ and Injections, Subcutaneous/ (2457)
62 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (1309)
63 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (564)
64 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (10216)

65 MDI.ti,ab,kf. (3837)
66 (injection adj3 therapy).ti,ab,kf. (4204)
67 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,kf. (1376)
68 (short acting adj3 insulin).ti,ab,kf. (576)
69 (rapid acting adj3 insulin).ti,ab,kf. (799)
70 or/61-69 [insulin injections] (21941)
71 Blood Glucose Self-Monitoring/ (7144)
72 Blood Glucose/ (168038)
73 (blood glucos$ or blood sugar$).ab,kf,ti. (87483)
74 72 or 73 (210806)
75 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kf,ti. (43311)
76 (capillary adj4 (test$ or measur$)).ab,kf,ti. (5095)
77 75 or 76 (48093)
78 74 and 77 (5795)
79 SMBG.ab,kf,ti. (1197)
80 glucometer$.ab,kf,ti. (1147)
81 71 or 78 or 79 or 80 [self monitoring of blood glucose] (11403)
82 44 and 70 [continuous or flash GMs AND MDI] (488)
83 81 and 39 [SMBG AND CSII] (1715)
84 82 or 83 (2028)
85 12 and 60 and 84 and 45 [T1DM and pregnancy and any of the comparator groups specific to this population + date limit] (56)
86 limit 85 to english language (55)
87 50 or 86 (1930)
88 Economics/ (27310)
89 exp "costs and cost analysis"/ (243824)
90 Economics, Dental/ (1915)
91 exp economics, hospital/ (25035)
92 Economics, Medical/ (9127)
93 Economics, Nursing/ (4002)
94 Economics, Pharmaceutical/ (2977)
95 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (852480)
96 (expenditure$ not energy).ti,ab. (31555)
97 value for money.ti,ab. (1740)
98 budget$.ti,ab. (30786)
99 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 (1007726)
100 ((energy or oxygen) adj cost).ti,ab. (4248)
101 (metabolic adj cost).ti,ab. (1480)
102 ((energy or oxygen) adj expenditure).ti,ab. (26059)
103 100 or 101 or 102 (30788)
104 99 not 103 (1000667)
105 letter.pt. (1129857)
106 editorial.pt. (563250)
107 historical article.pt. (362940)
108 105 or 106 or 107 (2035927)

109 104 not 108 (963183)
110 exp animals/ not humans/ (4809908)
111 109 not 110 [economic studies filter] (901889)
112 87 and 111 (162)

Update
Date searched: 05/04/22
Re-ran above search with search line 45 altered to:
45 (202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022*).dt,ez,da. [added to database since original search for this MTA]
Total: 112 87 and 111 (56)

The economics terms (lines 88-111) are based on the CRD NHS EED filter:

Centre for Reviews and Dissemination. *Search strategies: NHS EED MEDLINE using OvidSP*. York: Centre for Reviews and Dissemination; 2014. URL: https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (Accessed 27 April 2021).

Search strings used in the previous technology assessment on integrated sensor-augmented pump therapy systems were used as the basis for developing selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections:

Appendix 1: Literature search strategies. In: Riemsma R, Corro Ramos I, Birnie R, Büyükkaramikli N, Armstrong N, Ryder S, et al. Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation. Health Technol Assess 2016;20(17):v-xxxi, 1-251. http://dx.doi.org/10.3310/hta20170

The following were used as sources of search terms for pregnancy and related concepts:

Tessier V. Périnatalité: Perinatality: Rappel favorisé sur la précision. Canadian Health Libraries Association - Association des bibliothèques de la santé du Canada; 2017. URL: https://extranet.santecom.qc.ca/wiki/!biblio3s/doku.php?id=concepts:perinatalite (Accessed 26 April 2021).

Kyrgiou M, Mitra A, Arbyn M, Paraskevaidi M, Athanasiou A, Martin-Hirsch PPL, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2015. http://dx.doi.org/10.1002/14651858.CD008478.pub2

Cochrane Pregnancy and Childbirth's Trials Register: Detailed search methods used to maintain and update the Specialised Register. 2018. URL: https://pregnancy.cochrane.org/sites/pregnancy.cochrane.org/files/public/uploads/cochrane_pregnancy_and_childbirth_search_methods_2018_1.docx (Accessed 26 April 2021).

Embase (via Ovid)

Date searched: 07/04/21
Database: Embase <1974 to 2021 April 06>

Search Strategy:

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1 insulin dependent diabetes mellitus/ (120816)
2 diabetic ketoacidosis/ (13238)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kw,ti. (89502)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kw,ti. (39710)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kw,ti. (42510)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kw,ti. (41428)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kw,ti. (17695)
8 hypoglycemia/ or insulin hypoglycemia/ or nocturnal hypoglycemia/ or hyperglycemia/ (170292)
9 (hyperglyc?em$ or hypoglyc?em$).ab,kw,ti. (171683)
10 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kw,ti. (219849)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 [population: T1DM] (553786)
12 exp artificial pancreas/ (2523)
13 "glucose monitoring/insulin pump system"/ (22)
14 closed loop.ab,kw,ti. (13576)
15 (artificial adj2 (pancreas or beta cell$)).ab,kw,ti. (2733)
16 (bionic adj2 pancreas).ab,kw,ti. (84)
17 (automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kw,ti. (501)
18 ((minimed or medtronic) and (670G or 780G)).ab,dm,dv,kw,ti. (204)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,dm,dv,kw,ti. (452)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (16596)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kw,ti. (9770)
22 SAPT.ab,kw,ti. (499)
23 predictive low glucose.ab,kw,ti. (216)
24 basal iq.ab,dm,dv,kw,ti. (35)
25 ((minimed or medtronic) and 640G).ab,dm,dv,kw,ti. (162)
26 (paradigm$ adj3 (veo or pump$)).ab,dm,dv,kw,ti. (251)
27 (veo adj3 pump$).ab,dm,dv,kw,ti. (63)
28 (g4 adj3 platinum).ab,dm,dv,kw,ti. (215)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,dm,dv,kw,ti. (56)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (10839)
31 insulin infusion/ (8362)
32 insulin pump/ or implantable insulin pump/ (7947)
33 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kw,ti. (23717)
34 (pump$ adj2 (therap$ or treatment$)).ab,kw,ti. (6135)
35 ((subcutaneous adj2 insulin$) or CSII).ab,kw,ti. (7277)
36 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,dm,dv,kw,ti. (1656)

37 (medtronic adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (3033)
38 (tandem adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (1171)
39 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,dm,dv,kw,ti. (174)
40 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 [insulin pumps/CSII] (36842)
41 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kw,ti. (10589)
42 (glucose adj (sensor$ or sensing)).ab,kw,ti. (5548)
43 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kw,ti. (8880)
44 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,dm,dv,kw,ti. (4614)
45 41 or 42 or 43 or 44 [continuous or flash glucose monitors] (20610)
46 11 and 20 [T1DM and closed loop] (4008)
47 11 and 30 [T1DM and SAPT] (1705)
48 11 and 40 and 45 [T1DM and pumps and GMs] (4222)
49 46 or 47 or 48 (7461)
50 limit 49 to dc=20140825-20210331 (4304)
51 limit 50 to english language (4181)
52 exp pregnancy/ (689502)
53 exp pregnancy disorder/ (556137)
54 exp cesarean section/ (102040)
55 pregnant woman/ (87246)
56 pregnancy outcome/ (64095)
57 perinatal care/ or prepregnancy care/ or prenatal care/ (57272)
58 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kw,ti. (1450554)
59 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kw,ti. (456116)
60 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kw,ti. (466666)
61 apgar.ab,kw,ti. (19962)
62 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 [pregnancy, planning pregnancy, pregnancy complications; broad] (1960053)
63 blood glucose monitoring/ (28324)
64 glucose blood level/ (264217)
65 (blood glucos$ or blood sugar$).ab,kw,ti. (130659)
66 64 or 65 (300664)
67 self monitoring/ (8184)
68 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kw,ti. (68060)
69 (capillary adj4 (test$ or measur$)).ab,kw,ti. (6781)
70 67 or 68 or 69 (76851)
71 66 and 70 (9977)

72 SMBG.ab,kw,ti. (2499)
73 glucometer$.ab,kw,ti. (2303)
74 63 or 71 or 72 or 73 [self monitoring of blood glucose] (35625)
75 insulin/ and exp injection/ (5682)
76 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (2615)
77 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (783)
78 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (15107)
79 MDI.ab,kw,ti. (6724)
80 (injection adj3 therapy).ab,kw,ti. (6301)
81 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ab,kw,ti. (2372)
82 (short acting adj3 insulin).ab,kw,ti. (969)
83 (rapid acting adj3 insulin).ab,kw,ti. (1412)
84 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 [insulin injections / MDI] (34894)
85 45 and 84 [continuous or flash GMs AND MDI] (1390)
86 74 and 40 [SMBG AND CSII] (5427)
87 85 or 86 (6255)
88 11 and 62 and 87 [T1DM and pregnancy and any comparator group specific to the pregnancy population] (446)
89 limit 88 to dc=20140825-20210331 (242)
90 limit 89 to english language (235)
91 51 or 90 (4272)
92 Health Economics/ (33568)
93 exp Economic Evaluation/ (318503)
94 exp Health Care Cost/ (302491)
95 pharmacoeconomics/ (7520)
96 92 or 93 or 94 or 95 (558862)
97 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1149601)
98 (expenditure$ not energy).ti,ab. (43069)
99 (value adj2 money).ti,ab. (2579)
100 budget$.ti,ab. (40898)
101 97 or 98 or 99 or 100 (1188152)
102 96 or 101 (1417777)
103 letter.pt. (1175320)
104 editorial.pt. (692507)
105 note.pt. (850530)
106 103 or 104 or 105 (2718357)
107 102 not 106 (1310667)
108 (metabolic adj cost).ti,ab. (1614)
109 ((energy or oxygen) adj cost).ti,ab. (4538)
110 ((energy or oxygen) adj expenditure).ti,ab. (33372)
111 108 or 109 or 110 (38389)
112 107 not 111 [economic studies filter] (1302843)
113 91 and 112 (312)

Update
Date searched: 05/04/22

Re-ran above search with search lines 50 and 89 altered to:
50 limit 49 to dc=20210405-20220405
89 limit 88 to dc=20210405-20220405
Total: 113 91 and 112 (91)

The economics terms (lines 92-112) are based on the CRD NHS EED filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED Embase using OvidSP. York: Centre for Reviews and Dissemination; 2014. URL: https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase (Accessed 27 April 2021).

EconLit with Full Text (via EBSCOhost)

Date searched: 07/04/21
Search screen: Advanced Search

#	Query	Limiters/Expanders	Results
S27	S4 AND S26	Limiters - Published Date: 20140101-20210431 Search modes - Boolean/Phrase	7
S26	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	Search modes - Boolean/Phrase	11,027
S25	TI (minimed or medtronic or tslim or "t slim" or "control iq" or "basal iq" or camAPS or camdiab or dexcom or smartguard or "smart guard" or diabeloop or dblg1 or ilet or "beta bionics" or omnipod or mylife or tidepool or bigfoot or anydana or paradigm* or veo or platinum or animas or vibe or dana or kaleido or medtrum or touchcare or ypsopump or cellnovo or tandem or "accu chek" or accuchek or freestyle or libre or enlite or (guardian and sensor) or eversense or glucomen) OR AB (minimed or medtronic or tslim or "t slim" or "control iq" or "basal iq" or camAPS or camdiab or dexcom or smartguard or "smart guard" or diabeloop or dblg1 or ilet or "beta bionics" or omnipod or mylife or tidepool or bigfoot or anydana or paradigm* or veo or platinum or animas or vibe or dana or kaleido or medtrum or touchcare	Search modes - Boolean/Phrase	10,312

	or ypsopump or cellnovo or tandem or "accu chek" or accuchek or freestyle or libre or enlite or (guardian and sensor) or eversense or glucomen)		
S24	TI (SMBG or glucometer*) OR AB (SMBG or glucometer*)	Search modes - Boolean/Phrase	1
S23	TI (("blood glucos*" or "blood sugar*") AND ("self monitor*" or "test* strip*" or "finger prick*" or fingerprick* or "finger stick*"or fingerstick* or lancet* or meter* or (capillary N4 (test* or measur*)))) OR AB (("blood glucos*" or "blood sugar*") AND ("self monitor*" or "test* strip*" or "finger prick*" or fingerprick* or "finger stick*"or fingerstick* or lancet* or meter* or (capillary N4 (test* or measur*))))	Search modes - Boolean/Phrase	4
S22	TI (("short acting" or "rapid acting") N3 insulin*) OR AB (("short acting" or "rapid acting") N3 insulin*)	Search modes - Boolean/Phrase	1
S21	TI ((basal* and bolus) N3 (injection* or regime* or routine* or system*)) OR AB ((basal* and bolus) N3 (injection* or regime* or routine* or system*))	Search modes - Boolean/Phrase	0
S20	TI injection N3 therapy OR AB injection N3 therapy	Search modes - Boolean/Phrase	1
S19	TI MDI OR AB MDI	Search modes - Boolean/Phrase	21
S18	TI (multiple N4 (inject* or insulin* or regime* or routine*)) OR AB (multiple N4 (inject* or insulin* or regime* or routine*))	Search modes - Boolean/Phrase	275
S17	TI (insulin* N3 (inject* or therapy*)) OR AB (insulin* N3 (inject* or therapy*))	Search modes - Boolean/Phrase	9
S16	TI (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS) OR AB (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)	Search modes - Boolean/Phrase	45
S15	TI ("glucose sensor*" or "glucose sensing") OR AB ("glucose sensor*" or "glucose sensing")	Search modes - Boolean/Phrase	0
S14	TI ((continu* or flash or intermittent* or sensor or sensors or "real time") N4 glucose N4 (monitor* or measurement*)) OR AB ((continu* or flash or	Search modes - Boolean/Phrase	1

	intermittent* or sensor or sensors or "real time") N4 glucose N4 (monitor* or measurement*))		
S13	TI ((subcutaneous N2 insulin*) or CSII) OR AB ((subcutaneous N2 insulin*) or CSII)	Search modes - Boolean/Phrase	2
S12	TI ((pump* N2 (therap* or treatment*)) OR AB ((pump* N2 (therap* or treatment*))	Search modes - Boolean/Phrase	2
S11	TI ((insulin* N3 (pump* or infus* or deliver* or catheter*)) OR AB ((insulin* N3 (pump* or infus* or deliver* or catheter*))	Search modes - Boolean/Phrase	2
S10	TI (SAPT or "predictive low glucose") OR AB (SAPT or "predictive low glucose")	Search modes - Boolean/Phrase	0
S9	TI (sensor* N3 (augment* or integrat* or pump* or insulin)) OR AB (sensor* N3 (augment* or integrat* or pump* or insulin))	Search modes - Boolean/Phrase	12
S8	TI (automat* N2 ("insulin deliver*" or "insulin dosing" or "glucose control*" or "glyc#emic control*")) OR AB (automat* N2 ("insulin deliver*" or "insulin dosing" or "glucose control*" or "glyc#emic control*"))	Search modes - Boolean/Phrase	0
S7	TI bionic N2 pancreas OR AB bionic N2 pancreas	Search modes - Boolean/Phrase	0
S6	TI (artificial N2 (pancreas or "beta cell*")) OR AB (artificial N2 (pancreas or "beta cell*"))	Search modes - Boolean/Phrase	0
S5	TI "closed loop" OR AB "closed loop"	Search modes - Boolean/Phrase	354
S4	S1 OR S2 OR S3	Search modes - Boolean/Phrase	688
S3	TI (hyperglyc#em* OR hypoglyc#em*) OR AB (hyperglyc#em* OR hypoglyc#em*)	Search modes - Boolean/Phrase	19
S2	TI (ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis or dka) OR AB (ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis or dka)	Search modes - Boolean/Phrase	0
S1	TI (diabet* or insulin* or insulindepend* or dm1 or dmt1 or t1dm or t1d or iddm or "dm 1" or "dm t1" or "t1 dm") OR AB (diabet* or insulin* or insulindepend* or dm1 or dmt1 or t1dm or t1d or iddm or "dm 1" or "dm t1" or "t1 dm")	Search modes - Boolean/Phrase	683

Update
Date searched: 06/04/22
Re-ran above search with line 27 changed to: Published Date: 20210101-20220431
Total: 1

Health Technology Assessment (HTA) database (via CRD website)

Date searched: 07/04/21
Search interface: https://www.crd.york.ac.uk/CRDWeb/

((closed loop) OR (artificial NEAR2 pancreas) OR (bionic NEAR2 pancreas)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	2
((minimed or control iq or camAPS or camdiab or dexcom)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((sensor augmented) OR (SAPT)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((automat* NEAR2 (insulin OR glucose OR glycemic OR glycaemic))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	0
((insulin NEAR2 (pump* OR infus*)) OR (subcutaneous NEAR2 insulin*) OR (CSII)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	10
((continu* or flash or intermittent* or sensor or sensors or real time) AND (glucose) AND (monitor* or measurement*)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	6
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	3
((diabet* or insulin*) AND (pregn*) AND (injection* or MDI or self monitoring or SMBG)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
Total unique records:	16

No new records so update search not needed.

International HTA database (via INAHTA website)

Date searched: 07/04/21
Search interface: Advanced search builder https://database.inahta.org/search/advanced

(closed loop) FROM 2014 TO 2021	0
(artificial pancreas) FROM 2014 TO 2021	2
(bionic pancreas) FROM 2014 TO 2021	0
(minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2021	2
("Pancreas, Artificial"[mh]) FROM 2014 TO 2021	2
("sensor augmented") FROM 2014 TO 2021	1
(SAPT) FROM 2014 TO 2021	0
("Insulin Infusion Systems"[mh]) FROM 2014 TO 2021	7
(insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2021	8
(CSII) FROM 2014 TO 2021	2
((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2021	15
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2021	7
((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2021	4
Total:	50
Total after duplicate removal (using EndNote):	22

Update

Date searched: 06/04/22
Re-ran search above search in one line with end date altered to 2022:

(((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2022) OR (((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2022) OR (((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2022) OR ((CSII) FROM 2014 TO 2022) OR ((insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2022) OR (("Insulin Infusion Systems"[mh]) FROM 2014 TO 2022) OR ((SAPT) FROM 2014 TO 2022) OR (("sensor augmented") FROM 2014 TO 2022) OR (("Pancreas, Artificial"[mh]) FROM 2014 TO 2022) OR ((minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2022) OR

((bionic pancreas) FROM 2014 TO 2022) OR ((artificial pancreas) FROM 2014 TO 2022) OR ((closed loop) FROM 2014 TO 2022)

Total: 32

Notes: After checking several lines from the original search above and finding some of the new records were for HTAs were published before 2021, it was decided that all 32 should be exported and de-duplicated with the previous results in EndNote.
Total after de-duplication in EndNote: 10

EconPapers (via Research Papers in Economics (RePEc))

Date searched: 07/04/21
Search interface: Advanced search https://econpapers.repec.org/scripts/search.pf
Filters selected: Working Papers, Journal Articles, Books & Chapters.
Sort by Date modified (to enable easy exclusion of pre-2014 records)

Search terms (entered in 'Free text search')		Update
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND ("closed loop" OR "artificial pancreas" OR "artificial endocrine pancreas" OR "bionic pancreas")	13	5
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND (minimed OR "control iq" OR camAPS OR camdiab OR 276excom)	0	0
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND ("sensor augmented" OR SAPT)	0	0
insulin AND (pump* OR infusion* OR subcutaneous) AND (continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)	3	2
insulin AND (pump* OR infusion* OR subcutaneous) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)	2	1
CSII AND (continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)	2	1
CSII AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)	1	0
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND pregn* AND (injection* OR MDI OR "self-monitoring" OR SMBG)	2	0
Total:	23	9

Total after duplicate removal (using EndNote):	16	6

Update

Date searched: 06/04/22
Re-ran search above searches with box ticked for added to EconPapers in the last 1 year (New or updated items, selected Modified last 1 year and Date is Creation/revision of Metadata). For numbers see right-hand column in original strategy table above.

Agency for Healthcare Research and Quality (AHRQ) website

Date searched: 12/04/21

Search Publications: https://www.ahrq.gov/research/publications/search.html

Search terms	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	0		0	
diabetes	6	0 relevant	6 (0 new)	
insulin	0		0	

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 0 new.

Search Evidence Based Reports: https://www.ahrq.gov/research/findings/evidence-based-reports/search.html

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	0 relevant; about pancreatic adeno-carcinoma	1 (0 new)	
Browsed Topic: Endocrine conditions	25 reports, of which 10	0 relevant	26 reports, of which 11 published	0 relevant

	published 2014-present		2014-present (1 new)	

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 1 new, 0 relevant.

Full Research Reports: https://www.ahrq.gov/research/findings/final-reports/index.html
Checked 10 reports listed; none relevant.

Update. Checked again 06/04/22. 0 new reports listed.

Technology Assessment Program: https://www.ahrq.gov/research/findings/ta/index.html
Checked all reports and projects listed; none relevant

Update. Checked again 06/04/22. 0 new published reports listed. 1 new revised report listed, but not relevant.

Technology Assessment Archive (up to 2016): https://archive.ahrq.gov/clinic/techarch.htm
Used ctrl + F to search webpage for:

diabet
closed
pancreas
insulin
glucose

- nothing relevant found

AHRQ Research Studies: https://www.ahrq.gov/research/findings/studies/index.html

Search term	**Total results**	**Comments**	**Total at update 04/22**	**Comments at update 04/22**
Closed loop	4	0 relevant (all about closed loop communi-cation systems; not diabetes)	5 (1 new)	0 relevant (all about closed loop communi-cation systems; not diabetes)
Artificial pancreas	0		0	

Bionic pancreas	0		0	
insulin delivery	3	0 relevant	0	
minimed	0		0	
control iq	0		527 (technical changes to search likely)	See new search in row below
control iq AND diabetes	-	-	58	Checked 2021 and 2022. None relevant
camAPS	0		0	
camdiab	0		0	
dexcom	0		0	
insulin pump	0		0	
insulin pumps	0		0	
insulin infusion	1	0 relevant	1 (0 new)	
insulin infusions	0		0	
CSII	0		0	
glucose monitoring	3	0 relevant (2 x type 2 diabetes, 1 about behaviour change)	6 (3 new)	0 relevant
glucose monitors	0		0	
glucose monitor	1	1 possibly relevant	1 (0 new)	
flash	0		0	
insulin AND injections	0		0	
daily injections	0		0	
blood glucose	13	0 relevant; either type 2 diabetes, or not about self-monitoring	15 (2 new)	0 relevant
smbg	0		0	
Total possibly relevant studies:		*1*		*0*

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 6 new, 0 relevant.

Canadian Agency for Drugs and Technologies in Health (CADTH) website

Date searched: 12/04/21
Search box on homepage https://www.cadth.ca/
Limit results by 'Result Type: Reports; Projects in Progress'.
Sort by Newest to Oldest (to enable easy exclusion of pre-2014 records)

Search terms	Total results	Number of new (not in previous sets), possibly relevant results	Total at update 04/22	Number of new (not in previous results or sets), possibly relevant results
"closed loop"	34	5	19	1
artificial pancreas	22	2	9	0
bionic pancreas	5	0	2	0
automated insulin delivery	18	0	10	0
minimed	16	1	5	0
"control IQ"	2	0	1	0
camAPS	0	0	0	0
camdiab	0	0	0	0
Dexcom	10	1	2	0
"insulin pump"	41	1	12	0
"insulin infusion"	51	0	5	0
CSII	23	0	3	0
"glucose monitor"	25	0	10	0
"glucose monitoring"	80	4	29	1
"insulin injections"	41	0	3	0
"daily injections"	43	0	8	0
"self monitoring" AND glucose	124	0	0	0
SMBG	31	0	5	0
Total unique, possibly relevant results:		*14*		*2*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 2 new, 2 potentially relevant.

Note: Assume website has been restructured or search interface / system changed since original search. Searched for words without quotation marks in 'Contains all the words' and terms in quotation marks in 'Advanced Search'. Sorted by Last updated and checked records for 2021 and 2022.

Swedish Agency For Health Technology Assessment And Assessment Of Social Services (SBU) website

Date searched: 12/04/21
Search box on home page: https://www.sbu.se/en/

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	not relevant; 'dialysis for acute hepatic failure'	1 (0 new)	
bionic pancreas	0		0	
diabetes > Filter on subject and publication type > Publication year From 2014 to 2021	30	0 relevant	5 new	0 relevant
insulin > Filter on subject and publication type > Publication year From 2014 to 2021	5	0 relevant	1 new	0 relevant
Total possibly relevant studies, published since 2014:		*0*		*0*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 0 relevant.

Cost-Effectiveness Analysis (CEA) Registry (via Tufts Medical Center)

Date searched: 14/04/21
Search interface: Basic search, Search for: Methods
http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx

Search terms	Total results	Results published since 2014	Number of new (not in previous sets), possibly relevant results	Results added since 2021	Number of new (not in previous CEA search or sets), possibly relevant results
closed loop	0	0	0	0	
artificial pancreas	0	0	0	0	

bionic pancreas	0	0	0	0	
insulin delivery	4	4	4	0	
minimed	2	2	1	0	
control IQ	0	0	0	0	
camAPS	0	0	0	0	
camdiab	0	0	0	0	
dexcom	1	1	1	1	1
insulin pump	10	9	7	0	
insulin pumps	3	2	0	0	
insulin infusion	20	15	5	0	
insulin infusions	0	0	0	0	
CSII	19	14	0	0	
glucose monitoring	16	14	6	2	0
glucose monitors	0	0	0	0	
glucose monitor	16	14	0	2	0
flash	6	2	0	0	
insulin injections	5	5	0	1	1
daily injections	17	11	1	1	0
blood glucose	47	22	2	3	0
smbg	17	10	0	1	0
Total unique, possibly relevant results:			*27*		*2*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 2 potentially relevant, but duplicates of those found in MEDLINE in original search.

ScHARRHUD

Date searched: 14/04/21
Search interface: https://www.scharrhud.org/index.php?recordsN1&m=search

closed loop OR artificial pancreas OR bionic pancreas AND 2014 > 2021:YR	0
(minimed OR control iq OR camAPS OR camdiab OR dexcom) AND 2014 > 2021:YR	0
sensor augmented OR sapt AND 2014 > 2021:YR	0
automated insulin OR insulin delivery AND 2014 > 2021:YR	0
insulin pump* OR insulin infusion* OR CSII AND 2014 > 2021:YR	1 (not relevant; type 2 diabetes)
glucose monitor* AND 2014 > 2021:YR	0
flash AND 2014 > 2021:YR	0
insulin inject* AND 2014 > 2021:YR	0
insulin injections AND 2014 > 2021:YR	0
daily injections AND 2014 > 2021:YR	0

MDI AND 2014 > 2021:YR	0
blood glucose AND 2014 > 2021:YR	0
smbg AND 2014 > 2021:YR	0

Update

*Note (07/04/22): Searching * in any field limited to 2021 to 2022 in Date in ScHARRHUD retrieved 0 results. Searching * in any field limited to 2020 to 2022 in Date in ScHARRHUD retrieved 302 results so no new records have been added since 2020. Therefore, the searches were not re-run.*

Additional targeted searches for individual parameters

Hypoglycaemia and Quality of Life

Date: 10/06/2022

Ovid MEDLINE(R) ALL <1946 to June 09, 2022>

1 hypoglycemia/ or insulin coma/ 29970
2 (hypoglycemi* or hypoglycaemi*).ti,ab,kf. 63398
3 1 or 2 70791
4 Quality-Adjusted Life Years/ 14835
5 (quality adjusted or adjusted life year$).tw,kf. 20920
6 (qaly$ or qald$ or qale$ or qtime$).tw,kf. 13223
7 (illness state$1 or health state$1).tw,kf. 7688
8 (hui or hui1 or hui2 or hui3).tw,kf. 1807
9 (multiattribute$ or multi attribute$).tw,kf. 1133
10 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).tw,kf. 18324
11 utilities.tw,kf. 8545
12 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).tw,kf. 15107
13 (euro$ adj3 (d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).tw,kf. 5797
14 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).tw,kf. 25017
15 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw,kf. 2184
16 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).tw,kf. 14297
17 quality of life/ and ec.fs.10868
18 quality of life/ and (health adj3 status).tw,kf. 10904
19 (quality of life or qol).tw,kf. and Cost-Benefit Analysis/ 7271
20 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or

effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. 47789
21 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).tw,kf. 4707
22 *quality of life/ and (quality of life or qol).ti. 61866
23 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).tw,kf. 36382
24 quality of life/ and health-related quality of life.tw,kf. 40638
25 models,economic/ 11001
26 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 202159
27 3 and 26 907
28 limit 27 to yr="2020 -Current" 177
29 (hypoglycemi* or hypoglycaemi*).ti. 21153
30 1 or 29 36314
31 26 and 30 358
32 limit 31 to yr="2020 -Current" 55 [Hypos and QoL 2020 onwards hypo terms in title or MeSH indexing]
33 28 not 32 122 [Hypos and QoL 2020 onwards hypo terms only in abstract or keywords]

Total: 177 exported in two batches (55 (line 32) and 122 (line 33)

Website searches

Date: 10/06/2022

Checked:

https://hypo-resolve.eu/publications

Quantitative papers sent by team members and noted in original sifting for economic evaluations.

10.2 Appendix 2: Additional characteristics of included RCTs

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
Tauschmann 2018 NCT02523131	UK, US	Modified 640G insulin pump (investigational use only; Medtronic, Northridge, CA, USA), Enlite 3 glucose sensor (Medtronic), and Contour Next Link 2.4 glucometer (Ascensia Diabetes Care, Basel, Switzerland).	a run-in period of at least 4 weeks. Participants were trained to perform a glucose sensor calibration check before breakfast and evening meals.	12 week		Next generation sensor-augmented Medtronic insulin pump 640G (Medtronic Minimed, CA, USA) incorporating the Medtronic Enlite 3 family real time CGM. Glucose suspend features will be turned off.	training on the effective use of real-time continuous glucose monitoring for optimisation of insulin therapy.	12 weeks	Similar to intervention
Bergenstal2021 NCT03040414	7 endocrinology practices, 4 in the USA, 1 Germany, 1 Israel, 1Slovenia	MiniMed 670G, Mean total daily insulin dose was 50 units (SD 21) in the 670G group, with an average of 25 units (SD 11; 51%)	a run-in phase, each participant was trained to use the study pump (without automated insulin delivery) and the	26 weeks two x 12 week periods.	12 weeks of 670G followed by 12 weeks of AHCL or vice versa	advanced hybrid closed loop systems consisted of the same Medtronic 670G insulin pump and Guardian Sensor 3 continuous glucose	The AHCL system was started with an auto mode target glucose setpoint of 120 mg/dL (6·7 mmol/L).	12 weeks, 2–4 weeks of start-up/run-in for device naive participants	12-week periods of closed-loop use (119 unscheduled visits occurred when using the advanced hybrid closed-loop system (1·1 per participant

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		of the insulin delivery as basal and 25 units (SD 12; 49%) as bolus	continuous glucose monitor. participants and a parent or guardian when applicable were trained on use of their assigned closed-loop system.			monitor, with only the software differing between systems			
Benhamou 2021 NCT04042207	France	DBLHU system: Dexcom G6 CGM system, Kaleido insulin pump, DBLHU handset software (Sony XZ1 all in one pump and CGM controller) v2019.5.9.2779, Diabeloop	2 week run-in, where patients used Medtronic 640g with smartguard	two consecutive crossover cycles of 4 week treatment periods	Hospital visits at weeks 4, 8, 12, 16 (i.e. at end of each DBLHU or PLGS treatment period in order to switch treatment sequences 24/7 helpline available to all patients	Standard Open Loop-PLGS system. an open-loop insulin delivery system, coupling an Enlite® CGM sensor with a Medtronic 640G insulin pump through Smartguard® safety system (Medtronic, Northridge, USA). *	Same as intervention (crossover trial)	Same as intervention (crossover trial)	Same as intervention (crossover trial)
Thabit2015 NCT01961622 and NCT01778348	UK,Germany, Austria	The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, UK)	run-in period lasting 4 to 6 weeks, training regarding the use of the insulin pump and the CGM device	**12 weeks**	During the first 2 days of closed-loop use, participants were contacted by telephone or email. Washout period	SAP (Identical insulin pumps and continuous glucose-monitoring devices were used during the	me as for HCL but HCL training was replaced by "Likewise on the first day of the control period, participants attended the	12 weeks,	Participants were not contacted within the first two days.

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
					lasting 4 to 6 weeks between intervention 1 and intervention 2.		clinical research facility for a similar duration." Participants were not contacted within the first two days.		
Ware20222925299	UK, USA (paediatric diabetes centres, 7 UK & USA)	Cambridge model predictive control algorithm (version 0.371) in two hardware configurations: FlorenceM and CamAPS FX	14 days run-in period, Masked CGM (Freestyle Libre Pro FGM system) whilst wearing their own insulin pump. After run-in, intervention participants and parents trained to use study insulin pump and study CGM, used in open loop mode for 3-4 weeks.	24 weeks	Follow up at 3 months and 6 months Participants contacted monthly to record adverse events	Insulin pump therapy, with or without sensor (usual care)	14 day run-in wearing masked CGM (Freestyle Libre Pro FGM system alongside their own insulin pump, with or without senso.**	24 weeks	Follow up at 3 months and 6 months Participants contacted monthly to record adverse events
Ware 2022 NCT03784027	Austria (Graz, Innsbruck, and Vienna), Germany (Leipzig), Luxembourg (Luxembourg), and the United Kingdom (Cambridge and Leeds)	The hybrid closed-loop system comprised an unlocked smartphone (Galaxy S8, Samsung) hosting the proprietary CamAPS FX application (CamDiab), which ran the Cambridge	caregivers were trained in the use of the trial glucose sensor, the trial insulin pump, and the CamAPS FX application. The application was used in open-loop mode for 2 to 4 weeks	initial treatment for 16 weeks and then crossed over to the second trial treatment after a washout period of 1 to 4 weeks	After two initial contacts by telephone or email in the first week of each treatment period, caregivers were contacted monthly to allow staff to record adverse events, device deficiencies, and	The CamAPS FX application was used during each trial period. During the sensor-augmented pump therapy period, closed-loop functionality was disabled.	Same as intervention group-crossover trial	initial treatment for 16 weeks and then crossed over to the second trial treatment after a washout period of 1 to 4 weeks	Crossover trial

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		proprietary model predictive control algorithm (version 0.3.71). The smartphone communicated wirelessly with both the Dana Diabecare RS insulin pump (Sooil) and the Dexcom G6 transmitter (Dexcom)	during the run-in period.		other relevant information. All the participants and caregivers had access to a 24-hour telephone helpline to the local research team.				
Boughton 2022 NCT04025762	UK (n=3 centres), Austria (n=1 centre) (diabetes outpatient clinics)	CamAPS FX hybrid closed loop system. CamAPS FX app (CamDiab, Cambridge UK), Cambridge adaptive model predictive control algorithm (v. 0.3.71); Dexcom G6 continuous glucose monitor, Dana Diabecare RS insulin pump	Baseline measurements and questionnaires. Study device training in SAP mode (auto mode disabled) for 3-4 week run-in period. If assigned to HCL first, this was used at home over 16 weeks	16 weeks	3 telephone or email contacts in the first 2 weeks of treatment period. Then monthly contact from study team to record adverse events, device deficiencies and other relevant information 24hr helpline available	Same devices as for closed loop intervention, but with auto mode function disabled	Baseline measurements and questionnaires. Study device training in SAP mode (auto mode disabled) for 3-4 week run-in period. If assigned to HCL first, this was used at home over 16 weeks	16 weeks	As for intervention (crossover trial)
Collyns, Wheeler 2022 NCT04073576	New Zealand (two centres)	MiniMed 670G with the addition	Two to 4 week run-in phase	4 weeks	None reported	Traditional sensor	Two to 4 week run-in phase	4 weeks	None reported

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		of: a choice of target set points of 5.6 mmol/L (100 mg/dL) or 6.7 mmol/L (120 mg/dL); and an automated correction bolus feature delivered up to every 5 min, correcting to 6.7 mmol/L (120 mg/dl).				augmented pump therapy with predictive low glucose management (SAP+PLGM)			
Kariyawasam 2022 NCT03671915	France (2 centres), Belgium (1 centre), paediatric endocrinology departments	DexCom G6 CGM and Diabeloop device (Diabeloop for Kids DBL4K HCL system), and Kaleido insulin pump (ViCentra, Netherlands), managed by DBLG1 application on an Android smartphone	Training session from investigators and clinical staff on how to insert and calibrate subcutaneous CGM, interpret data on the DexCom, and adjust insulin dose. Run-in period of 72 hours in hospital	6 weeks	Email or telephone contacts during the closed loop home phase, for assessments of safety and adherence, and for review of technical aspects of treatment	DexCom G6 CGM, combined with the participant's usual insulin pump, programmed with the usual basal settings. No additional functions activated.	As for intervention	6 weeks	As for intervention (crossover trial)
Stewart 2018 ISRCTN83316328	England (3 antenatal clinics)	Florence D2A closed loop system,	30-60 minute training session on device for	4 weeks	24 hour phone line staffed by research team	As intervention, but with auto	As for intervention	4 weeks	As for intervention (crossover trial)

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		University of Cambridge. Readings transmitted by Bluetooth to an android mobile phone Florence D2A control algorithm, version 0.3.41p DANA pump	closed loop group			mode disabled (SAP)			
von dem Berge 2022 NCT03815487	Germany (single centre)	Minimed 670G insulin pump, with a Guardian 3 glucose sensor connected to a Guardian Link 3 Transmitter (all Medtronic, Inc.	System briefing by diabetes educators for participants and parents 2 week run-in period with SAP functionality	8 weeks	Not reported	As intervention, but without closed loop functionality (PLGM)	As for intervention	8 weeks	As for intervention (crossover trial)
McAuley 2022 ACTRN12619000515190	Australia (two centres)	Guardian Sensor3 glucose sensor, MiniMed 670g insulin pump, Guardian Link3 transmitter and algorithm	Multidisciplinary education from diabetes nurse educators, dietitians, endocrinologists 3 to 6 week run-in period with	16 weeks	Clinical review visits, with device upload and review of pump settings in the first month and at mid point of each treatment period	As intervention with equipment used exclusively in manual mode (SAP)	As for intervention (crossover trial)	16 weeks	As for intervention (crossover trial)

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
			standard SAP therapy						

10.3 Appendix 3: RCTs additional outcomes

Outcomes	FLAIR 2022	Benhamou 2021	Tauschmann 2018	Thabit 2015	Ware 2022	Ware 2022	Boughton 2022	Collyns, [illegible] 2022	Kariyawasa [illegible] 2022	Stewart 2018	von dem [illegible] 2022	McAuley 2022
Intermediate measures												
· Fear of hypoglycaemia	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	YES
· Rate of severe hypoglycaemic events	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES
· Rate of severe hyperglycaemic events	YES	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO
· Episodes of diabetic ketoacidosis	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO
· Rate of ambulance call outs	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Rate of hospital out-patient visits	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Clinical outcomes												
· Retinopathy	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Neuropathy	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Cognitive impairment	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· End-stage renal disease	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Cardiovascular disease	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Additional clinical outcomes in women who are pregnant/have recently given birth:												
· Premature birth	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Miscarriage related to fetal abnormality	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Increased proportion of babies delivered by caesarean section	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Macrosomia (excessive birth weight)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Respiratory distress syndrome in the new-born	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Device related outcomes												
· Adverse events related to the use of devices	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Patient-reported outcomes												
· Heath-related quality of life	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Psychological well being	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
· Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

10.4 Appendix 4: Properties of RCTs not included for NMA but used for comparing HCL recipients in observational studies

	HbA1c% mean sd	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe *mean sd **Median IQR*	*N hypo severe *mean sd*	*DKA Event *mean sd*
Abraham et al., 2021 HCL MiniMed™ 670G- Guardian™ 3 sensor, Guardian™ Link 3 transmitter) vs. CSII or 10% on multiple injections/day +/- CGM vs. ; 5yr (3.1); N = 135 ; Tx 26 wks.											
Inter Base	7.8 (1.0)	41.8(15.4)	53.1(13.0)	*2.9(1.7,6.4)	NR	*1.1(0.6,3.2)	*0.6(0.2,1.8)	0.4(0.1,1.0)	*NR*	*3 (3.0)*	*3(4.5)*
Inter end	7.5 (1.1)	34.4 (13.0)	62.5 (12.0)	*2.2(1.7,6.4)	NR	*0.8(0.4,2.0)	*0.4(0.2,1.8)	0.3(0.1,0.5)			
DIFF	-0.3	-7.4	9.4	*-0.7	NR	*-0.3	*-0.2	-0.1	*7*		
Comp base	7.7 (0.8)	39.4(14.5)	54.6(12.5)	*4.8(2.6,9.0)	NR	*2.2(0.8,4.60)	*1.3(0.3,2.8)	0.7(0.2,1.7)	*NR*	*3(4.4)	*3(4.4)
Comp end	7.6	37.9 (13.8)	56.1 (12.2)	*4.1 (2.6,8.7)	NR	*1.8(0.7,4.1)	*1.0(0.4,2.3)	0.6(0.2,1.6)			
DIFF	-0.1	-1.5	1.5	*-0.7	NR	*-0.4	*-0.3	-0.1	*13*		
Rep.Net effect 95%CI	*-0.3 (-0.5,0.0)*	*-4.3 (-8.8,0.2)*	*6.7 (2.7,10.8)*	*-1.9 (-2.5,-1.3)*	*NR*	* *-1.0 (-1.2,-0.50)*	*-0.5 (-0.7,-0.3)*	*-0.3 (-0.4,-0.2)*	*- 6*	*0	*0
Breton 2020 : HCL vs. SAP ; 11.3 yr vs.-10.8 yr ; N 78 vs N 23 : Tx 16 weeks											
Inter Base *N78*	7.6 (1.0)	45 (18)	53 (17)	*1.2 (0.5,2.4)	NR	NR	*0.1 (0.0,0.4)	NR	NR	NR	NR

	HbA1c% mean sd	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe *mean sd **Median IQR*	*N hypo severe *mean sd*	*DKA Event *mean sd*
Inter end	7.0 (0.8)	31 (10)	67 (10)	*1.6 (0.8,2.4)	NR	NR	*0.2 (0.1,0.4)	NR	NR	NR	NR
DIFF	-0.6	-14	14	0.4	NR	NR	0.1	NR	*0.5/week (0.1,0.8)	0	0
Comp base *N23*	7.9 (0.9)	47 (17)	51 (16)	*1.0 (0.2,2.1)	NR	NR	*0.1 (0.0,0.3)	NR	NR	NR	NR
Comp end	7.6 (0.9)	43 (14)	55 (13)	*1.8 (1.1,3.0)	NR	NR	*0.3 (0.1.0.6)	NR	NR	NR	NR
DIFF	-0.3	-4	4	0.8	NR	NR	0.2	NR	*0.6 / week (0.1,1.0)	0	0
Net effect 95%CI	*-0.4 (-0.9,0.1)*	*-10 (-14,-6)*	*-10 (-14,-6)*	*-0.4 (-0.83,-0.02)*	NR	NR	*-0.07 (-0.19,0.02)*	NR	*P 0.16*	*0*	*0*
Brown et al., 2021 : HCL vs SAP ; 33 yr;; N = 112 vs. N = 56 ; Tx 6 months											
Inter Base *N112*	7.40 (9.6)	36 (19)	61 (17)	3.58 (3.39)	NR	NR	0.90 (1.36)	NR	NR	NR	NR
Inter end	7.06 (0.79)	27 (12)	71 (12)	1.58 (1.15)	NR	NR	0.29 (0.29)	NR	NR	NR	NR
DIFF	-0.34	-9	10	-2	NR	NR	-0.61	NR	*0.4/week (0.1,0.9)	0	1*(dev rel)*
Comp base *N56*	7.4 (0.76)	38 (15)	59 (14)	2.84 (2.54)	NR	NR	0.56 (0.79)	NR		NR	NR
Comp end	7.39 (0.92)	38 (15)	59 (14)	2.25 (1.46)	NR	NR	0.35 (0.32)	NR		NR	NR
DIFF	0.01	0	0	-0.59	NR	NR	-0.21	NR	*0.5/week (0.2,0.9)	0	0
Net effect 95%CI	*-0.3 (-0.53,-0.13)*	*-10 (-13,-8)*	*11 (9,14)*	*-0.88 (-1.19,-0.57)*	NR	NR	*-0.01 (-0.19,-0.02)*	NR	*P 0.06*	0	*1(dev rel)*

Superseded – see updated external assessment report (15 November 2022)

1.1 Appendix: Exploratory paediatric modelling

As reviewed in section 1.2.1.4.3 above the EAG has concerns about the reliability of using the iQVIA CDM to model a paediatric population. Exploratory analysis using the EAG NMA results for the subset of paediatric studies and a scenario analysis that applies the NSHE paediatric pilot results are presented. Given the mean baseline age the time horizon is extended to the iQVIA CDM maximum of 80 years.

Table 30: Exploratory paediatric modelling: HbA1c (s.e.) changes

	NMA	NMA paed.	NHSE pilot paed.
HCL	-0.28% (0.033%)	-0.31% (0.059%)	[redacted]
PLGS	-0.06% (0.079%)	-0.11% (0.125%)	[redacted]
CSII+CGM	0.00%	0.00%	[redacted]

Patient baseline characteristics are revised to reflect the NHSE paediatric pilot baseline data.

Table 31: Exploratory paediatric modelling: baseline characteristics

	NHSE pilot paed.	
	Mean	s.d.
Age	[redacted]	[redacted]
Duration diabetes	[redacted]	[redacted]
HbA1c	[redacted]	[redacted]
Male	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]

It is further assumed that paediatric patients have not developed any of the complications associated with diabetes and modelled by the iQVIA CDM. As reviewed in section

1.2.1.4.3 the ERG presents a scenario using the Pittsburg CVD modelling. For the EAG NMA results a scenario assuming CSII is 75% isCGM and 25% rtCGM is presented.

Note that the NHSE paediatric pilot reported time in hypoglycaemia of [redacted] prior to HCL and [redacted] with HCL, a ratio of [redacted] which is similar to the [redacted] of the EAG base case for CSII+CGM to HCL.

The paediatric pilot also reports the means of the HFS2-ws at baseline and at 6 months for the subset of children of at least 12 years of age, [redacted] and [redacted] respectively, and means of an amended HFS for parents with young children of [redacted] and [redacted] respectively. This suggests child quality of life decrements for the comparator of [redacted] and for HCL of [redacted]. The EAG presents a scenario that applies the child disutilities for the time horizon of the model. It also provides a scenario analysis that trebles this for 15 years to allow for parental quality of life changes.

Table 32: Exploratory paediatric modelling: base case disaggregate results

		PLGS		HCL	
	CSII	Value	net vs CSII	Value	net vs CSII
LYs Undiscounted	60.123	60.291	0.168	60.942	0.819
QALYs					
iQVIA CDM modelled	19.252	19.301	0.049	19.448	0.196
NHSEs	0.000	0.000	0.000	0.000	0.000
SHEs	0.000	0.000	0.000	0.000	0.000
Total QALYs	19.252	19.301	0.049	19.448	0.196
Costs					
Treatment	£114,157	£138,421	£24,264	£154,762	£40,606
Routine OP	£16,129	£16,146	£17	£16,212	£83
SHEs	£0	£0	£0	£0	£0
Other management	£2,182	£2,192	£10	£2,214	£32
CVD	£2,088	£2,067	-£21	£2,000	-£88
Renal	£13,468	£12,774	-£693	£11,008	-£2,459
Ulcer/Amp./Neuropathy	£1,754	£1,707	-£47	£1,691	-£63
Eye	£26,850	£25,264	-£1,586	£21,707	-£5,143
Total Costs	£176,628	£198,572	£21,944	£209,595	£32,966

Table 33: Exploratory paediatric modelling: base case results summary

	CSII	PLGS	HCL
LYs Undiscounted	60.123	60.291	60.942
Total QALYs	19.252	19.301	19.448
Total Costs	£176,628	£198,572	£209,595
ICER vs CSII	..	£447,834	£168,196

As with the adult modelling, PLGS is extendedly dominated by HCL and the EAG does not consider it further.

HCL is estimated to increase overall discounted survival compared to CSII+CGM by 0.819 years, though it should be noted that this will be a slight underestimate due to around 10% of patients remaining alive at the end of the 80 year time horizon. The additional treatment costs of £40,606 are partially offset by savings in renal complications of £2,459 and in eye diseases of £5,143 resulting in total net costs of £32,966. Coupled with the gain of 0.196 QALYs yields a cost effectiveness estimate of £168,196 per QALY.

Table 34: Exploratory paediatric modelling: scenario analyses

	Δ Costs	Δ QALYs	ICER
Base case	£32,966	0.196	£168k
SA01a: Only paediatric studies	£30,924	0.266	£116k
SA02a: NHSE paediatric pilot	£25,448	0.465	£54,727
SA02b: SA2a + HFS2-ws QoL	£25,448	0.722	£35,259
SA02c: SA2a + triple HFS2-ws QoL	£25,448	0.984	£25,868
SA02d: SA02a + reduced complications costs	£32,091	0.465	£69,013
SA03: Pittsburgh CVD modelling	£32,245	0.169	£191k
SA04: CSII 75% isCGM and 25% rtCGM	£26,961	0.196	£138k

The base case cost effectiveness estimate of £168k per QALY improves quite markedly to £116k per QALY if only paediatric studies are included.

The cost effectiveness hugely improves to £10,979 if the [redacted] of the NHS paediatric pilot is applied. This more than doubles the undiscounted survival gain from 0.819 to 2.025 years. Net treatment costs of £41,684 also have larger cost offsets from reduced renal complications, £5,458, and reduced eye complications £10,646. Total net costs of £25,448 and gains of 0.465 QALYs result in a cost effectiveness estimate of £54,727 per QALY. Including the quality of life effects of the improvements reported in the HFS2-ws during the pilot improves the cost effectiveness to £35,259 per QALY, while if both parents also have a similar quality of life improvement for 15 years it improves further to £20,602 per QALY. Also applying the change in the HFS2-ws to account for the quality of life of hypoglycaemia improves the cost effectiveness estimate to £35,259 per QALY. If 2 parents experience similar quality of life improvements for 15 years the cost effectiveness further improves to £20,602 per QALY. Reducing the cost of complications to account for their possible overestimation worsens the cost effectiveness to £69,013 per QALY.

In all of the above, the HbA1c effect, the HFS2-ws effect and the composition of CSII+CGM may change as the patient moves from childhood into adulthood.

1.2 Appendix: Non-specific mortality

The iQVIA CDM explicitly models deaths from MI, CHF, stroke and renal disease. These causes of death need to be removed from the England and Wales life tables to yield "non-specific mortality" estimates. Due to Covid-19 the EAG uses the 2015-2017 England and Wales life table. An adjustment factor is applied to the annual probabilities of death, being the fraction of all deaths among those of a given age that are not caused by the following ICD-10 codes.

Table 35: ICD-10 codes for deaths modelled within iQVIA CDM

ICD10	Cause of death
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I50	Heart failure
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
N17	Acute renal failure
N18	Chronic kidney disease
N19	Unspecified kidney failure

The iQVIA modellers suggest that hypertension may also be reasonable to exclude, codes I10-I13 and I15, this resulting in a slightly different set of estimates. But there may be competing risks in that those who died of, say, myocardial infarction had they not died of it been at greater risk of dying from other comorbidities than the average. As a consequence, the adjustment may be too large which may argue for a sensitivity analysis of simply applying the unadjusted all-cause mortality while recognising that the best estimate may lie somewhere between this and those of the base case.

Table 36: All cause and non-specific mortality that excludes that modelled by iQVIA CDM

	All cause mortality		Non-specific base case		Non-specific inc. hyper.	
Age	Male	Female	Male	Female	Male	Female
0	0.00431	0.00356	0.00430	0.00356	0.00430	0.00356
1	0.00024	0.00022	0.00024	0.00021	0.00024	0.00021
5	0.00009	0.00009	0.00009	0.00008	0.00009	0.00008
10	0.00008	0.00006	0.00007	0.00006	0.00007	0.00006
15	0.00017	0.00010	0.00017	0.00010	0.00017	0.00010
20	0.00050	0.00018	0.00049	0.00018	0.00049	0.00018
25	0.00055	0.00025	0.00053	0.00025	0.00053	0.00025
30	0.00072	0.00036	0.00069	0.00035	0.00069	0.00035
35	0.00099	0.00056	0.00094	0.00053	0.00093	0.00053
40	0.00146	0.00085	0.00136	0.00080	0.00134	0.00079
45	0.00225	0.00138	0.00203	0.00130	0.00201	0.00129
50	0.00326	0.00210	0.00291	0.00195	0.00287	0.00194
55	0.00468	0.00312	0.00417	0.00290	0.00412	0.00288
60	0.00744	0.00491	0.00666	0.00455	0.00658	0.00451
65	0.01181	0.00775	0.01061	0.00715	0.01050	0.00709
70	0.01796	0.01210	0.01609	0.01100	0.01592	0.01089
75	0.03064	0.02079	0.02725	0.01853	0.02697	0.01831
80	0.05310	0.03779	0.04689	0.03333	0.04632	0.03284
85	0.09361	0.07158	0.08259	0.06288	0.08149	0.06171
90	0.15812	0.13211	0.13999	0.11701	0.13762	0.11421
95	0.26151	0.22718	0.23152	0.20122	0.22761	0.19641
100	0.38711	0.35129	0.34272	0.31115	0.33693	0.30370
105	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000

1.3 Appendix: Baseline characteristics

NG17 provides the following additional patient baseline characteristics.

Table 37: NG17 additional patient baseline characteristics

	Mean	s.d.	Source
Systolic blood pressure (mmHg)	131.3	16.3	Repose trial
Diastolic blood pressure (mmHg)	80	0	IQVIA CDM default
Total Cholesterol (mg/dL)	90	16.2	Repose trial
High density cholesterol (mg/dL)	28.8	7.2	Repose trial
Low density cholesterol (mg/dL)	50.4	16.2	Repose trial
Triglyceride (mg/dL)	25.2	18	Repose trial
Body mass index (kg/m2)	27.2	5	Repose trial
Estimated GFR (ml/min/1.72m)	78.58	13.24	REPOSE6
Haemoglobin (gr/dl)	14.5	0	IQVIA CDM default
White blood cell count (10	6.8	0	IQVIA CDM default
Heart rate (bpm)	72	0	IQVIA CDM default
Waist to hip ratio	0.93	0	IQVIA CDM default
Waist circumference	87.84	n/a	IQVIA CDM default
Urinary Alb. creatinine (mg.mmol)	4.78	10.19	Repose trial
Serum Creatinine (mg/dL)	1.1	0	IQVIA CDM default
Serum Albumin (g/dl)	3.9	0	IQVIA CDM default
Prop. Smoker	0.192	n/a	Repose trial
Cigarettes/ day	15	n/a	HSE 2017/18 DM subset
Alcohol consumption (Oz/week)	7.7	n/a	WHO
Prop. Physical activity	62%	n/a	HSE 2017/18 T1DM subset
Fasting glucose	180.72	n/a	IQVIA CDM default
Prop. Family history stroke	0.0436	n/a	IQVIA CDM default
Prop. Family history CHD	0.1474	n/a	IQVIA CDM default

NG17 provides the following patient baseline complication rates.

Table 38: NG17 patient baseline complication rates

	Mean	s.d.	Source
MI	2.2%	n/a	Repose trial

Angina	1.2%	n/a	Repose trial
Peripheral vascular disease	0.0%	n/a	Assumption
Stroke	0.3%	n/a	Repose trial
Heart failure	0.6%	n/a	Repose trial
Atrial Fibrillation	0.0%	n/a	Assumption
Left ventricular hypertrophy	0.0%	n/a	Assumption
Microalbuminuria	12.0%	n/a	Repose trial
Gross proteinuria	4.5%	n/a	Repose trial
End stage renal disease	0.0%	n/a	Assumption
Background retinopathy	34.8%	n/a	Repose trial
Proliferative diabetic retinopathy	9.3%	n/a	Repose trial
Severe vision loss	0.0%	n/a	Assumption
Macular Oedema	0.0%	n/a	Assumption
Cataract	0.0%	n/a	Assumption
History of foot ulcer	0.0%	n/a	Assumption
History of amputation	0.0%	n/a	Assumption
Neuropathy	7.1%	n/a	Repose trial

NICE National Institute for Health and Care Excellence

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes Multiple Technology Appraisal
Comments on the Assessment Report

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Tandem	1	45	2.3.1.3	We recommend revision of the description for the Tandem hybrid closed loop system to the following, for clarity and accuracy: "The Control-IQ system (Tandem Diabetes Care) is a CE marked advanced hybrid closed loop system that combines a t:slim X2 insulin pump, the embedded Control-IQ automated insulin dosing algorithm, and a compatible CGM. The system subcutaneously delivers insulin by automatically increasing, decreasing, and suspending delivery of basal insulin based on CGM readings and predicted 30-minute glucose values. It delivers patient entered meal boluses and can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold. Data from Control-IQ can be uploaded on the Diasend/Glooko cloud data systems for patient and clinician review. Control-IQ is not licensed for use in children under 6 years, or for people who require less than a total daily dose of 10 units/day or who weigh less than 55 pounds, as those are the required minimum values needed to operate the system safely."	Thank you for clarifying
Tandem	2	60	4.1.3	The report states that the relevant comparators for the clinical evidence review for effectiveness are non-integrated, real time continuous glucose monitoring with continuous subcutaneous insulin infusion and intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion. However, the systematic review and network meta-analysis also includes studies with low glucose suspend and predictive low glucose suspend. As such, the randomized controlled trials by Brown et al.[1] and Breton et al.[2], with % HbA1c difference of -0.33% and -0.4% for hybrid closed loop vs sensor augmented pump, respectively, should have been included in the review and network meta-analysis. Since the cost-effectiveness model applies the results of the network meta-analysis and the cost-effectiveness is driven by the HbA1c change and durability of that change, omission of these studies is a critical limitation and leads to underestimation of the clinical benefit of hybrid closed loop. [1] Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, Laffel LM, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med 2019;381(18):1707-17. [2] Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med 2020;383(9):836-45.	The two studies were identified and excluded for the following reasons: Brown: >10% not on prior intervention pump or monitor, results were not reported separately/stratified by prior intervention. Berton: >10% not on prior intervention pump or monitor, results were not reported separately/stratified by prior intervention. Please see 4.1.3 for inclusion and exclusion criteria.

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					The EAG followed the pre-specified inclusion and exclusion criteria listed in section 4.1.3.
Tandem	3	198	7.2.1.7	The model includes additional training costs for hybrid closed loop that are based on 3 consultant led OP visits, 3 nurse led OP visits, 3 nurse follow up call or emails, and an additional nurse hour for a fitment visit. We would like to point out that it is common practice for manufacturers and distributors to provide hybrid closed loop system training (i.e., continuous glucose monitoring and hybrid closed loop trainings [redacted]. For Tandem's hybrid closed loop system, users self-train on the Dexcom CGM and Control-IQ technology using virtual online training tools, which is followed up by additional training by Air Liquide. Of note, Tandem's virtual trainings have been found to be effective and preferred by users.[1] While we recognize there are costs incurred by the diabetes centers, we want to ensure that these costs are not overestimated given significant resources and costs incurred by distributors and manufacturers. [1] Jordan E. Pinsker, Harsimran Singh, Molly McElwee Malloy, Alexandra Constantin, Scott Leas, Krista Kriegel, and Steph Habif. A Virtual Training Program for the Tandem t:slim X2 Insulin Pump: Implementation and Outcomes. Diabetes Technology & Therapeutics. Jun 2021.467-470.http://doi.org/10.1089/dia.2020.0602	This does not apply to the base case or the majority of the analyses. This only applies to the sensitivity analysis around an additional £1,132 cost for transferring from CSII+CGM to HCL. The sensitivity analysis should be viewed in the light of the additional information from Tandem.
Tandem	4	199	7.2.1.7	We would like to refer to Air Liquide's pricing for Tandem's hybrid closed loop system as the cost estimate in the model is higher than actual product prices.	The costings have been supplied by NHS Supply Chain using current tender prices.
Tandem	5	199	7.2.1.7	The model's cost for the continuous glucose monitoring component of the continuous glucose monitoring with continuous subcutaneous insulin infusion appears to be largely for intermittently scanned glucose monitoring (i.e., model assumes 90% patients using intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion and 10% using real time continuous glucose monitoring with continuous subcutaneous insulin infusion), whereas the input for clinical benefit is largely based on studies on real time continuous glucose monitoring with continuous subcutaneous insulin infusion. This approach is not appropriate; we recommend separately evaluating real time continuous glucose monitoring and intermittently scanned glucose monitoring.	The pooled comparator of 90% CSII+isCGM and 10% CSII+rtCGM reflects current NHS practise. It is not appropriate to separately model the cost effectiveness of HCL against CSII+rtCGM and CSII+isCGM as this could result in perverse incentives for patients to

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					seek to adopt the more costly CSII+rtCGM.
Tandem	6	204	7.2.2.1	We have serious concerns with these findings, given the following limitations: • Assessment of Clinical Effectiveness: The report states that the relevant comparators for the clinical evidence review for effectiveness are non-integrated, real time continuous glucose monitoring with continuous subcutaneous insulin infusion and intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion. However, the systematic review and network meta-analysis also includes studies with low glucose suspend and predictive low glucose suspend. As such, the randomized controlled trials by Brown et al.[1] and Breton et al.[2], with % HbA1c difference of -0.33% and -0.4% for hybrid closed loop vs sensor augmented pump, respectively, should have been included in the review and network meta-analysis. Since the cost-effectiveness model applies the results of the network meta-analysis and the cost-effectiveness is driven by the HbA1c change and durability of that change, omission of these studies is a critical limitation and leads to underestimation of the clinical benefit of hybrid closed loop. • Costs: The model includes cost inputs that are not appropriate. o The cost input for continuous glucose monitoring with continuous subcutaneous insulin infusion appears to be largely for intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion (i.e., model assumes 90% patients using intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion and 10% using real time continuous glucose monitoring with continuous subcutaneous insulin infusion), whereas the input for clinical benefit is largely based on studies on real time continuous glucose monitoring with continuous subcutaneous insulin infusion. o The cost input for hybrid closed loop is higher than actual product prices. The above-mentioned limitations contribute to an incremental cost-effectiveness ratio of £178,925, which as NICE states is an order of magnitude larger than if NHS adult pilot baseline patient characteristics and effect were used (incremental cost-effectiveness ratio of £12,398) and other cost-effectiveness analyses in the peer-review literature. Tandem urges NICE to address these limitations in its assessment of the clinical benefit and cost-effectiveness of hybrid closed loop. [1] Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, Laffel LM, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med 2019;381(18):1707-17. [2] Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med 2020;383(9):836-45.	Please see 4.1.3 for Brown and Breton For costs please see above points.

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Air Liquide Healthcare Ltd	1	13		[redacted]	The costs that are applied are those supplied by NHS Supply Chain using current tender prices.
Air Liquide Healthcare Ltd	2	199	7.2.1.7 & Table 26	[redacted]	The costs that are applied are those supplied by NHS Supply Chain using current tender prices.
Air Liquide Healthcare Ltd	3	204	7.2.2.1	Air Liquide would like to highlight the following limitations: Assessment of Clinical Effectiveness: The report notes that the comparators for the clinical evidence review are non-integrated, real time continuous glucose monitoring with continuous subcutaneous insulin infusion (rtCGM+CSII) and intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion (isCGM+CSII). The review and meta-analysis also include studies with low glucose suspend (LGS) and predictive low glucose suspend (PLGS). The randomised controlled trials by Brown et al.[1] and Breton et al.[2], with % HbA1c difference of -0.33% and -0.4% for hybrid closed loop (HCL) vs sensor augmented pump (SAP), respectively, should be included in the review and MA. As the cost-effectiveness model applies the results of the MA and the cost-effectiveness is driven by the HbA1c change, leaving out these studies is a limitation and leads to underestimation of the benefit of HCL. Costs - The model has cost inputs that are not balanced. The cost input for continuous glucose monitoring with continuous subcutaneous insulin infusion (CGM+CSII) appears to be largely for isCGM+CSII (i.e., model assumes 90% patients using isCGM+CSII and 10% using real time continuous glucose monitoring with continuous subcutaneous insulin infusion (rtCGM+CSII)), whereas the input for clinical benefit is largely based on studies on rtCGM+CSII. The costs for HCL is higher than actual product prices as stated above. The limitations contribute to an ICER of £178,925, which as NICE reports is an order of magnitude larger than if NHS adult pilot baseline patient characteristics and effect were used (ICER of £12,398) and other cost-effectiveness analyses in the literature. NICE should address these limitations in its assessment of the clinical benefit and cost-effectiveness of HCL.	The EAG were advised by clinical advisors that SAP/PLGS is a technology between HCL and CGM. If SAP/PLGS is not integrated then it is a valid comparator. We included studies were the comparators had the functions (integrated) disabled or not clear. The EAG can provide a subgroup analysis with and without SAP studies. Please see 4.1.3 for Brown and Breton For costs please see above points.

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				[1] Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, Laffel LM, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med 2019;381(18):1707-17. [2] Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med 2020;383(9):836-45.	
ABCD Diabetes Technology Network UK				The Diabetes Technology Network UK are grateful for the opportunity to give feedback on this important draft assessment of hybrid closed loop (HCL) systems. **Key Issues** 1. **Comparators used were not as specified in the original question:** On page 5, the document states that the objectives of this analysis are *"to examine what is the clinical effectiveness of HCL in those with T1DM who have difficulty managing their condition despite prior use of at least **ONE** of the following technologies: CSII, CGM and Flash GM."* However, all the analyses and indeed the cost effectiveness has been done against people using **TWO** technologies - CSII + CGM. In this way, we do not believe the clinical or cost effectiveness analyses meet the objectives set out. This has ultimately led to a significant under-estimate of the clinical effectiveness, and thus the cost effectiveness. The analysis included trials comparing hybrid closed loop (HCL) with sensor augmented pump (SAP) therapy. SAP includes an insulin pump and rtCGM which are not linked by an algorithm, but where the patient makes treatment decisions based on the rtCGM data. From a clinical perspective of currently available systems, comparators such as SAP and PLGM are redundant and in fact are not offered by most providers. We fail to understand why analyses comparing HCL to CSII + SMBG, HCL to CSII+ isCGM or HCL to isCGM / CGM were not conducted or included in the analysis. The analysis performed by The Scottish Health Technology Group is more relevant and found HCL to be cost effective compared to CSII + SMBG.	The comparators are (as per NICE scope): Continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated) Intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion The EAG were advised by clinical advisors that SAP/PLGS is a technology between HCL and CGM. If SAP/PLGS is not integrated then it is a valid comparator. We included studies were the comparators had the functions (integrated) disabled or not clear. The EAG can provide a subgroup analysis with and without SAP studies. CSII+SMBG was not listed as a comparator in the NICE scope

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ABCD Diabetes Technology Network UK				**2. isCGM was assumed to be similar to rt-CGM for this analysis -** While clinical effectiveness was evaluated using studies that used CSII+ rtCGM (SAP) as a comparator, cost-effectiveness was done using prices of isCGM which is significanltly cheaper. This requires that clinical data or benefits seen with CSII +rtCGM can applied to CSII + isCGM. No evidence is presented to support this claim, which in our clinical opinion is flawed, and which has a significant impact on the cost-effectiveness analysis (Table 26 on p199 of the report gives an average annual cost for HCL systems of £5744, against an average annual cost of SAP systems using CSII plus CGM of £4184, a difference of £1560). Observational data suggests that isCGM and rtCGM are not, in fact equivalent in terms of outcomes[1]. From a clinical perspective, there are key differences between isCGM and rtCGM 1. Data on isCGM systems can only be accessed when the patient actively “swipes” the reader, while rtCGM systems provide continuous data. 2. SAP systems used in the trials use CSII and rtCGM and some had “predictive low” and “predictive high” alarms that offer additional functionality over and above that provided by isCGM that only offers threshold alarms. 3. Data from the sensor in SAP systems is transmitted and displayed straight on the pump, and sensor glucose data is pre-populated in bolus advisors incorporated in these systems. This does not happen with isCGM systems. We would therefore argue that the approach in the draft report is significantly flawed. using clinical data from studies comparing HCL with CSII and rtCGM while judging cost-effectiveness of HCL against sensor-augmented pump therapy (CSII plus rtCGM or isCGM not linked in a HCL system) assuming 90% of the comparator group to be using isCGM is likely to significantly underestimate the cost-effectiveness of HCL systems. Indeed, using the costs of the systems as studied, the relative cost of using HCL instead of SAP should be £0, not £1560 as suggested in the report. The benefits from HCL over SAP are at no additional cost, and as such the ICER of HCL over SAP should be dominant/cost effective.	Point of view, no response required.

[1] Lower glycated hemoglobin with real-time continuous glucose monitoring than with intermittently scanned continuous glucose monitoring after 1 year: The CORRIDA LIFE study *Diabetes Technology and Therapeutics* (2022) 24(12). DoI: 10.1089/dia.2022.0152

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				This may explain the huge difference in ICER from this report when compared to the ICER obtained when using the NHS England Pilot data and cost effectiveness analyses from the SHTG and from Sweden. If this flawed analysis stands, this will prohibit access to a technology which we know dramatically improves outcomes in people living with diabetes, as shown in the ABCD DTN-UK real world data.	
ABCD Diabetes Technology Network UK				**3. Serious errors of understanding:** The document has a number of serious errors such as the incorrect use of critical outcomes such as time in range and time below range and also repeated reference to an outdated version of the NICE guidance in which there was no recommendation for isCGM or rt-CGM. The latest NICE guidance recommends ALL people with T1D should have access to isCGM or rt-CGM based on discussion with their care team on the basis of 16 factors set out in the recommendation. This is backed up by a published cost-effectiveness analysis that is under the willingness to pay threshold. Therefore, the primary question should have been around the cost effectiveness of HCL over and above the standard set by the current NICE guidance which is isCGM or rtCGM with MDI. The analysis done, comparing SAP with HCL, is not of clinical relevance.	The NICE scope listed two comparator: • Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion. The EAG were advised by clinical advisors that SAP/PLGS is a technology between HCL and CGM. If SAP/PLGS is not integrated then it is a valid comparator. We included studies were the comparators had the functions (integrated) disabled or not clear. The EAG can provide a subgroup analysis with and without SAP studies.

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ABCD Diabetes Technology Network UK				4. **Lack of analysis showing the HbA1c level at which HCL provides a ICER below the treatment threshold:** Clinical data from the NHS England HCL pilot, and also the ADAPT study[2], suggest that those with higher starting HbA1c results achieve a greater reduction in HbA1c with HCL systems. The cost-effectiveness analysis as presented proposes that the HbA1c reduction achievable using HCL systems remains constant irrespective of baseline HbA1c. This is a different approach to that taken in NICE TA151, where a regression analysis was used to identify the threshold HbA1c level below which pump therapy was cost effective. We believe this type of analysis would have provided the NHS with the most effective way to use this technology. As evidence from the Real World ABCD DTN-UK HCL pilot shows, the systems are strongly cost effective when used in people using CSII + isCGM with baseline HbA1c > 8.5%. A regression analysis using data from RCT's that had low baseline HbA1c levels, the ADAPT RCT with a baseline of 8.9% and the NHSE pilot with baseline of 9.4% would have provided a threshold HbA1c level below which these systems would have met the payment thresholds. The report acknowledges that the studies used in the report had a narrow range of HbA1c that is not representative of the reality of clinical practice in England. Only 9.8% of people achieve the NICE target HbA1c of 48 mmol/mol (6.5%) or less. 67.2% have an HbA1c over 58 mmol/mol (7.5%) of which 39.2% have an HbA1c over 70 mmol/mol (8.5%). Using a population with baseline HbA1c 7.6% significantly underestimates the potential risk of future complications as well as minimising the benefit achievable using HCL systems, both of which will underestimate the benefits of HCL systems. **Additional information :** We have completed a regression analysis of benefit from HCL based on the NHSE HCL pilot data (adults) that we are happy to share with the NICE committee.	HbA1c threshold analyses: This has been provided to NICE prior to the first Committee meeting. Within the cost effectiveness it is not just the HbA1c effect, but the starting HbA1c that matters. Hypoglycaemia: The EAG will read Bosi et al prior to the Committee meeting. However, the patients of Bosi et al may not be representative of those who would receive HCL if approved by NICE. QoL: The psychological benefits are in part addressed by the scenario analyses around changes in the HFS, brought about through changes in non-severe and severe hypoglycaemia episodes. To the extent that these tend to be correlated with any other psychological benefits they have not

[2] Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study *Lancet Diabetes and Endocrinology* (2022) https://doi.org/10.1016/S2213-8587(22)00212-1

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				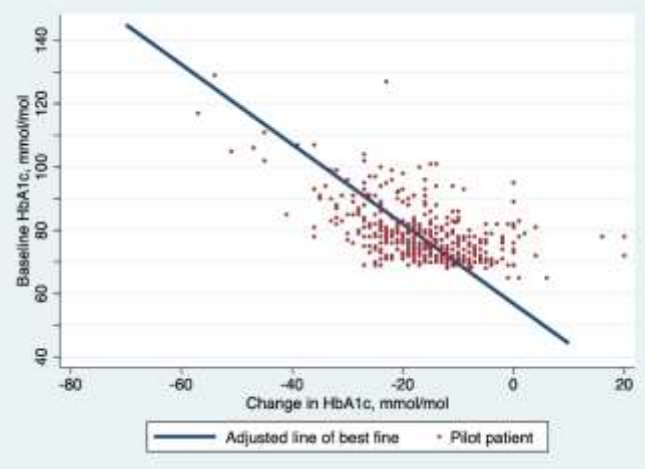 This analysis shows the regression line for baseline HbA1c and change in A1c. Of course, the line is truncated at 69 mmol/mol as that was the entry criteria. **Hypoglycaemia** The studies chosen in the NICE analysis all excluded people with problematic hypoglycemia. It is therefore not surprising that no difference in hypoglycaemia was seen. We would urge the panel to consider the SMILE study [Bosi et al; Lancet Diabetes Endocrinol. 2019 Jun;7(6):462-472], an RCT of 153 participants at high risk of hypoglycemia, defined as impaired awareness of hypoglycaemia or a recent episode of severe hypoglycaemia, who were randomised to Predictive Low Glucose Management (PLGM, a precursor technology of HCL) or to remain on stand alone pump therapy. PLGM was associated with a 73% reduction in episodes of sensor detected hypoglycaemia and an 87% reduction of severe hypoglycaemia. The time below 3.0 and 3.9 mmol/l seen in this study are similar to those seen with HCL and are significantly lower than populations using pump alone or CGM alone. As insulin suspension occurs at even higher glucose levels in HCL than in PLGM, it is scientifically reasonable to assume that similar reductions can be expected in high risk participants using HCL **Quality of life** As clinicians supporting people with diabetes who move across to HCL systems, the most stark change in outcomes in the clinical setting is the reported improvement in quality of life. Type 1 diabetes is an extremely	been overlooked. If there are additional aspects of the technology that lead to psychological benefits these have not been addressed, but these additional technological benefits are not described by the ABCD DTN. This remains subject to the concerns around hypoglycaemia event rates.

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				demanding condition to live with, requiring almost hourly monitoring and decision making throughout the day in an attempt to keep glucose levels in the target range. HCL reduces this burden. In the NHS ABCD HCL pilot audit we observed a reduction in diabetes related distress from [redacted]. This reflects our clinical experience: there is no other technology which better improves psychological burden in Type diabetes than HCL therapy. However, the draft report overlooks the psychological benefits of this therapy which is disappointing given this is a clear and central benefit of HCL therapy. DTN-UK urge NICE to reassess the cost effectiveness of HCL by using appropriate comparators (isCGM or isCGM+ CSII) using the costs of these interventions. Further specific points are highlighted below.	
ABCD Diabetes Technology Network UK	1	49	2.3.3	The assessment reports outdated NICE guidance from a previous version of NG17 (Type 1 diabetes in adults: diagnosis and management). In paragraph 1.6.10 the most recent version of NG17 recommends “Offer adults with type 1 diabetes a choice of real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM, commonly referred to as 'flash'), based on their individual preferences, needs, characteristics, and the functionality of the devices available.” Furthermore, the updated guidance recommends that one of the factors to be taken into account when selecting a CGM device is “The person's insulin regimen or type of insulin pump, if relevant (taking into account whether a particular device integrates with their pump as part of a hybrid closed loop or insulin suspend function)”. Taken together, these recommendations indicate that rtCGM has been evaluated by NICE already as a cost-effective intervention, and where somebody is already using an insulin pump the choice of CGM device should take into account the possibility of adding CGM to insulin pump therapy to make a HCL system. This is very different from the outdated recommendations used for the report.	The EAG are happy to update figure 1 to incorporate the factors associated with CGM use
ABCD Diabetes Technology Network UK	2	6		The analysis presented does not tally with the overall question posed which talks about clinical effectiveness of HCL in those with T1DM who have difficulty managing their condition despite prior use of at least ONE of the following technologies: CSII, CGM and Flash GM. however, all the analyses and indeed the cost effectiveness are done against people using TWO technologies - CSII + CGM	The population included in the analysis had a prior intervention. The analysis was presented in relation to the comparators rather than prior use of interventions (eligibility criteria and not comparator).
ABCD Diabetes Technology	3	37	2.2.1	We would urge the NICE committee to consider the diabetes technology pathway that identified the way the different guidance for use of diabetes technology are currently used. [Choudhary et al; Diab Med.2019 May;36(5):531-538]	Point of view for the committee

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Network UK					
ABCD Diabetes Technology Network UK	4	45	2.3.1.1	The Medtronic 670G system is no longer available in the UK and has been superseded by the Minimed 780G. Of note, there are significant advances in the algorithm and real-world data suggest that there is greater Time in Range (equivalent to lower HbA1c) with M780G compared to Minimed 670G.	The Medtronic 670G was listed in the NICE scope. The aim was to assess HCL as an overall technology rather than specific models.
ABCD Diabetes Technology Network UK	5	48	Fig 1	This is outdated. As per NICE guidance in March 222, ALL people with Type 1 diabetes are recommended to use isCGM or rtCGM according to various factors as explained in point 1.	The EAG are happy to update figure 1 to incorporate the factors associated with CGM use
ABCD Diabetes Technology Network UK	6	49	2.3.3.1	Where capillary glucose monitoring is used or relevant, NICE guidance recommends a minimum of 4, but up to 10 capillary readings a day which is relevant from a cost perspective.	Capillary glucose monitoring was considered for pregnant women. This will only really apply from a cost perspective if there are differences between comparators.
ABCD Diabetes Technology Network UK	8	50	2.3.3.1	The paragraph states that most CGM systems require calibration by finger-check once or twice a day. This is in correct and outdated as current CGM systems used in HCL do not require calibration.	The EAG are happy to amend the word most to some as we should consider exceptions where manual calibration is required.
ABCD Diabetes Technology Network UK	9	55	3.1.2	Again, we see that the question as posed asks about people who are using at least 1 technology. However, none of the analyses are conducted against 1 technology. The review identifies “difficulty in managing diabetes as not maintaining HbA1c < 6.5% or TIR <70%. We would like to point out that based on NDA audit, 67.2% of people with T1D have HbA1c > 7.5%, and <20% achieve TIR of 70%, compared to > 50% of those using HCL. This should be considered in the analyses.	Eligibility of population was previous use of at least 1 technology however the comparators are CSII+rtCGM/flash The thresholds were informed by clinical

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					advisors in the scope development workshop.
ABCD Diabetes Technology Network UK	10	69	4.2.1.2	We reiterate that we cannot see the logic of comparing HCL with LGS / PLGS when these are both redundant technologies that are not currently available and that cost the same as HCL. This flawed approach has led to inappropriate conclusions being made.	The economic modelling, for the cost reasons identified by the ABC DTN, that PLGS is extendedly dominated. As such it does not form a major part of the economics, with the main comparison being between HCL and CSII+CGM.
ABCD Diabetes Technology Network UK	11	74	Table 3	With respect, this table suggests a lack of understanding of the CGM analysis with TIR acronym being used erroneously across the table and in the document. We recommend reading the international consensus on use of CGM **Time In Range** usually denotes time spent between 3.9 and 10 mmol/l **Time below range** < 3.9. < 3.5 or < 3.0 mmol/l is used to denote exposure to hypoglycemia **Time Above range** (>10mmol/l or > 13.9 mmol/l) is used to denote exposure to hyperglycaemia. This incorrect use of terminology suggests the reviewers may not fully understand the systems or data being analysed.	Table 3 illustrates the cut-offs that were reported in some of included studies. Our main analysis followed the cut-offs that you kindly present
ABCD Diabetes Technology Network UK	12	82	4.2.3	We again raise the point that the NMA is comparing the wrong comparators. The scope was to identify the benefits of HCL in those using at least one other technology - however the analysis is done against those using two technologies - again with LGS / PLGS being redundant. This analysis could however highlight the benefits of HCL over CSII or isCGM / rtCGM by allowing studies that compared these to PLGM to be compared to HCL.	Eligibility of population was previous use of at least 1 technology however the comparators were CSII+rtCGM/flash. The EAG was advised by clinical advisors that SAP/PLGS is a technology between HCL and CGM. If SAP/PLGS is not integrated then it is a valid comparator. We

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					included studies were the comparators had the functions (integrated) disabled or not clear. The EAG can provide a subgroup analysis with and without SAP studies.
ABCD Diabetes Technology Network UK	13	94	Bassi 2022	This study shows the mean difference in TIR with closed loop to be 14.6 (19.1 for M780G and 9.8% for Control IQ) which is in line with data seen in the NHS England real world study and demonstrates benefits are greater in those with higher baseline HbA1c.	Point of view, no response required
ABCD Diabetes Technology Network UK	14	94	Table 5	This shows data comparing SAP with HCL. We are missing the studies that show the benefit of HCL over CSII alone or over isCGM.	Table 5 presents observational evidence. We present studies that were identified (please note that RCT evidence was prioritised). CSII alone was not an eligible comparator in the NICE scope.
ABCD Diabetes Technology Network UK	15	104	4.2.11	EAG raise the question if discontinuation would increase with time, and that this may represent wastage of devices. We would like to highlight that if a person stops using a system, a significant cost which is the cost of the consumables (sensors and insulin pump tubing and reservoirs) would also cease, so there is a limited loss. Those who may stop closed loop, could possibly continue to use the pump in open loop, and so wastage would be minimal. If they have baseline HBA1c > 8.5% or problematic hypoglycaemia, they are still entitled to pump therapy as per NCIE TA151.	Point of view, no response required
ABCD Diabetes Technology Network UK	15	114	5.1.1	Concerns are raised about the NHSE adult pilot. In response to point 1, we understand the reliance on EQ5D data for NICE. However, we hope NICE recognises the importance of Diabetes Distress as one of the most relevant and diabetes specific patient reported outcomes that is now used in most high quality diabetes research. In response to point 2, all patients in the pilot were on insulin pump therapy. As per NICE TA151, the pathway to using insulin pump therapy in almost all centres requires prior structured education in flexible insulin therapy. It is important to note that these patients had raised HbA1c despite the use of CSII and isCGM and structured education and showed significant improvement with HCL.	Point of view, no response required

	Comment no.	Page no.	Section no.	Comment	EAG response
				In response to point 3 - we can see that NICE recommends suspension of pump therapy if improvements are not achieved. This comment does not acknowledge that for many patients, an improvement may consist of reductions in hypoglycaemia or reductions in admissions for DKA, or even a reduction in HbA1c from 11% to 9.5%. In this circumstance, continuation of CSII is justified. It is in this population that changing to HCL showed life-changing benefits at ICER that is below the threshold to pay.	
ABCD Diabetes Technology Network UK	16	125	5.1.5.1	There are concerns raised about generalisability of these results due to lack of ethnic diversity. We would like to remind the group that in the NDA, approximately 90% of people with T1D are white Caucasian. Also, real world evidence with this system as seen in the NHS pilot demonstrate generalizability of the benefits of these systems across socio-economic strata. There are criticisms that the systems used were pre-commercial systems - and this should also be considered when considering studies listed in table 5, which were pre-production and have undergone improvements in algorithms since then (especially in terms of the medtronic systems).	Point of view, no response required
ABCD Diabetes Technology Network UK	17	140	6.2.1.2	It is relevant to note that the ICER for M670G by Jendle et al is very similar (164,236 SEK = £13,260) to the ICER from the NHS real world study (even after the £ has lost value against SEK recently). A key factor was that cost effectiveness was evaluated against the comparator that this document sets out - which is the use of one technology - in this case CSII. Similarly, the analysis by Roze et al, using CSII as a comparator gives an ICER of £20,421, again more closely aligning with the ICER seen in the NHS ABCD pilot real world study.	Point of view, no response required
ABCD Diabetes Technology Network UK	18	151	Discussion	A question is raised here about the assumption that their findings were generalisable to target populations despite different baselines - we would like to point out that daSilva et al show that outcomes for HCL in terms of time in range are very similar in all countries.	Point of view, no response required
ABCD Diabetes Technology Network UK	18	152	Discussion	A valid point is made that the willingness to pay threshold was different in the two studies by Jendle et al, as was the ICER. We would like to highlight that the comparator (CSII + SMBG in 2019 vs CSII+ isCGM in 2021) was different between the 2 studies which explains the difference in ICER. We are unable to comment on the difference in willingness to pay thresholds.	Point of view, no response required
ABCD Diabetes Technology Network UK	19	156	7.1	EAG observation point 1 says that Collyns et al compared AHCL to PLGS rather than to CSII + CGM. The cost for AHCL, PLGS and CSII + CGM is the same, and so there should be no cost difference between these systems. Ostenson et al report 1.8 events of Non Severe hypos / week. The EAG report that type of therapy was not clear. In Table 1, they report that 65% were using long and short acting insulin, indicating use of MDI. This study was published in 2013, before isCGM or rt-CGM were widely available in Europe, so these were using MDI + SMBG, while the remaining 35% would possibly be using CSII + SMBG, a similar split to those in the UK	Thank you, no response required

	Comment no.	Page no.	Section no.	Comment	EAG response
				The EAG mention that they could not source the rates of SHE not requiring medical attention. Leese et al report that only about 10% of SHE are reported to medical services [Want et al; Clin Diab Endo 2017 Aug 15;3:7..	
ABCD Diabetes Technology Network UK	20	168	7.2.1.2	We again iterate the fundamental flaw in comparator. We would agree that CSII+ isCGM may be a suitable comparator - and the NHS ABCD pilot data showed the benefit in this group. LGS and PLGS are not suitable comparators unless being used in a network meta analysis to compare CSII or isCGM with HCL as some studies were done with CSII vs PLGM, but there are no studies of CSII+ SMBG vs HCL.	CSII+ SMBG were not listed as comparators in the NICE scope. The EAG was advised by clinical advisors that SAP/PLGS is a technology between HCL and CGM. If SAP/PLGS is not integrated then it is a valid comparator. We included studies were the comparators had the functions (integrated) disabled or not clear. The EAG can provide a subgroup analysis with and without SAP studies.
ABCD Diabetes Technology Network UK	21	169	7.2.1.3	Rates of SHE and NSHE used in this analysis are based on Donnelly et al and are much lower than those seen / published in other studies. Most studies report between 2-3 episodes of NSHE per week in T1D and between 0.6-1.0 SHE PPY which is in line with clinical experience. Rates of NSHE have increased with the use of isCGM or rt-CGM as more episodes are identified, while rates of SHE have reduced (ABCD audit data - Deshmukh et al; Diabetes Care; 2020 Sep;43(9):2152-2160 SHE Ratzki-Leewing et al - 55.7 NSHE / PPY; 2.4 SHE / PPY Svensson et al - 2.0 NHSE / week Pedersen-Bjergaard et al [Diab Ob Met. 2019 Apr;21(4):844-853 showed 91 NSHE PPY; 0.7 SHE PPY	The EAG presents scenario analyses of NSHE PPY for HCL of 20.8, 57.2 and 13.0 which based upon the time below range estimates result in rates for CSII+CGM of 27.1, 74.6 and 17.0 respectively. The scenario around SHEs assumes 0.26 PPY for HCL which yields an

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				The EAG also comment on the fact that the rates of SHE reported in Leese (0.115) are an order of magnitude lower than those reported in Donnelly, This is well recognised, as many SHE are treated at home by friends and family and it is estimated that only 10% of SHE are treated by Ambulance or hospital admission.. NSHE rates seen in Abrahams et al of about 2.0/week are much more consistent with observational data. Low rates seen in Brown, Breton and Kariyawasam may reflect exclusion of those with high rates of hypoglycemia as well as use of SAP in the control arm rather than CSII + SMBG or isCGM. The EAG also must consider the impact of hypoglycemia is different in different populations. Young children, who may not be able to alert parents of symptoms of hypoglycaemia may suffer from a much greater impact of hypoglycaemia - this is why glucose levels are often kept high to prevent hypoglycemia. Similarly, with duration of T1D, proportion of people with impaired awareness increases, increasing their risk of SHE. We have just completed data collection of a 600 participant study (Divilly et al; looking at rates of SHE and NSHE, and see NHSE events of 2.0 / PPW similar to observational population data across the years (Diabet Med; 2022. Sep; 39(9) Rates of time below range for people on isCGM are reported in Choudhary et al; Diab Ob Metab 2022 Jul, 17 and shows real world TBR across different age groups, Time below range is between 3.5 - 4.25%, TBR is about 2% on HCL, suggesting a 50% reduction. Rates of SHE and NSHE on CSII are reported in Beato-Vibora et la, Diab Med 2015 and are 0.3PPY on CSII; similar to Quiros et al Diab Med Feb 2016 The EAG assumes no change in NSHE with HCL. This is a correct assumption when compared to PLGS, as they effectively both reduce hypoglycemia to a similar level. But when compared to a more appropriate comparator of CSII, isCGM or CSII + isCMG, there is a 50% reduction in Time below range and a similar reduction in NSHE can be assumed [Re Bosi et al; Lancet 2018] The Gordon study used for assessment of hypoglycemia used data from a study of T1D with Dapagliflozin. It is important to recognise that this study excluded those with problematic hypoglycaemia and also required participants to be using > 0.3 units/kg/day. We also would like to draw the EAG's attention to cost effectiveness analysis of CGM published by NICE. Table HE006 provides SHE rates for rtCGM, isCGM and SMBG and table HE007 provides rates of NSHE for rt-CGM and isCGM	estimate of 0.34 for CSII+CGM. The scenario that includes this has an ICER of £163k per QALY. Increasing the SHE rate tenfold to 2.6 PPY for HCL and 3.39 PPY for CSII+CGM improves the ICER somewhat to £122k per QALY. However, it can also be noted that the SHE rates applied in the EAG scenario for HCL and CSII correspond quite closely with the 0.21 PPY and 0.34 PPY reported by the NHS adult pilot. The paediatric modelling addresses hypoglycaemia by using the reported changes in the HFS in the NHS paediatric pilot to assess their quality of life effects.

<table>
<tr><th></th><th>Comment no.</th><th>Page no.</th><th>Section no.</th><th>Comment</th><th>EAG response</th></tr>
<tr><td>Dexcom</td><td></td><td></td><td></td><td>Dexcom has reviewed the EAG assessment report and we provide our detailed comments below.

Dexcom welcomed the update of DG21, and particularly that the scope and ensuing protocol specified that hybrid closed loops would be compared separately to real-time continuous glucose monitoring (rtCGM) + pump on the one hand, and intermittent scanning continuous glucose monitoring (isCGM) + pump on the other hand. This is consistent with the evidence base for the two separate CGM technologies, which indicates that rtCGM is superior to isCGM for regulating blood glucose (Visser, 2021).

However, the EAG report appears to disregard the scope by only presenting the cost-effectiveness results for a single comparison between HCL and rtCGM/isCGM, with the inappropriate assumption that the two comparator technologies are interchangeable. The final ICER presented in the report is based on a comparator arm that combines the efficacy of rtCGM and the costs of isCGM. Indeed, the clinical evaluation does not include any evidence to support the efficacy of HCL compared to isCGM + CSII, as all of the identified randomized controlled trials relate to rtCGM + CSII.

Moreover, other differences between the monitoring modalities have not been included. Specifically, QoL benefits due to reduced fear of hypoglycaemia (FOH) have been excluded, as has the impact of HCL on the incidence of non-severe hypoglycaemic events (NSHE). Both of these outcomes were directly captured in the iDCL study (Brown, 2020).

As shown in the table below, the economic evaluation presented in the EAG report does not answer either of the research questions posed by the protocol, which specifies that the cost-effectiveness of HCL should be evaluated separately against rtCGM and isCGM. For the comparison against rtCGM + CSII, the current ICER overestimates the incremental cost of HCL (which should be zero). For the comparison against isCGM + CSII, the current ICER underestimates the incremental clinical benefits of HCL as it incorrectly applies efficacy data pertaining to rtCGM + CSII.

The table below also provides a framework for assessing the cost-effectiveness of HCL relative to each of the comparators, as per the protocol, in contrast to the cost-effectiveness assessment provided in the EAG report.

<table>
<tr><th></th><th>Incremental cost</th><th>Clinical benefit</th><th>ICER</th></tr>
<tr><td>Comparison between HCL and rt-CGM+CSII</td><td>£0</td><td>-0.33% (based on iDCL)</td><td>Dominant (same cost, better efficacy)</td></tr>
<tr><td>Comparison between HCL and is-CGM+CSII</td><td>£1,500 (likely to be less)</td><td>Likely to be at least an additional -0.3% (ie -</td><td>Likely to be cost effective once the model accounts for:</td></tr>
</table>
</td><td>Please see previous comment re pooled comparator of CSII+rtCGM and CSII+isCGM.

QoL due to HFS (FOH) is included in scenarios but is not included in the base case due to a lack of direct evidence for rates of NHSE and SHE.

Cost estimates are based upon current tender prices as supplied by the NHS supply chain.</td></tr>
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<table>
<tr><th></th><th>Comment no.</th><th>Page no.</th><th>Section no.</th><th>Comment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>0.66%) based on ALERTT1 RCT (Visser, 2021)</td><td>· Additional lowering of HbA1c due to superior efficacy of rtCGM vs isCGM
· QoL benefits</td></tr>
<tr><td>Comparison performed by EAG</td><td>£1,500 (based on isCGM + CSII cost)</td><td>-0.29% (based on inappropriate selection and pooling of studies based on rtCGM + CSII efficacy)</td><td>£179,000/QALY</td></tr>
</table>

All of this results in the EAG overestimating the ICER, which in the EAG base case was magnitudes higher than all other (published or stakeholder submissions) CEAs.

The minimum expectation of an economic model is that the methodology and assumptions are realistic enough to generate an analysis from which decisions on resource allocation can be confidently made. It is evident that the economic analysis in its current form is not fit for this purpose. All of this results in the EAG overestimating the ICER, which in the EAG base case was magnitudes higher than all other (published or stakeholder submissions) CEAs.
</td><td></td></tr>
<tr><td>Dexcom</td><td>1</td><td>3</td><td>Applicable where ever the systematic literature review is discussed</td><td>The report state that the clinical evidence identified 12 randomised trials (RCTs). However, the inclusion/exclusion criteria were not applied in a consistent manner, leading to the exclusion of relevant studies (e.g. the iDCL trial) and inclusion of studies that are no longer relevant (eg Thabit 2015).</td><td>We can confirm that we followed the pre-specified inclusion and exclusion criteria (listed in section 4.1.3.) in a systematic manner. The iDCL trial did not meet the inclusion criteria because a large proportion were on MDI and stratified analysis was not presented in the study.</td></tr>
<tr><td>Dexcom</td><td>2</td><td>3</td><td>Applicable where ever the utility in the health economic section is discussed</td><td>• The report states that evidence suggests that such technologies have the potential to improve the lives of people with type 1 diabetes and their families. However, no quality-of-life benefit has been included in the health economic analysis, leading to an underestimation of the utility in the analysis.</td><td>The EAG addresses FOH in scenario analyses through the Gordon mapping function for FHS to EQ-5D.</td></tr>
</table>

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				• The impact of advanced diabetes technologies like HCL systems on quality-of-life utility for patients with diabetes has multiple components that include improvements in health status and health outcomes and additional utilities due to improvements in the treatment process (the process of care utility e.g., avoidance of finger sticks, day to day diabetes burden and decision making) (Brennan et al. 2013). Certain diabetes complications like fear of hypoglycaemia (FoH) have been shown to independently affect the HRQoL of patients with diabetes and yet cannot be captured by multi-utility instruments like EQ-5D (Shi et al. 2014). Previous technology assessments by NICE have set the standard for incorporating diabetes-specific and treatment-related utilities in cost-utility analysis for diabetes technologies (TA151). In the case of a lack of instruments that measure an expected utility, the practice has also been to test several values of incremental utility to address the unmeasured but likely treatment-related QoL benefits. However, in the current report, the EAG excluded QoL measures for the reduction of FoH (which partially captures this benefit) and did not conduct a scenario analysis of what additional utility value the closed-loop system can add to patients' overall QoL. • The current assessment by the EAG underestimates the additional quality-adjusted life years by excluding the expected reduction in non-severe and severe hypoglycemic events and treatment-related quality-of-life benefits. Clinical trials included in the NMA conducted by the EAG have consistently shown a reduction in time below range which correlates with hypoglycemic events. The ability of the RCT to show a difference in SHE hospitalization depends on the background risk of SHE in the trial population and the sample size of the RCT. Given the limitation in resources required to conduct a large clinical trial powered to capture the reduction in severe hypoglycemia-related hospitalizations, the reduction in TBR should have been modeled as a surrogate measure for SHE and NSHE and included in the base case in line with the evidence from the NMA. Even when a sensitivity analysis was conducted for NSHE and SHE events, a value from a single study was used without conducting any sensitivity analysis around the rates provided. References: • Brennan VK, Dixon S. Incorporating process utility into quality-adjusted life years: a systematic review of empirical studies. Pharmacoeconomics. 2013 Aug;31(8):677-91. doi: 10.1007/s40273-013-0066-1. PMID: 23771494. • Shi L, Shao H, Zhao Y, Thomas NA. Is hypoglycemia fear independently associated with health-related quality of life? Health Qual Life Outcomes. 2014 Nov 30;12:167. doi: 10.1186/s12955-014-0167-3. PMID: 25433668; PMCID: PMC4268814. • Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. Technology appraisal guidance. Published: 23 July 2008 www.nice.org.uk/guidance/ta151	It is not clear what is meant by "a scenario analysis of what additional utility value the closed-loop system can add to patients' overall QoL"

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Dexcom	3	3	Applicable where ever the effect of HCL on HbA1C is discussed	The report finds that the HCL arm of RCTs achieved improvement in HbA1c % (HCL decreased HbA1c % by 0.28 (-0.34 to -0.21. However, due to the exclusion of relevant studies (eg iDCL trial) and the inappropriate pooling of studies with rt-CGM and isCGM, the treatment effect size is likely to be underestimated. NICE has made the assumption that rt-CGM and isCGM derive equivalent clinical utility, yet have made no attempt to validate this assumption. Randomized controlled trials and real-world evidence studies have shown that rtCGM is superior to isCGM in terms of reduction in glycated haemoglobin HbA1c, and increase in Time in Range, therefore, RCTs comparing between HCL and rtCGM+CSII are likely to underestimate the treatment benefit due to hbA1c reduction of HCL relative to isCGM+CSII by ~0.3%: • Visser MM, Charleer S, Fieuws S, et al. *Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): A 6-month, prospective, multicentre, randomised controlled trial*. *Lancet*. 2021; 397(10291):2275-83 • Brown RE, Chu L, Norman GJ, Abitbol A. *Real-world glycemic outcomes in adult patients with type 1 diabetes using a real-time continuous glucose monitor compared to an intermittently scanned glucose monitor: A retrospective observational study from the Canadian Imc diabetes registry (REAL-CGM-T1D)*. *Diabetic Med*. 2022; n/a(n/a):e14937. • Radovnická L, Hásková A, Do QD, et al. *Lower glycated hemoglobin with real-time continuous glucose monitoring than with intermittently scanned continuous glucose monitoring after 1 year: The CORRIDA Life study*. *Diabetes Technol Ther*. 2022.	Thank you, no response required.
Dexcom	4	3	Applicable where ever the QALY gain is discussed	Incremental QALYs in the model appear to be underestimated. The report states that “the change in HbA1c results in a gain in undiscounted life expectancy of 0.458 years and a gain of 0.160 quality adjusted life years (QALY)s”. A separate cost-utility analysis undertaken by Dexcom also using the IQVIA Core Diabetes Model found the incremental QALY gains to be 1.034 over a lifetime. This is despite the fact that the HbA1c treatment benefit used in this model was not dissimilar to that applied by the EAG (-0.33% vs -0.29%). See comment No. 2 for notes on QoL and QALYs We suggest that this difference is in part, due to the EAG model’s exclusion of: • Effect on quality of life (see above) Effect on non-severe hypoglycaemic events (see below)	The EAG has provided consultation access to its IQVIA CORE modelling space

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Dexcom	5	3	Applicable where ever the incremental cost of HCL is discussed	NICE proposes that the average price of a HCL system is around £1,500 more expensive than CSII+CGM, with NHS England supply chain being the evidence source. This price differential is highly impactful of the CSII+CGM ICER relative to HCL systems. Due to this, the annual component cost of the technologies must be clearly stated. The scope of this assessment only allows for the value of a HCL algorithm to be ascertained CSII+CGM CSII+ CGM = insulin pump + rtCGM (extensive RCT evidence base) Or CSII+CGM = insulin pump + isCGM (very limited evidence base) vs Hybrid Closed Loop CSII + CGM (rt-CGM only) + algorithm It is noteworthy that none of the sponsors evidence submissions communicated that the price of the HCL algorithm totalled £1,500. It is obvious that NICE has taken the lowest possible CSII+CGM price by using the price associated with isCGM. The outcome of this approach widens the price delta between CSII+CGM with little justification or visibility into the cost component of this analysis. It should also be highlighted that NICE have deemed it appropriate to use the outcomes of CSII+rtCGM but the prices associated with CSII+isCGM. An approach that minimises the clinical utility gain for CSII+CGM vs HCL while maximising the cost differential. It is expected that NICE will re-run the economic analysis using the cost and outcomes associated with CSII+rt-CGM **or** CSII+isCGM vs HCL as per the scope. NICE have also made the assumption that technology costs will increase by £500 in the coming years. Again, this assumption has been made without any justification and should be removed from the analysis.	It is correct that the main price difference arises due to 90% of the pooled comparator being CSII+isCGM. The EAG does not think it sensible to disaggregate the comparator into CSII+rtCGM and CSII+isCGM as any difference in NIC recommendations for these could lead to perverse incentives earlier in the treatment pathway at considerable cost to the NHS. The £500 increase is not with regards the future but with regards the possible market share of the different versions of HCL. The current EAG approach is a simple unweighted average of the cheaper HCLs which, if approved, are assumed to take the lion's share of the market due to their price.
Dexcom	6	3	Applicable throughout the report	The results section mention that 12 randomized trials were identified which compared HCL to CSII + CGM or sensor augmented therapy (SAP) therapy. However, all 12 randomized controlled trials evaluated real-time CGM. This statement highlights the fundamental flaw in this assessment report. The protocol and the scope for the report	The EAG did compared CSII+rtCGM (10%) and CSII+isCGM (90%) –

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				clearly define that two comparisons should be made; on the one hand HCL compared with real-time CGM + CSII, and on the other hand HCL compared to intermittent scanning CGM + CSII: **Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – final protocol, page 16**: "Intervention: hybrid closed loop systems Comparator: • Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated) • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion" All the randomized trials assess real-time CGM + CSII, however, this data has been applied to intermittent scanning CGM + CSII as well, in that the two technologies have been regarded as one. This not only disregards the protocol but reflects a fundamental lack of understanding of the two technologies and of the evidence base for each technology. Combining these comparators into one does not allow the correct incremental clinical benefits to be matched to correct incremental costs. This leads to inconsistencies in how the clinical evidence is evaluated in relation to the health economic section (e.g. clinical section includes only rtCGM + pump comparator evidence but the health economic uses costs mostly from isCGM [90%]). Therefore, the comparators need to be evaluated separately on both the clinical and health economic side. Incremental clinical benefits vs one comparator need to be combined with the incremental costs vs that same comparator.	percentages from Diabetes Technical Network. The EAG will run separate analysis.
Dexcom	7	3	Results	The results section mentions 'significantly decreased TIR (% above 10mmol/l)'; this should be called 'time above range', or TAR, and time within range (<3.9 mmol/L) should be called as time below range (TBR) as noted in the outcomes section of population/intervention/outcomes/study(PICOS) or intermediate measures. If all, terms defined as time within range with the range in parentheses then it should be consistent throughout this document.	Thank you for your comment.
Dexcom	8	4	Applicable where ever the cost-effectiveness is discussed	The findings in the cost-effectiveness section are a reflection of the series of mistakes made throughout the clinical- and health economics analyses, starting with the erroneous application of clinical evidence for real-time CGM to intermittent scanning CGM. This leads to inconsistencies in how the clinical evidence is evaluated in relation to the health economic section (e.g. clinical section includes only RTCGM + pump comparator evidence but the health economic uses costs mostly from ISCGM [90%]). Therefore, the comparators need to be evaluated separately on both the clinical and health economic side. Incremental clinical benefits vs one comparator need to be combine with the incremental costs vs that same comparator	Please see earlier response on comparators.
Dexcom	9	21	Table of contents	Table of contents, All sections 4.2.4 to 4.2.9 define time within range, these should be correctly defined as Time in Range (TIR), Time Below Range (TBR) and Time above range (TAR).	Typographical error

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Dexcom	10	37	Conclusions on hypoglycaemia	The report concludes that "the frequency and severity of hypos can be reduced by structured education and by the use of CSII (insulin pumps)". This statement does not mention real-time CGM, despite the significant evidence base behind the benefit of rtCGM on hypoglycaemia, e.g.Heinemann et al; *Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial.* Lancet 2018;391:1367-1377 https://pubmed.ncbi.nlm.nih.gov/29459019/ Beck RW et al; *Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial*. Jama. 2017 Jan 24;317(4), Lind M t al; *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*.	Thank you for sharing the references – noted.
Dexcom	11	37	Conclusions on hypoglycaemia	The report concludes that non-severe hypoglycaemia leads to a negative impact on quality of life. This conclusion is, however, as stated elsewhere in our comments, was not implemented in the health economic analysis, which leads to an underestimation of the benefit associated with hybrid closed loops. As we highlighted in previous comments, The current assessment by the EAG underestimates the additional quality-adjusted life years by excluding the expected reduction in non-severe and severe hypoglycemic events and treatment-related quality-of-life benefits. Clinical trials included in the NMA conducted by the EAG have consistently shown a reduction in time below range which correlates with hypoglycemic events. The ability of the RCT to show a difference in SHE hospitalization depends on the background risk of SHE in the trial population and the sample size of the RCT. Given the limitation in resources required to conduct a large clinical trial powered to capture the reduction in severe hypoglycemia-related hospitalizations, the reduction in TBR should have been modeled as a surrogate measure for SHE and NSHE and included in the base case in line with the evidence from the NMA.	As noted previously, the QoL and cost effects of NSHEs and SHEs are included in scenario analyses. They have not been included in the base case due to a lack of direct comparative evidence.
Dexcom	12	44	2.3.1	In the United States, the Federal Drug Administration, the FDA, has designated this type of device as an integrated continuous monitoring device (iCGM)" and defined it as follows: "An integrated continuous glucose monitoring system (iCGM) is intended to automatically measure glucose in bodily fluids continuously or frequently for a specified period of time. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycemic control. " (https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170088.pdf) To date, the only CGMs system to receive this designation is the Dexcom G6.	No response required.
Dexcom	13	45	2.3.1.2	It should be noted here that calibrations are needed for 780G when asked by the system. Real world data presented at ATTD demonstrate that with the 780G, on average between 255 to 365 blood glucose strips are required per year (Vigersky et al, Poster ADA 2022).	No response required.
Dexcom	14	45	2.3.1.3	It should be noted here that only Dexcom G6 is compatible with Control-IQ at the present time. For Control-IQ with the Dexcom G6 sensor no calibrations are needed	No response required.

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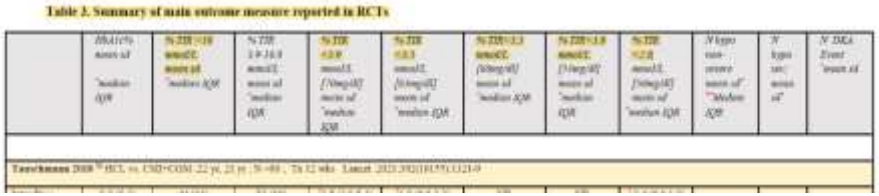
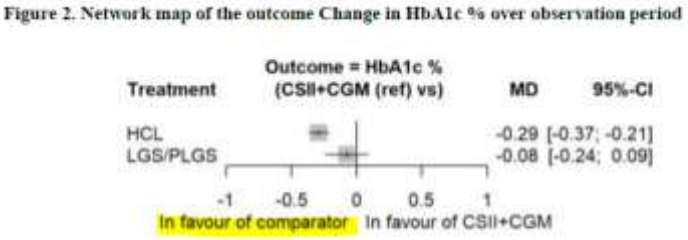
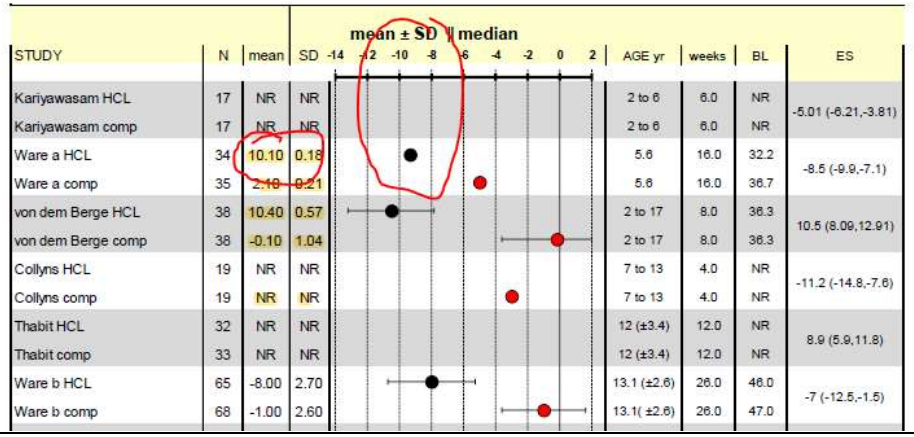
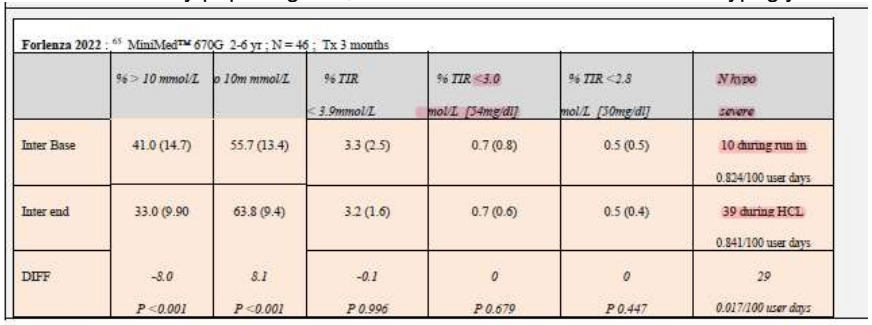
				Tandem Control-IQ will eventually be compatible with Dexcom G7.	
Dexcom	15	45	2.3.1.4	CamAPS FX is now compatible with YpsoPump, as part of the mylife Loop system from Ypsomed. CamAPS FX will eventually be compatible with Dexcom G7. Similarly as mentioned above, with the G6 sensor, these systems will not require any calibrations.	No response required.
Dexcom	16	49 & 50	Real time continuous blood glucose measurement	To note is that **when NICE discusses the guidelines for real-time CGM they make reference to the outdated guidelines, replaced by the current version published in 2022**. By referencing the outdated guidelines, the report does not recognize the fact that NICE's updated guidelines recommend rtCGM or isCGM routinely for patients with type 1 diabetes. The current guidelines clearly state that if a person with type 1 diabetes cannot use or does not want rtCGM or isCGM they should be offered capillary blood glucose monitoring.	
Dexcom	17	49 & 50	Real time continuous blood glucose measurement	The EAG report states that most rtCGM require calibration with SMBG. It is not clear how this conclusion was reached. Calibration with a finger-prick is not needed for Dexcom rtCGM. The report did not mention the use of finger-sticks in isCGM. An RWE study in Germany showed that patients with T1D on isCGM use 1.6 strips per day. (Van den boom and Kostev et al. 2020, Changes in the utilization of blood glucose test strips among patients using intermittent-scanning continuous glucose monitoring in Germany. Diabetes, Obesity and Metabolism, 22(6), 922-928.). Real-world use of SMBG for G6 has been reported by Linden et al: "Of those who did calibrate in September 2020, 75% calibrated fewer than once per week, 22% calibrated 1–7 times per week". (Linden et al, *Sustainable Use of a Real-Time Continuous Glucose Monitoring System from 2018 to 2020*,DIABETES TECHNOLOGY & THERAPEUTICS Volume 23, Number 7, 2021).	No response required.
Dexcom	18	53	3.1.1	Definition of the intervention: The report only mentions the HCL systems by Medtronic MiniMed 670G and MiniMed 780G while there are others, notably Tandem Control IQ and YpsoPump. The report should have highlited all HCL systems available that are being evaluated in this report.	Listed in the NICE scope
Dexcom	19	54	3.1.2	Defining the population: The report started by defining the target population of this review as patients with diabetes who have difficulty managing diabetes despite prior use of CSII, rtCGM, and isCGM. by applying this definition, other comparators become relevant and should have been included in the assessment. For instance, defining the population based on prior use of rtCGM would have included patients on MDI who are using rtCGM. The current assessment does not answer the question of what is the most appropriate treatment option for patients on MDI+rtCGM who are having difficulty managing their DM. The current report doesn't take into account the updated guidelines by NICE where rtCGM is recommended for patients with type 1 diabetes. This condition does not apply to pregnant or planning to be pregnant women, however, no conclusions were made on this segment of patients	No response required.

	Comment no.	Page no.	Section no.	Comment	EAG response
Dexcom	20	55	3.1.2	The report states that where possible analyses should be performed separately for women with type 1 diabetes who are pregnant/planning pregnancy. However, no such analyses seem to be have been performed.	Subgroup analysis was conducted (removing the study by Stewart). There was only one study identified.
Dexcom	21	55	3.1.3	The EAG correctly reports that HCL should be compared to • Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion. As mentioned above, however, the EAG does not follow the protocol, but instead combines isCGM + insulin pump and rtCGM + insulin pump into one group. The EAG literature review does not identify any clinical trials assessing isCGM + insulin pumps, so by combining the two different CGM technologies into one, incorrectly applies the evidence base for rtCGM + insulin pump to isCGM + pump. This has been shown for example in the RCT by Visser et al. 2021, which demonstrated included patients both on multiple daily injections and insulin pumps and showed an HbA1C value of –0.3 for real-time CGM compared to intermittent scanning CGM. (Visser MM, Charleer S, Fieuws S, et al. *Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial*. Lancet. 2021; 397:2275-83). Also, evidence from retrospective, observational , real world registry study (LMC Diabetes Canada) has shown that use of real-time CGM significantly reduced HbA1c; -0.3% than intermittently scanned CGM. Real time users had significantly greater time in range and lower time below range. (Brown RE, Chu L, Norman GJ, Abitbol A. *Real-world glycaemic outcomes in adult persons with type 1 diabetes using a real-time continuous glucose monitor compared to an intermittently scanned glucose monitor: A retrospective observational study from the Canadian LMC diabetes registry (REAL-CGM-T1D)*. Diabet Med 2022; 39: e14937.)	Please see previous comments
Dexcom	22	56	3.2	Overall aims and objectives assessment: The scope of the assessment is to evaluate the clinical effectiveness and the cost-effectiveness of HCL in managing patients who previously used one of the following: CSII, rtCGM, or isCGM. However, the review excluded studies that included patients who used CGM with MDI. As such, in its present form, the clinical review cannot answer the posed question.	No response required.
Dexcom		61	4.1.3	The comparators were defined as CSII+rtCGM and CSII+isCGM, however, as mentioned above, no studies were found for CSII+isCGM by the clinical review. Outcomes to be included clearly stated fear of hypoglycemia (FoH) and severe hypoglycemia (SHE), but these were not included in the base case.	No response required.
Dexcom	23	63	4.1.3	Studies where more than 10% of the sample did not meet the inclusion criteria (for example over 10% were inpatients).This criterion resulted in the exclusion of the iDCL study from the clinical review because the SAP arm	No response required.

	Comment no.	Page no.	Section no.	Comment	EAG response
				of the study included >10% of patients on MDI. However, several of the included studies were of poor quality and it cannot be ruled out that they did not even report potential presence of patients on MDI. Brown, S. A., Kovatchev, B. P., Raghinaru, D., Lum, J. W., Buckingham, B. A., Kudva, Y. C., ... & Beck, R. W. (2019). *Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes*. *New England Journal of Medicine*, *381*(18), 1707-1717.	
Dexcom	24	70	4.2.1.2	Broughton and Kariyawasam are real-time CGM studies and should have been labeled as such	The EAG to check labelling. Noted.
Dexcom	25	73	4.2.1.2	Table 3. all measures as defined as TIR example below  please note that outcomes (intermediate measures) define time in range on page 61 in this report as 3.9-10 mmol/l all other measures should not be called TIR and can be labelled as TBR or % time in a hypoglycaemic range <3.9, <3.5, <3.3, <3.0 and < 2.8 mmol/litre similar to table 2	The TIR values in table 3 were extracted from the studies.
Dexcom	26	81	4.2.3	Here the reference treatment class word should be called “comparator” And this network map should be in favor of treatment (HCL) as effect is -0.28  Figure 3. Results of the NMA of the outcome Change in HbA1c % over observation period	Typographical error.

<table>
<tr><th></th><th>Comment no.</th><th>Page no.</th><th>Section no.</th><th>Comment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>In this figure, it should be labelled as in favor of treatment not comparator</td><td></td></tr>
<tr><td>Dexcom</td><td>27</td><td>85</td><td>4.2.6</td><td>Figure 7, The values for mean (Sd) and plots in Change in % hyperglycemic range for Ware a, von dem Berge and Collyns studies do not match
 

<table>
<tr><th>STUDY</th><th>N</th><th>mean</th><th>SD</th><th>AGE yr</th><th>weeks</th><th>BL</th><th>ES</th></tr>
<tr><td>Kariyawasam HCL</td><td>17</td><td>NR</td><td>NR</td><td>2 to 6</td><td>6.0</td><td>NR</td><td rowspan="2">-5.01 (-6.21,-3.81)</td></tr>
<tr><td>Kariyawasam comp</td><td>17</td><td>NR</td><td>NR</td><td>2 to 6</td><td>6.0</td><td>NR</td></tr>
<tr><td>Ware a HCL</td><td>34</td><td>10.10</td><td>0.18</td><td>5.6</td><td>16.0</td><td>32.2</td><td rowspan="2">-8.5 (-9.9,-7.1)</td></tr>
<tr><td>Ware a comp</td><td>35</td><td>2.18</td><td>0.21</td><td>5.6</td><td>16.0</td><td>36.7</td></tr>
<tr><td>von dem Berge HCL</td><td>38</td><td>10.40</td><td>0.57</td><td>2 to 17</td><td>8.0</td><td>36.3</td><td rowspan="2">10.5 (8.09,12.91)</td></tr>
<tr><td>von dem Berge comp</td><td>38</td><td>-0.10</td><td>1.04</td><td>2 to 17</td><td>8.0</td><td>36.3</td></tr>
<tr><td>Collyns HCL</td><td>19</td><td>NR</td><td>NR</td><td>7 to 13</td><td>4.0</td><td>NR</td><td rowspan="2">-11.2 (-14.8,-7.6)</td></tr>
<tr><td>Collyns comp</td><td>19</td><td>NR</td><td>NR</td><td>7 to 13</td><td>4.0</td><td>NR</td></tr>
<tr><td>Thabit HCL</td><td>32</td><td>NR</td><td>NR</td><td>12 (±3.4)</td><td>12.0</td><td>NR</td><td rowspan="2">8.9 (5.9,11.8)</td></tr>
<tr><td>Thabit comp</td><td>33</td><td>NR</td><td>NR</td><td>12 (±3.4)</td><td>12.0</td><td>NR</td></tr>
<tr><td>Ware b HCL</td><td>65</td><td>-8.00</td><td>2.70</td><td>13.1 (±2.6)</td><td>26.0</td><td>46.0</td><td rowspan="2">-7 (-12.5,-1.5)</td></tr>
<tr><td>Ware b comp</td><td>68</td><td>-1.00</td><td>2.60</td><td>13.1(±2.6)</td><td>26.0</td><td>47.0</td></tr>
</table></td><td>The figure cited here is not figure 7. The sd in figure 7 is not reported</td></tr>
<tr><td>Dexcom</td><td>28</td><td>87</td><td>4.2.8</td><td>Again Ware a, Benhamou studies mean (sd) and plots are not matching</td><td>If this is referring to igure 7 then please see above</td></tr>
<tr><td>Dexcom</td><td>29</td><td>93</td><td>4.2.10</td><td>Forenza 2022 study paper Pg 328, section 3.1 there were no severe hypoglycemia in this study
 
<table>
<tr><th colspan="6">Forlenza 2022 : [65] MiniMed™ 670G 2-6 yr ; N = 46 ; Tx 3 months</th></tr>
<tr><th></th><th>% > 10 mmol/L</th><th>o 10m mmol/L</th><th>% TIR
< 3.9mmol/L</th><th>% TIR <3.0
mol/L [54mg/dl]</th><th>% TIR <2.8
mol/L [50mg/dl]</th><th>N hypo
severe</th></tr>
<tr><td>Inter Base</td><td>41.0 (14.7)</td><td>55.7 (13.4)</td><td>3.3 (2.5)</td><td>0.7 (0.8)</td><td>0.5 (0.5)</td><td>10 during run in
0.824/100 user days</td></tr>
<tr><td>Inter end</td><td>33.0 (9.90</td><td>63.8 (9.4)</td><td>3.2 (1.6)</td><td>0.7 (0.6)</td><td>0.5 (0.4)</td><td>39 during HCL
0.841/100 user days</td></tr>
<tr><td>DIFF</td><td>-8.0
P <0.001</td><td>8.1
P <0.001</td><td>-0.1
P 0.996</td><td>0
P 0.679</td><td>0
P 0.447</td><td>29
0.017/100 user days</td></tr>
</table></td><td>Please see point 3.1 in the Forlenza publication: Safety: There were 10 episodes of devicerelated severe hyperglycemia (blood glucose >300 mg/dl with ketones >0.6 mmol/L or symptoms of nausea, vomiting or abdominal pain) during run-in (0.824/100 user-days) and 39 during study phase (0.841/100 user-days).</td></tr>
</table>

	Comment no.	Page no.	Section no.	Comment	EAG response
				The last column in this table, 10 during run-in and 39 during HCl are severe hyperglycemia	
Dexcom	30	122	5.1.4.1	The EAG is critical against the iDCL trial because there was 21% of MDI users in the control group. However, 21% is a minority, and some of the studies which were indeed included in the EAG review were poorly reported and may not have even reported the proportion of patients who used MDI. Furthermore the EAG is critical against the trials on the basis that patients in the comparator arm used low glucose suspend (LGS). Yet some of the trials included in the final review also had LGS (e.g. Collyns, 2021). Indeed, the network meta analysis (NMA) included a comparison between HCL and LGS.	The EAG followed the protocol, studies were excluded if 10% of the population did not meet inclusion criteria. Stratified analysis was not provided by the study.
Dexcom	31	133	5.1.7.2	Review of the evidence for HCL: The EAG reports that *"Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families. People seem to report a better quality of life, diabetes burden and quality of sleep and less anxiety with technologies*". This has been shown for example in *Improvements in parental sleep, fear of hypoglycemia, and diabetes distress with use of an advanced hybrid closed-loop system*. Diabetes Care, 45(5), 1292-1295. https://doi.org/10.2337/dc21-1778) As we mentioned in our previous comments ,the impact of advanced diabetes technologies like HCL systems on quality-of-life utility for patients with diabetes has multiple components that include improvements in health status and health outcomes and additional utilities due to improvements in the treatment process (the process of care utility e.g., avoidance of finger sticks, day to day diabetes burden and decision making) (Brennan et al. 2013). Certain diabetes complications like fear of hypoglycaemia (FoH) have been shown to independently affect the HRQoL of patients with diabetes and yet cannot be captured by multi-utility instruments like EQ-5D (Shi et al. 2014). Previous technology assessments by NICE have set the standard for incorporating diabetes-specific and treatment-related utilities in cost-utility analysis for diabetes technologies (TA151). In the case of a lack of instruments that measure an expected utility, the practice has also been to test several values of incremental utility to address the unmeasured but likely treatment-related QoL benefits. However, in the current report, the EAG excluded QoL measures for the reduction of FoH and did not conduct a scenario analysis of what additional utility value the closed-loop system can add to patients' overall QoL. Despite this conclusion however, no QoL utilities were included in the health economic base case or in the sensitivity analysis.	See previous comments re scenario analyses around NSHEs and SHEs, which use the mapping function of Gordan to estimate the effects upon FHS and then maps this onto EQ-5D.
Dexcom	32	144	6.2.1.2	• EAG statement: "Nevertheless, the fact that the study used a nationally representative simulation cohort for Scotland meant that the findings were generalisable to the population unlike the results of the other identified economic studies that used baseline data for different countries" • The EAG suggests that economic models that used baseline characteristics from other countries are not generalizable to the UK population. The generalizability of the models can be evaluated by looking into the underlying risk equations that the model uses. For instance, the model is sensitive to changes in age and	No response required.

	Comment no.	Page no.	Section no.	Comment	EAG response
				HbA1c values at baseline whilst race has a minimal impact on the model. Some of these factors need to be tested in multiple sensitivity analyses even within the same population. It is important to mention that the sensitivity analysis done by EAG using the NHS pilot study has resulted in a significant drop in the ICER from 179k to 126k. The EAG should elaborate on the differences between the base case baseline characteristics and the NHS England study and examine which one of the two cohorts is more representative of the target population in this assessment. • It is important to note that the SHTG study clearly stated the limitation of their analysis as it may not fully capture the positive impact of reducing the burden of day to day diabetes management associated with using a closed loop system as a result of the lack of relevant quality of life studies.It could be expected that more automated management of type 1 diabetes would yield even greater utility benefit, however such studies were not been identified in the published literature	
Dexcom	33	147	6.2.1.4	In its quality assessment of reported studies, the report mentions that the cost-effectiveness studies using the CORE IQVIA model provided only brief descriptions of the model. This is because there are multiple separate publications that describe the model in detail (eg *Validation of the IMS CORE diabetes model,* September 2014. Value in Health 17(6):714–724. In order for the EAG to get more information about the CORE IQVIA model, it would have been possible to study these publications.	The EAG has summarised the published validation studies of the IQVIA CORE model.
Dexcom	34	148	6.2.1.4	• EAG statement; the SHTG used a published algorithm to model cardiovascular disease and convert TIR into HbA1c reduction. • The IQVIA Core Diabetes model is a validated model (Two validations published), and it uses the UKPDS risk equations for estimated CVD complications. The conversion of TIR to HbA1c should be interpreted with caution due to the limited data on how TIR correlates with CVD and other long-term diabetes complications.	The EAG has summarised the published validation studies of the IQVIA CORE model. These validation exercises can be read as showing that the model is less than perfect.
Dexcom	35	149	6.2.1.4	The report states that the underlying risk equations for clinical progression used with the CORE model were not justified. The IQVIA CDM provides multiple risk equations that should be used based on the target population (T1D vs T2D). For the T1D, the risk equations are mainly derived from the EDIC/DCCT trials. The validation study (Palmer 2004) expands on formulas and risk factors that are used in the T1D model. Palmer, A. J., Roze, S., Valentine, W. J., Minshall, M. E., Foos, V., Lurati, F. M., ... & Spinas, G. A. (2004). *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*, *20*(sup1), S5-S26. •	The EAG has summary of the published validation studies of the IQVIA CORE model notes the strengths and weaknesses of these, also incorporating observations around the EDIC/DCCT trials and the probable amount of

	Comment no.	Page no.	Section no.	Comment	EAG response
					paediatric data available to populate the model.
Dexcom	36	150	6.2.1.4	As we highlighted previously and as noted by the SHTG study, the analysis does not capture any QoL that can be expected due to reduction in fear of hypoglycaemia or improvement in the treatment process and possible reduction day to day burden for patients with T1D. The EAG should have at least conducted scenario analysis of a range of minimum and maximum estimated utility values for HCL.	See previous cooments on scenario analyses around NHSE and SHE rates and their effect upon the HFS, and thence EQ-5D QoL.
Dexcom	37	153	6.2.1.4	The report highlights as a major limitation of most cost-effectiveness studies that they "may not be generalisable since they did not use baseline characteristics and treatment effects data for their target populations". A way to address this limitation in the EAG report would have been to use the UK NHS HCL trial in the base case, since this trial reflects current real-world practice in the NHS. When this is not done, the EAG misses out on the opportunity to address what it sees as one of the major issues with the current evidence base	The EAG presents analyses for both the Diabetes Audit CSII population and the NHS adult pilot population.
Dexcom	38	167	7.2.1.1	Study cohort characteristics from Heller et al, previous pump users were excluded. It is applicable to patients who switched from MDI to CSII, not necessarily applicable to the target population by this assessment: Poorly controlled with HbA1c 9.1% Patients were excluded if they used a pump in the last 3 years	Point of view, no response required.
Dexcom	39	168	7.2.1.2	The two separate comparators to HCL; CSII+isCGM and CSII+rtCGM *were not* evaluated separately, which is a break from the protocol and the scope of the review (*Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – final protocol,* NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE, *Diagnostics Assessment Programme, Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes, final scope* 2022). The scope of this review clearly states that rtCGM and isCGM will be reviewed separately. None of the studies retrieved by the clinical review shows clinical evidence for isCGM vs HCL. The EAG assumed CSII+CGM proportion using isCGM based on feedback from the Diabetes Technical Network rather than validated data.	As per previous comments the EAG thinks that the only sensible comparator is a pooled comparator that reflects current use of CSII+CGM in the NHS.
Dexcom	40	169	7.2.1.2	When reviewing the severe hypoglyecimic events (SHE) and non severe hygoglycemic events (NSHE) outcomes, the EAG didn't differentiate between pediatric and adult studies. The rate of SHE and NSHE is different between age groups. Moreover, NSHE reported or extracted from clinical trials was based on the time below range and different cut points for TBR. Almost all studies except Ware et al. 2022 showed a higher ratio of TBR for the control group. Ware et al.2022 studies are for very young age groups (5.6 and 13 years) and comparing the results with other studies should be done with caution.	This is a reasonable point and argues for applying the NMA results for time below range using only adult studies.
Dexcom	41	174	7.2.1.2	As highlighted in previous comments, the EAG assessment of NSHE and SHE lacks the context of background risk and prevalence of SHE and NHSE in the T1D population. RCTs with small sizes are not equipped to capture the difference in SHE rates and therefore an appropriate surrogate measure like TBR should be utilized.	This is the approach of the EAG in its scenario analyses around NHSE and SHE rates. Applying

	Comment no.	Page no.	Section no.	Comment	EAG response
				All studies show a reduction in TBR in the HCL arm, and therefore at least NSHE should have been included in the base case. The NMA showed 0.83 reduction in TBR < 3.9 in HCL compared to CSII+isCGM.	the improvement in TBR to a baseline rate of NHSEs, and as relevant SHEs.
Dexcom	42	175	7.2.1.2	Table 19 is labeled as base case average rates of SHE and NSHE. In the previous page, the EAG decided not to use SHE and NSHE in the base case and so it is unclear what was the final decision. The 0.26 rate of SHE for HCL is based on the number reported by McAuley et al. for SHEs. However, McAuley explained that 4 out of the 7 SHEs events in the HCL were due to device problems and the actual rate of SHE is 0.13. EAG disregarded this and didn't conduct any sensitivity analysis around this rate. It is also important to highlight that HCL clearly shows a net improvement of 2% in TBR < 3.9 mmol which is in line with the 0.13 rate of SHE compared to SAP.	It is correct to note that the table values are not applied in the base case, but are rather applied in scenario analyses. There are also typos in the sentence that follows: "*The annual SHE rates correspond reasonably closely with the NHSE adult pilot annual rates of 0.21 at baseline and 0.34 at six months*." With the 0.34 being the baseline and the 0.21 the six month value for SHE PPY.
Dexcom	43	183	7.2.1.4	The EAG approves of the 0.045 worsening in HbA1c based on the DCCT trial but did not use it in the base case.	The EAG does not agree that the EDIC/DCCT implies a 0.045 annual worsening, but it does apply this as a scenario – with limited effect upon the ICER.
Dexcom	44	185	7.2.1.4	The EAG states that the worsening of HbA1c that was observed in EDIC is more relevant to real-world settings where the intensity of follow-up is less optimal compared to a controlled trial environment with intense follow-up. The EAG discarded the evidence from the prospective cohort studies that showed worsening of HbA1c over time and used the cross-sectional UK Diabetes audit data where no individual patient follow-up is available to justify using a static HbA1c progression.	It is possible that there is survivor bias but this is difficult to address. As noted above the EAG supplies a scenario with an annual 0.045 worsening which shows

	Comment no.	Page no.	Section no.	Comment	EAG response
				This assumption is flawed by survival bias. Patients with better HbA1c are probably living longer than patients who have poor glycemic control and who might have died earlier. As an example the study by the Barbara Davis center which shows worsening of HbA1c in patients who didn't initiate CGM. Champakanath, A., Akturk, H. K., Alonso, G. T., Snell-Bergeon, J. K., & Shah, V. N. (2022). *Continuous Glucose Monitoring Initiation Within First Year of Type 1 Diabetes Diagnosis Is Associated With Improved Glycemic Outcomes: 7-Year Follow-Up Study*. Diabetes Care, 45(3), 750-753.	only a limited effect upon the ICER. It is possible that this effect might be larger if modelling the more poorly controlled NHSE adult pilot population.
Dexcom	45	186	7.2.1.4	The EAG didn't use the CDM to calculate the treatment costs and the disutility/costs of NSHE and SHEs. Instead, they multiplied the costs/event rates by the survival for each group. This will empirically result in a slightly different estimate from using the CDM but the estimates of both methods should be very close.	Agreed.
Dexcom	46	189	7.2.1.6	The EAG questioned the estimates of TTO from Evans et al as being unreasonably high for SHE. However, the decline in marginal disutility is mostly related to frequent events like NSHE. It is not wise to apply the decline in disutility concept to less frequent events like SHE requiring medical care and which have a significant impact on patients' quality of life. The differentiation between frequent non-severe events and frequent severe events was discussed by Lauridsen et al. 2014	The functions of Currie and Gordon are both linear in SHE rates. It is only in NHSE rates that they are non-linear.
Dexcom	47	197	7.2.1.6	The report states that "*Choice of disutility approach for SHE events has a significant impact on the ICER"*. The EAG used the values from Gordon et al and did a sensitivity analysis using the values from Currie et al. The ICER using Gordon was 163k and fell to 121k when using Currie et al values. EAG justified using the SHE disutility from Gordon as it is specific to T1D using insulin, data from RCT, and a higher response rate compared to Currie et al. Gordon et al stated the following for SHE: . "In this study, we have demonstrated that incident severe hypoglycemia was associated with a 14.62-point increase in HFS, which would equate to a reduction in EQ-5D of 0.035". It is not clear how the EAG have calculated the QALYs in their sensitivity analysis. However, we note on using Gordon et al: • less than 1% of the study population experienced a SHE event. • Based on the occurrence of hypoglycemia in the 4 weeks preceding the 52 weeks visit a small number of patients experience some covariates included in the modeling (characteristic of the disease area and the factors being modeled) and analyses may not be sufficiently powered to detect statistically significant differences in the endpoints assessed. Furthermore, the data included in this study reflects a clinical trial setting and therefore the results must be treated with caution when applying inferences to a real-world setting	The rates of Table 19 are applied to the functions reported in Gordon et al to estimate the effect upon quality of life. The EAG report acknowledges the rarity of SHEs within Gordon et al and the possible difficulty of reliably estimating their effect given the 4 week assessment periods of the trial. This underlies the additional sensitivity analyses around the effects of SHEs as per SA07a and SA07b.
Dexcom	48	199	7.2.1.7	The EAG inflated all CGM costs by 5%. However, for isCGM only 75% of sensors last for 14 days (FreeStyle Libre 2 users manual	The cost effectiveness modelling assumes no

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				https://www.binsons.com/uploads/userfiles/files/documents/products/Libre%202%20User%20Manual.pdf) and there should hence be more inflation for isCGM. This will affect costs of CSII+CGM. The difference in costs between HCL and CSII+CGM can be partly attributable to assuming a much higher cost for rtCGM especially Dexcom G6. Costs of test strips used in the isCGM group was not included. The EAG assumed that rtCGM requires calibration which is not true for Dexcom G6 that is factory calibrated. A RWE study in Germany showed that isCGM users utilize 1.6 strips/day on average (van den Boom, L., & Kostev, K. (2020). *Changes in the utilization of blood glucose test strips among patients using intermittent-scanning continuous glucose monitoring in Germany*. Diabetes, Obesity and Metabolism, 22(6), 922-928.) cPAS appendix is not accessible to evaluate the additional analysis.	test strip costs due to factory calibration of CGM.
Dexcom	49	201	7.2.1.7	NSHE were assumed to have no costs for NHS and this is not substantiated.The costs of NSHE are less than SHE event. Studies have shown a correlation between glucose testing and insulin dosing behaviours which can impact diabetes outcomes (Brod et al. 2011). Another study showed that patients experiencing NSHE may require glucagon intramuscular or subcutaneous injection (Foos et al. 2015). Brod, M., Christensen, T., Thomsen, T. L., & Bushnell, D. M. (2011). *The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value in Health*, *14*(5), 665-671. Brod, M., Wolden, M., Christensen, T., & Bushnell, D. M. (2013). *Understanding the economic burden of nonsevere nocturnal hypoglycemic events: impact on work productivity, disease management, and resource utilization*. *Value in health*, *16*(8), 1140-1149. Foos, V., Varol, N., Curtis, B. H., Boye, K. S., Grant, D., Palmer, J. L., & McEwan, P. (2015). *Economic impact of severe and non-severe hypoglycemia in patients with type 1 and type 2 diabetes in the United States*. Journal of medical economics, 18(6), 420-432.	It is correct that no costs have been included for NSHEs.
Dexcom	50	202	7.2.1.7	The EAG used a much lower cost for SHE not requiring medical assistance of £1.8 compared to £36 costs previously used in other TA. The EAG calculation methods excluded follow up visits after the SHE event assuming that patients are receiving an ongoing care and their SHE will not result in an increase in resource utilization. The EAG discarded the evidence that SHE do result in increased resource utilizations for patients with diabetes. Bajpai, S., Wong-Jacobson, S., Liu, D., Mitchell, B., Haynes, G., Syring, K., ... & Chinthammit, C. (2021). Health care resource utilization and cost of severe hypoglycemia treatment in insulin-treated patients with diabetes in the United States. *Journal of Managed Care & Specialty Pharmacy*, *27*(3), 385-391.	The EAG restricted itself to UK evidence on costs for SHEs and provided a reasonable review of these in its report. It also presents scenario analyses around these to take into account possible additional training costs for those experiencing NHSEs/SHEs.

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Dexcom	51	204	7.2.2.1	EAG assumed that the CDM does not permit periodic capital costs to be modelled. In fact, you can model periodic costs by using the treatment algorithm function and specify when the switch to the next treatment should happen. That would require creating multiple treatments in the algorithm.	This did not occur to the EAG and is correct. It would be a little involved and would greatly complicate the modelling of treatment effects lasting less than a lifetime. But there are no reasons to think that the EAG method is inaccurate, and it greatly eases performing scenario analyses around costs.
Dexcom	52	205	8.2.2.2	The EAG did not conduct a sensitivity analysis testing for a lower cost of rtCGM.	This is correct.
Dexcom	53	206	8.2.2.2	The SA that used NHS pilot study shows HCL as cost-effective below a willingness to pay threshold (WTP) 20,000. This is shows that evidence for SAP using rtCGM in the RCTs included in the clinical review is not applicable to isCGM which would explain the difference in cost-effectiveness. It also worth mentioning that baseline characteristics of NHS pilot also resulted in significant drop in the ICER even without applying the effect from NHS study. This drop can be possibly related to the age of the cohort and other characteristics .	It does not demonstrate this but it dos point towards considering this aspect further. The baseline characteristics also have an effect as noted in the scenario analyses.
Dexcom	54	209	8.1	Patients who were included in the NHS study are CSII+isCGM. This explains the difference in treatment effects between the NMA and the NHS study. The EAG made a statement that iQVIA model is overestimating renal and eye complications but that doesn't explain why the clinical evidence is very different and comparing the two ICERs using the same model has nothing to do with overestimating events.	It may explain some of the difference. The EAG has provided consultation access to its IQVIA CORE modelling space.
Diabetes UK	1	General	General	We are concerned with the lack of real-world evidence included in this assessment. Whilst we appreciate the strict inclusion criteria that has been used to identify studies that can be considered in this report we would like to reiterate that it is vital the committee also considers the substantial real-world evidence on the benefits of the technology.	The EAG did present observational studies in the report.

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Diabetes UK	2	General	General	We welcome the publication of this assessment and opportunity to comment on the findings. Following the outcome of the committee meeting we look forward to being invited to consult again on the draft recommendations to represent the views of people living with diabetes in this appraisal of a landmark, life-changing technology. We also re-affirm the view that the committee should make recommendations on the class of hybrid closed loop technologies and not individual systems. As developments in technology are happening at pace we want to ensure the guidance is future-proofed and does not run the risk of becoming out of date soon after publication.	No response required
Diabetes UK	3	13		The independent economic assessment estimates that hybrid closed loop costs on average £1500 more annually than insulin pump with CGM or a Sensor Augmented Pump. However, we believe this is no longer the case as the majority of companies producing systems do not charge extra for the algorithm function. We have been told that amongst the companies who still charge for the algorithm function the lower cost of the pump device, for example, can offset this and the cost difference would not be expected to be as high as estimated here.	Costs were supplied by the NHS Supply Chain at current tender prices. The cost of CSII+CGM was based upon 10% CSII+rtCGM and 90% CSII+isCGM as indicated by the Diabetes Technical Network.
Diabetes UK	4	63		We feel that the exclusion of qualitative data has limited the scope of this report. We understand that it is much harder to assess easy measurable qualitative data but feel it is vital when judging factors like burden of disease and ease of treatment. We estimate that one in four people with type 1 diabetes has high levels of diabetes distress and we hear from many who struggle to cope with the relentlessness of managing their condition. It is also worth noting that diabetes distress costs the health system as well as being a major burden for a person living with diabetes. [redacted]	Worry if linked to or correlated with the HFS is explored in the economic analyses. Any QoL gain purely from increased convenience of HCL compared to CSII+CGM is not included in the economic analysis.
Diabetes UK	5	68-79		The randomised control trial studies used in this assessment refer to a baseline HbA1c which is lower than the reality of the type 1 population. This means that whilst the trial results do demonstrate the benefits to HbA1c reduction of using the technology it underestimates the potential benefits for the UK population.	It is taken from the UK Diabetes Audit CSII population. Scenarios are

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				The studies use a baseline of approximately 53mmol (7.5%) where the current threshold for dual therapy of an insulin pump and CGM in the current pathway is 69mmol (8.5%) Furthermore, The latest National Diabetes Audit reported that just 1 in 5 (19.5%) adults with type 1 diabetes had an HbA1c result of 53 mmol/ml (7.5%) or lower. It is important to consider the number of people in the UK with higher HbA1cs than those included in the selected studies to more accurately assess the potential benefits of this technology.	presented for the more poorly controlled NHSE adult pilot population.
Diabetes UK	6	68-79		We also think that the prioritization of randomized control trials has resulted in a lack of information about some groups of people who could benefit greatly from the intervention but are less likely to participate in a study. There are many people who may not be deemed health literate enough to use the technology, for example, when there is growing evidence demonstrating the improvements that automated insulin delivery can provide to those who have had difficulty managing their diabetes in other ways. There is also a lack of detail about deprivation and ethnicity in the research, and this should not inadvertently become a barrier to access for groups that could potentially benefit from using hybrid closed loop. We feel that there should be more research in this area and note the strong evidence of the existing inequality gaps in access to other wearable technologies currently.	Thank you, point of view – no response required.
Diabetes UK	7	108-109		We would counter the lack of quality of life data used in this report and feel it is an oversimplification to separate clinical and quality of life outcomes. For example, experiencing fewer hypos will inevitably lead to less time spent managing diabetes and increased confidence with self-management of diabetes will often help people towards reaching their target time in range. People living with type 1 diabetes and their parents and carers are all different, so prioritising specific treatment outcomes over and above another is a difficult task that will almost inevitably miss out certain individuals and experiences. Broadly speaking, people living with type 1 diabetes want to live well managing their condition, whether in terms of clinical or quality of life. The same tends to apply for parents and carers of people living with type 1 diabetes. The below quotes, from people living with type 1 diabetes who changed to a hybrid closed loop system, illustrates the far-reaching and holistic improvements to their quality to life: **“Mental health impact, [in] that I can do what I want and the system all but eliminates hypos and takes that stress away. It has also allowed me to run tighter control so again eased the worry of losing my eyesight. At a review last week, my consultant Ophthalmologist said my continued stable eyesight was down to my**	Thank you, point of view – no response required

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				exceptional control, something not achievable without [hybrid closed loop] tech." [redacted]	
Diabetes UK	8	215		The studies included don't show the significant reductions in hypoglycaemia that can result from using hybrid closed loop technology. We feel this should be highlighted, particularly as the review of the included studies suggested that the use of a CGM and insulin pump together resulted in fewer hypoglycemic events.	Point of view – no response required
Diabetes UK	9	215		[redacted]	Thank you, point of view – no response required

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				[redacted]	
Expert (Fiona Regan)	1	39	1st line	Refer to 'diabetic person', this should be a person with diabetes rather than defining a person by their medical condition	EAG happy to amend the text.
Expert (Fiona Regan)	2	50	2nd paragraph	NICE guidance on CGM changed in 03/2022 to recommend rtCGM for all patients with type 1 diabetes including adults (including pregnant women) and children	The current NICE website for NG17 still suggests for CGM assessing both rtCGM and isCGM and if multiple devices meet the patient needs choose the one with the lowest cost.
Insulet International	1	31	2	Reflecting on the impact of living with T1D described at section 2 of the EAC report, we wish to reiterate to NICE and the EAC that diabetes management technology has a tremendous impact on PWD and their caregivers, and HCPs. People living with T1D require insulin to stay alive. They therefore need to interact with their technology every day. It is estimated that people with T1D make an average of 180 decisions per day related to the management of their condition (Alleviating the burden of diabetes with AI – THINK Blog, Latts 2019). Although AID systems are similar in their use, the features and benefits differ depending on the specific AID technology. These differences include tubed and tubeless form factors, differing sensor compatibility and differences in algorithm design and behaviour. In combination, these differences can significantly impact on how an individual interacts with their technology. Offering choice in diabetes management technology to PWD, both in terms of technology type and available range within a class, is therefore critical to achieving effective diabetes care.	While less than perfect the EAG scenarios around the quality of life benefits to patients from reduced NHSEs/SHEs also explore similar benefits being experienced by carers/patients.
Insulet International	2	37	2.1.3	We welcome the EAC commentary on the significant detrimental impact of hypoglycaemia on people with T1D and the conclusion that it remains a "major problem in T1D".	Thank you, point of view – no response required. Please see previous

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				Hypoglycaemia and DKA outcomes were recorded in a multicentre prospective clinical trial of Omnipod® 5 in adults and children with T1D. Across 235 participants, time in range was significantly improved from standard therapy by 15.6 ± 11.5% or 3.7 h/day in children and 9.3 ± 11.8% or 2.2 h/day in adults (both P < 0.0001). This was accomplished with a significant reduction in time in hypoglycemia <70 mg/dL among adults (median [interquartile range]: 2.00% [0.63, 4.06] to 1.09% [0.46, 1.75], P < 0.0001), while this parameter remained the same in children. We request that the EAC and NICE acknowledge that diabetes management technology is a rapidly evolving and innovative area, and new HCL technologies will become available in the UK NHS over the coming years which seek to further address this unmet need and better support PWD and their caregivers to effectively manage their diabetes. • Brown SA, et al. Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System with Customizable Glycemic Targets in Pediatric and Adult Participants with Type 1 Diabetes. *Diabetes Care.* 2021;44(7):1630-1640. https://doi.org/10.2337/dc21-0172	response for Brown study.
Insulet International	3	215	8.4	We note the EAC commentary that "carer and patient reported outcomes are not systematically captured or reported" and request that the EAC and NICE acknowledge that this is an area being addressed by some manufacturers and also currently across the diabetes scientific community. One example from industry includes a recent publication on Omnipod® 5 AID system that aimed to evaluate psychosocial outcomes in T1D and reported significant improvements in diabetes-related psychosocial outcomes for adults with T1D. • Polonsky WH, et al. How Introduction of Automated Insulin Delivery Systems May Influence Psychosocial Outcomes in Adults with Type 1 Diabetes: Findings from the First Investigation with the Omnipod® 5 System. *Diabetes Res and Clin Pract*. 2022;190:109998. https://doi.org/10.1016/j.diabres.2022.109998	Thank you, point of view – no response required
Insulet International	4	43-44	2.3.1	We note the use of the term "Advanced HCL" as a separate category of intervention within the EAC report and request that the category is maintained as "HCL". Whilst this terminology has been adopted by some manufacturers to describe their systems, and has sometimes been used to describe a "next generation" iteration of an HCL system, we caution against adopting this label as a category as there is no fixed definition of what constitutes an "Advanced" system. Every HCL system is different, with varying algorithms and features included. There is no clear line that distinguishes an "HCL" system from an "Advanced HCL" system. A HCL algorithm can be very advanced and sophisticated. For example, an algorithm could be designed such that optimal performance is achieved without needing to add further features such as automatic correction boluses.	Advanced was labelled in the published evidence that met the inclusion of this review. this evidence was assessed as a single arm trial.

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				Furthermore, although the name Advanced HCL may imply to the healthcare provider or PWD that this system could be better than a “standard” HCL system, there is no evidence to support or guarantee this. In fact, HCL system designs may trade-off between simplicity for users versus optimization of outcomes. A system with automatic meal detection and automatic correction boluses may be less burdensome for the user but may then also achieve less optimal outcomes than if the user had performed precise carbohydrate counting and bolused 15 minutes before their meals. Finally, it is not clear how even further innovations and improvements, that will surely come with time, would be categorized and described beyond the term “Advanced HCL”. The standard and accepted terminology is “hybrid closed-loop", which indicates systems where the user is still expected to deliver boluses for meals, versus fully closed-loop, where the user does not need to deliver boluses for meals. All hybrid closed-loop systems are designed to be used alongside user-initiated meal boluses. We request that the term “Advanced” is removed when describing HCL technology by the EAC and NICE.	
Insulet International	5	41	2.2.1	We note the statement “The most advanced system is the iLet from BetaBionics which is a dual pump which infused insulin if blood glucose is too high, and glucagon if it is too low”. Because the iLet System is still in development, does not have regulatory clearance in any region, and we consider that these technology descriptions within section 2.2.1 should remain at category-level descriptions, we request this sentence be removed. Instead, the EAC and NICE could include a more general statement that dual-hormone systems are in development that can infuse insulin if blood glucose is too high, and glucagon if it is too low.	Thank you, point of view – no response required
Insulet International	6	48	2.3.3	The NICE clinical pathway to illustrate the management of T1D in the NHS is incorrect as currently printed. NG17 was updated in August 2022 and we request that the latest pathway is applied in this evaluation and associated documentation.	Please see earlier response on this point.
Insulet International	7	90	4.2.10	We understand that single-arm studies of HCL systems have been identified and summarized in Section 4.2.10. We believe that two published outpatient single-arm studies of the Omnipod® 5 AID System meet the criteria defined in this EAC report. We consider these studies important to include as they represent a different HCL algorithm and different system profile (e.g., tubeless insulin pump) than the other studies included. Therefore the inclusion of these studies will increase the breadth and scope of the results summary and conclusions to be more generalizable across multiple	Thank you for highlighting the two studies. The Sherr study was published closer to the submission date of this report. The EAG will closely assess the

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				different HCL systems. Furthermore, inclusion criteria state that studies of "people who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: CSII, rtCGM, flash glucose monitoring" are included. While these two studies did allow participants who had never used an insulin pump or who had never used a glucose sensor to participate, the number of such participants was very low as reported in the publications. In Brown, et al. (2021), 89.6% of participants had previously or currently used an insulin pump and 97.5% had previously or currently used a CGM. In Sherr, et al. (2022), 85.0% of participants had previously or currently used an insulin pump and 97.5% had previously or currently used a CGM. The criteria on page 63 states that "studies where more than 10% of the sample did not meet the inclusion criteria" were excluded; therefore these two studies meet the criteria to be included as only 2.5% had not previously used CGM. Additionally, the group mean outcomes at baseline with their usual therapy showed that the mean HbA1c was >6.5% and the mean TIR was <70% for all age groups, therefore meeting the criteria set forth on page 63: "research papers were included where it could not be established if all study participants had difficulty managing their condition....if the group mean met this criterion". The two publications we request be considered for inclusion as follows: Single-arm study of 3 months of Omnipod 5 use in 235 people with type 1 diabetes ages 6-70 years: • Brown SA, Forlenza GP, et al. Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System with Customizable Glycemic Targets in Pediatric and Adult Participants with Type 1 Diabetes. *Diabetes Care.* 2021;44(7):1630-1640. https://doi.org/10.2337/dc21-0172 Single-arm study of 3 months of Omnipod 5 use in 80 people with type 1 diabetes ages 2 to <6 years: • Sherr JL, et al. Safety and Glycemic Outcomes with a Tubeless Automated Insulin Delivery System in Very Young Children with Type 1 Diabetes: A Single-Arm Multicenter Clinical Trial. *Diabetes Care.* 2022;45(8):1907-1910. https://doi.org/10.2337/dc21-2359	eligibility of the studies.
Insulet International	8	104	4.2.13	The results for the subgroup analysis by age could benefit from further explanation. The statement "When comparing the subgroups separately, for the outcome TIR % between 3.9-10 mmol/L, HCL was significantly statistically worse compared to CSII+CGM (MD = -2.76, 95% CI = -5.33 to –0.19) in the under 18's" is surprising. Generally, studies have shown great improvements in TIR for children using HCL systems as compared to CSII+CGM. When examining Table 6, it looks like % TIR 3.9-10.0mmol/L improved by 7.74% in HCL compared to worsening by –2.76% in LGS/PLGS. Additionally, it is unclear what the numbers in Table 6 are representing. We request the EAC and NICE consider this feedback when presenting these data to Committee.	Table 6 illustrates the overall effect when conducting the subgroup analysis.

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Insulet International	9	167	7.2	In our opinion, many of the estimates applied in the CORE economic model are consistently too conservative and are not reflective of NHS clinical experience. The cumulative effect of this approach by the EAC across multiple data points is that the cost effectiveness analysis is skewed and therefore not reflective of the impact on a typical person living with T1D. This significantly limits its relevance in informing NICE recommendations on HCL technology. To provide a few specific examples of where this conservative approach by the EAC is driving a significant underestimate of effect in the economic analysis: **HbA1C reduction:** The estimates of treatment effect have been derived from a network meta-analysis of RCTs with mean baseline HbA1c above 7.5% in only two of the RCT's used for the NMA. The treatment effect applied is therefore largely based on use of HCL in people who were already below, or close to, target HbA1c. This is not reflective of UK clinical experience, for example, latest National Diabetes Audit data estimate more than two-thirds of people have HbA1c >7.5%. By not considering the impact of a higher baseline HbA1c, which will likely be associated with greater improvement in glycaemic control, the EAC are underestimating the treatment effect. **Reduction in Hypoglycaemic Events:** Annual event rates of NSHE in people with T1D are not reflective of published clinical experience. The rates of NSHE used in the EAC analysis are derived indirectly by coupling the 20.8 annual NSHE rate for HCL of Brown et al (2019) and Breton et al (2020) with the EAC NMA time below 3.0 mmol/l net effect estimates. These rates were justified as being consistent with the NHSE rates reported by Donnelly (2005), 43 pp/year, which was assumed to represent the rate of people using MDI+SMBG. Other published studies have reported higher rates of NHSE, for example, Östenson et al (2014) reports an average NSHE rate across 7 countries of 94 pp/year. It's likely that the impact of NSHE and absolute treatment effect of HCL vs CSII is substantially underestimated in the EAC analysis. **Utility of hypoglycaemia avoidance**: The EAC utilised estimates from Gorden et al (2020) in the base case, with Currie et al (2006) applied in sensitivity analyses, which we consider underestimates the disutility of NSHE in the base case. We would recommend utilising a different disutility estimate, such as Currie et al in the base case, which we consider may more appropriately estimate the disutility of NHSE. The utility gain of falling from 16 NHSE per year to none appears to be around 0.003 (figure 24 EAC report), meaning that a person would be willing to give up around 1 day per year of full life for this. In the published literature, the risk of severe and non-severe hypoglycaemia has been reported to impact well-being in several ways: fear, affected sleep, exercise, work productivity and life choices (Chatwin et al. 2021). A measure of the willingness of people with T1D to trade off life to avoid hypoglycaemic events is that they may choose to avoid insulin doses or maintain higher glucose levels over extended periods. By doing so they are	The EAG presents scenarios around all of these points. The choices for the base case have been justified in terms of a lack of direct evidence for the exclusion of hypoglycaemia from the base case, and Gordon et al having a considerably higher follow-up rate than Currie et al which was only 31%.

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				accepting the risk of shortening their lives, potentially by years on average, and experiencing harm from diabetes related complications. This would suggest that there could be a good case for selecting Currie et al as the estimate of disutility in the basecase rather than Gordon et al, and to use Lauridsen et al (2014) for sensitivity analyses. • National Diabetes Audit, 2020-21 Type 1 Diabetes England and Wales • Östenson CG, Geelhoed-Duijvestijn P, Lahtela J, et al. Self-reported non-severe hypoglycaemic events in Europe. Diabet Med. 2014 Jan;31(1):92-10 • Chatwin H, Broadley M, Valdersdorf Jensen M, Hendrieckx C, Carlton J, Heller S, Amiel S, de Galan B, Hermanns N, Finke-Groene K, Speight J, Pouwer F. 'Never again will I be carefree': a qualitative study of the impact of hypoglycemia on quality of life among adults with type 1 diabetes. BMJ Open Diabetes Res Care. 2021 Aug;9(1):e002322.	
Insulet International	10	203	7.2.1.7	We consider that the EAC has applied a very conservative approach to some of the model costs, which are also driving an underestimate of effect. For example: **Cost of stroke:** The EAC applies the cost for stroke in the year of the event at £4,728 and £175 in subsequent years. To provide comparison, average per patient costs of £15,000 -£30,000 (Youman et al. 2002), and separately £13,452 in year one to £17,963 after five years (Xu et al. 2018) have been reported in the published literature. **Cost of NSHE:** The EAC has assumed NSHE have no cost to the NHS. Brod et al (2011) and Orozco-Beltran et al. (2014) report that 8% - 25% of NSHE are associated with additional HCP appointments in people with T1D. Considering the frequency of NSHE, this could represent a substantial cost to the NHS. • Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics. 2003;21 Suppl 1:43-50 • Xu XM, Vestesson E, Paley L, Desikan A, Wonderling D, Hoffman A, Wolfe CD, Rudd AG, Bray BD. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. Eur Stroke J. 2018 Mar;3(1):82-91 • Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011 Jul-Aug;14(5):665-71 • Orozco-Beltrán D, Mezquita-Raya P, Ramírez de Arellano A, Galán M. Self-reported frequency and impact of hypoglycemic events in Spain. Diabetes Ther. 2014 Jun;5(1):155-68.	The costs applied are largely the IQVIA CORE model defaults, and are those applied in the previous NIC assessments using the IVQIA CORE model. It is correct that costs for NHSEs are £0 throughout. If there are additional patient visits as a result of NHSEs this could affect the analyses.
Insulet International	11	133	5.1.7.2	We welcome the EAC conclusion that the evidence suggests that HCL technologies have the potential to improve the lives of people with T1D and that improvements in quality of life are reported. However, this does not appear to have been explored in the economic analysis by the EAC, as only the disutility of complications, adverse events	Thank you, point of view. Additional analysis will be conducted post

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				and premature mortality have been included. We request that the EAC carry out additional analyses to model the impact of improvements in quality of life associated with use of HCL systems, either by applying a theoretical utility gain or the differences in health-related quality of life that have been reported.	committee requests.
Insulet International	12	General	General	We welcome the opportunity to provide feedback on the EAC report at this stage, but look forward to NICE's consultation on its draft recommendations on the class of HCL technology after November Committee meeting. Feedback from all stakeholders across the diabetes community is essential to inform guidance that truly supports and enables access to effective technology. We request that NICE confirm the public consultation dates as soon as possible.	Thank you, no response required.
JDFR	1			Following the updated Guidelines NG17 and NG18, JDRF believes the comparator should be HCL vs standard treatment, with standard treatment being MDI plus sensing.	Thank you, no response required.
JDFR	2	133	5.1.7.2	Quality of Life. A number of studies were not looked at showing improved quality of life in people with type 1 diabetes using Hybrid Closed Loop (HCL). In *Psychosocial and Human Factors During a Trial of a Hybrid Closed Loop System for Type 1 Diabetes* [3] Diabetes management distress decreased, and diabetes technology attitudes became more positive over the trial period. In *Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in Children and Adults: A Focus on Superiority Over Predictive Low-Glucose Suspend Technology*[i4] Fear of hypoglycaemia, quality of life, diabetes treatment satisfaction, and diabetes distress improved, while the percentage of patients with poor sleep quality was reduced, thus reducing the burden of living with type 1 diabetes. Closed loop technology could have a tremendous impact on the lives of people with type 1 diabetes and their families or carers. Closed loop technology enables the person with type 1 diabetes to not have to think about their condition as often, as they have the reassurance of their technology automatically testing their glucose levels and	Thank you, no response required.

[3] Psychosocial and Human Factors During a Trial of a Hybrid Closed Loop System for Type 1 Diabetes Management; Adams et al, October 2018 https://pubmed.ncbi.nlm.nih.gov/30239219/

[4] Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in Children and Adults: A Focus on Superiority Over Predictive Low-Glucose Suspend Technology; Beato-Vibora et al, December 2020 https://pubmed.ncbi.nlm.nih.gov/31855446/

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				adjusting their insulin accordingly. This reduces the need for adjusting for exercise levels and activity, for the weather and other factors which are difficult to quantify but can destabilise a person's glucose levels and result in potential hypers or hypos. As this technology is much easier to use and live with than other traditional methods of type 1 diabetes self-management, such as finger prick tests and injections, it is particularly suited to a number of groups of people. The reduction in daily decision making could particularly support people with mental health issues or learning disabilities, as well as children and young adults beginning to manage their diabetes independently. Quality of life would be vastly improved by hybrid closed loop technology. One of our supporters shared their story with us: “Two and a half years after DIY looping my closed loop system I met the criteria to change sensors and soon after this my clinic became an early adopter of CamAPS FX and I was offered access to the system... Within days of starting the CamAPS FX system I began to notice improvements in my diabetes. Although it wasn’t perfect it was much better than my DIY system, even in the initial three weeks where I was still learning to use the technology. I also began to notice my mood improving too. After my first week with CamAPS FX my time in range was already better than I had managed to achieve (with a lot of effort) with my DIY version. Things have continued to improve and I’m now spending much less time worrying about my diabetes and just getting on with my life again. The regular lows have disappeared as have the deep hypos and spikes. The CGM is very accurate (when I use a blood glucose meter to calibrate it) and so my confidence in the system grows daily. I spend hardly any time interacting with the system other than at mealtimes or telling it I’m heading out to exercise.” We also heard from parents of a child with type 1, aged 5. “Since his diagnosis, we’ve been on a number of different pumps and sensors which didn’t really work out at all. Then we were able to join the study [clinical trial for the artificial pancreas system] which was amazing. Using the app has meant that multiple people can access their child's data at any time, meaning that his care is not in the hands of just one person”. This aspect of the app gives the parents reassurance and support, as well as a greater sense of freedom. Being able to involve people remotely in their son’s care is an “absolute game changer.” The app has also reduced the impact of monitoring the child’s blood glucose levels at night, and they can now check by looking at the phone app rather than going up and doing a blood test. His HbA1c has been “fantastic” since starting on the system. They also feel that using the CamAPS FX has helped identify problems before they arise. They expressed that they “knew that it wasn’t going to fix everything, but it was going to help us manage the condition better. I would say that that goal - of better management - is being	

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				achieved". "With the amount of tech that's needed for the closed loop system, the more things there are that can go wrong." But despite occasional issues, the parents are clear they wouldn't go back. "I feel very, very, very grateful for the opportunity to be on the app and I definitely would not want to go back." Most importantly, the app has meant that type 1 diabetes doesn't stop their son getting the most from school and home life. "He's a very happy, healthy boy and that's the main thing."	
JDFR	3	188	7.2.1.6	It has been assumed that non-severe hypos (NHSE) have no cost to the NHS. Brod et al[5] and Orozco-Beltran et al[6] report that 8% - 25% of NSHE are associated with additional HCP appointments in people with T1D. Considering the frequency of NSHE, this could represent a substantial cost to the NHS, not to mention the impact on the person with type 1 diabetes' quality of life.	Please see comment above.
JDFR	4	209	8.1	With regards to patient reported outcomes not resulting in clear trends, type 1 diabetes is a complex, personal condition where not one size fits all, thus it is unlikely there will be a consensus/trend. JDRF's 2022 report *Research to Reality*[7] found that "Each person with type 1 will have their own needs, desires and priorities so will value outcomes differently. What works for one may not be effective, safe, or convenient for another. Furthermore, there are differences between individuals but also differences between life stages of one individual. For instance, treatment needs may change at junctures such as leaving home, pregnancy, or starting or changing a career."	Thank you, no response required.
JDFR	5		General	The base HbA1C in the chosen RCTs was 7.3% - 7.6%. A similar 0.3% drop has been assumed for all patients, and hasn't taken into account the greater benefits to patients with a higher baseline (Many people will have a much higher A1c and the drop, or improvement, will therefore be much more significant along with the associated clinical benefits).	Scenarios are presented around this.
JDFR	6		General	JDRF recommends that this appraisal be device agnostic in order to widen availability to hybrid-closed loop systems and keep the guidance relevant and up-to-date in the future as new manufacturers and devices are made available. There should be provision for people with type 1 diabetes to move between standard therapy and hybrid closed loop therapy easily according to their needs and changing circumstances.	Thank you, no response required.

[5] The impact of non-severe hypoglycemic events on work productivity and diabetes management; Brod et al, July 2011 https://pubmed.ncbi.nlm.nih.gov/21839404/

[6] Self-reported frequency and impact of hypoglycemic events in Spain; Orozco-Betran et al, June 2014 https://pubmed.ncbi.nlm.nih.gov/24515748/

[7] Research to Reality; JDRF, April 2022 https://jdrf.org.uk/wp-content/uploads/2022/04/Research-to-Reality.pdf

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JDFR	7		General	JDRF looks forward to consulting on the draft recommendations after the November committee meeting.	Thank you, no response required.
Medtronic	1	4	1	The EAG discussion section states: **"*the relevance of the RCT populations and outcome measure results for the decision problem is debatable and not easy to judge".*** The effect size from the network meta-analysis used in the base case shows a very modest reduction in HbA1c of 0.28%. This is at odds with the much larger reduction in HbA1c achieved with current advanced algorithm hybrid closed loop (AHCL) technologies and reported in more recent studies[1–5]) and the substantial body of real-world evidence including the recent NHS England observational study in approximately 900 people with Type 1 diabetes. We suggest that the studies used in the network meta-analysis are not sufficient for decision making and **we ask the Committee to use the NHS England observational study outcomes for HbA1c in the base case analysis of clinical and cost effectiveness.** The NICE MTA process was paused to allow the real-world data collection from the NHS England observational study on HCL technologies in adults and children. The protocol and scope of this study were designed to answer the clinical effectiveness question in the NICE MTA scope and fully reflect the patient pathway in NHS England in a real-world cohort of around 900 people. The NHS England observational study in adults reported a 1.6% reduction in HbA1c[14]. This 1.6% reduction in HbA1c is over 5 times the effect size of 0.28% reported in the network meta-analysis that informed the base case. The NHS England observational study data is of good provenance and of sufficient quality and relevance to address the research question in the MTA. This would also be aligned to the NICE strategy of using real-world data to resolve gaps in knowledge and drive forward access to innovations for patients. The recently published ***NICE Real World Evidence Framework*** which states: ***"even if randomised evidence is available, it may not be sufficient for decision making in the NHS for several reasons including:*** • *the comparator does not reflect standard of care in the NHS* • *relevant population groups are excluded* • *there are major differences in patient behaviours, care pathways or settings that differ from*	Thank you, no response required. A point for the committee.

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				implementation in routine practice • *follow up is limited"* The recently published ADAPT RCT[1] involved in three European countries, including the UK and investigated the effect of AHCL on HbA1c compared with multiple day injections (MDI) plus flash glucose monitoring (FGM) or continuous glucose monitoring (CGM) in sub-optimally controlled adult patients with T1D. The HbA1c reduction in intervention arm of ADAPT was 1.6% (delta 1.4%). The comparator in this RCT reflects the standard of care in NHS England and the RCT reported a remarkably similar reduction in HbA1c to that seen in the NHS England observational study and was achieved regardless of starting technology (1.6% in the intervention arm, delta 1.4%). This effect is also over 5 times higher than the 0.28% reported in the network meta-analysis.	
Medtronic	2	80	Fig 1	The EAG discussion section states: ***the relevance of the RCT populations and outcome measure results for the decision problem is debatable and not easy to judge.*** We agree with the EAG conclusion that the relevance of the RCT populations and outcome measure results for the decision problem is debatable and **ask the Committee to consider the following limitations of the network meta-analysis that derived such a pessimistic effect estimate of 0.28% reduction in HbA1c which was used in the base case for clinical and cost effectiveness:** • 12 RCTs were selected for systematic review and network meta-analysis however, as described the MTA assessment report, studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining mean difference between intervention and comparators. Studies did not consistently describe comparators. Cross-over studies did not provide data at different cross-over time points. • Studies included are mainly safety studies with 11/12 studies having Time in Range (TIR) as the primary endpoint. These were not powered to measure HbA1c reduction as the sample sizes were too small. • The study selection for the network meta-analysis is not representative of the newest generation of MiniMed 780G and Control-IQ hybrid closed loop technologies, currently in use in NHS England, which correct for hyperglycemia. • The observed effect size in the newly published RCT with standard of care as the comparator[8] and the real-world evidence of MiniMed 780G and Control-IQ, have not been considered in the meta-analysis and these	Thank you, no response required. A point for the committee.

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				studies demonstrate effect sizes up to 5 times higher than that reported from the network meta-analysis. • The NHS England Observational Study reported a 1.6% reduction in HbA1c in adults[6]. This effect size is also 5 times higher than that reported from the network meta-analysis. • The ADAPT RCT[1] reported a remarkably similar reduction in HbA1c to that seen in the NHS England observational study and this was achieved regardless of starting technology (1.6% in the intervention arm, delta 1.4%). This effect is also over 5 times higher than the 0.28% reported in the network meta-analysis. • Consideration should also be given to the effect size in the substantial body of evidence in non-RCT quantitative data and real-world data publications, including real-world data publication on over 4,100 and people with Type 1 diabetes and a recent real world data analysis from 12.870 MiniMed™ 780G system users in EMEA [16,2,] • HbA1c reduction is greater from higher starting point so has a non-linear relationship. Most of the studies selected for NMA were not powered for the secondary endpoint of HbA1c and assumptions re TIR conversion to HbA1c are not validated and should be interpreted with caution. • Participants in the selected studies were a well-controlled population with a baseline HbA1c of 7.5% before introduction of the HCL system. However, HbA1c of 7.5% is not reflective of the average HbA1c in NHS England (63% of Type 1 in NHS England have HbA1c >7.5%, National Diabetes Audit 2021) and is lower than HbA1c stated in scope which specifies studies with a baseline A1c >8%. • Control-IQ is not represented in any of the studies and MiniMed780G is the intervention in adults in only 1/12 of the studies. This 780G study is not powered to measure HbA1c as it is a safety study, not clinical effectiveness. • Many of the studies include mixed populations which are subject to substantial clinical heterogeneity due to differences in behaviour between younger children, adolescents and adults. Effect estimates derived from the clinical effectiveness analysis for children are subject to substantial heterogeneity because of differences in the age of participants included in the studies. There are likely to be substantial differences in control of diabetes between younger children whose treatment is supervised by parents, and teenagers who manage their treatment independently and who are also undergoing endocrine changes during puberty[7] • Pickup et al[17] explored appropriate and inappropriate meta-analysis of the evidence base for diabetes technology and concluded that appropriate meta-analysis should only include trials that are of sufficient	

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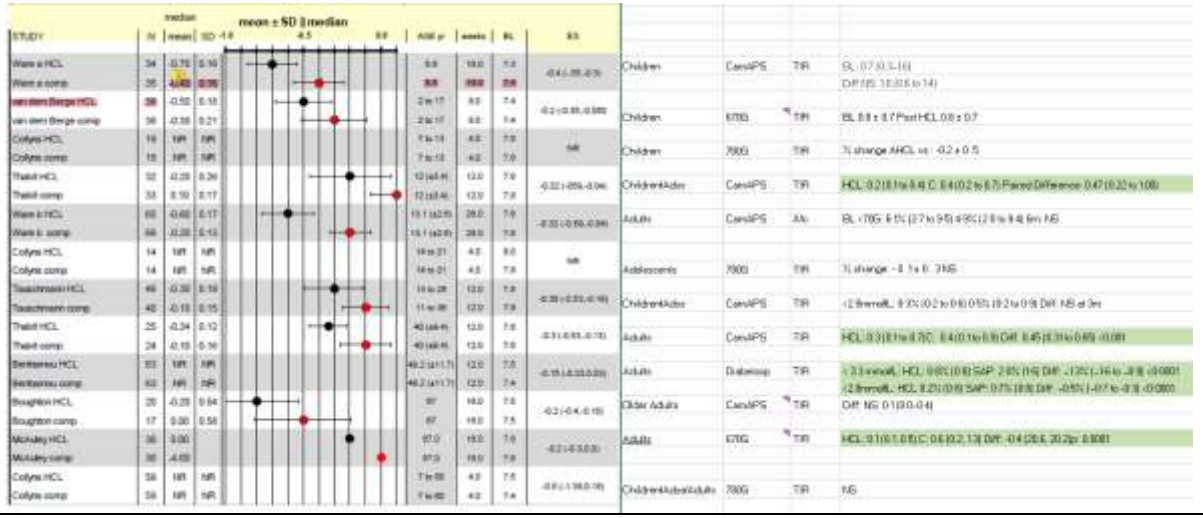
				duration to accurately measure outcomes such as severe hypoglycaemia, and they should not use obsolete technology that is of proven inferiority to current technology. They propose that when evidence synthesis is intended for decision making (e.g. decisions on cost effectiveness or comparative treatment efficacy), rather than for summary of the literature, the trial inclusion criteria for meta-analysis should be restricted to a specific target population with relatively narrow definitions associated with the intended use of the treatment, such as a point in disease progression, a level of disease severity, the fact of previous treatment failure, and so on. Alternatively, meta-regression or individual patient data meta-analysis should be used to relate treatment effects to patient characteristics that might be potential effect-size modifiers, such as age, disease duration, or baseline risk. In conclusion, many of the studies include mixed populations which are subject to substantial clinical heterogeneity. The RCT populations and outcome measure results (Table 1) are not reflective of currently available technologies and cannot be relied upon for decision making. **The outcome effects from the network meta-analysis do not reflect the consistent body of primary evidence and real-world data that has been published since and we ask the Committee to consider the weighting of this body of evidence.** **Table 1** 	
Medtronic	3	3	3	The HbA1c reduction in the base-case is not a clinically relevant reduction in HbA1c and does not reflect the	Thank you, no response

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				findings of the ADAPT RCT[1] nor the HbA1c reduction reported in the NHS England observational study, which was designed to address the decision problem in the MTA. A limitation of the meta-analysis is the ranges of control, which are not representative of patient populations in a real-world setting. In NHS England, approximately 50% of patients would have an A1c> 8.0%. To address the discrepancy between the outcomes shown in the NMA and real-world evidence, data from the ADAPT trial can be used to shed light on the improvement in control introduced by switching a subject not at target from MDI + CGM to MiniMed780G. Using the ADAPT data, a regression analysis[15] has been performed (figure 1) with the resulting equation: A1c change from baseline to 6months = 3.7 – 0.59 * BaselineA1c For example, a subject with a baseline HbA1c of 8% is expected to decrease on average by 1.02% at 6 months resulting in an A1c= 6.98%. All participants in the study had a baseline HbA1c >=8%, with average baseline HbA1c = 9% and observed average reduction after 6 months use of the MM780G = -1.54 (vs -0.2 in the control group). Figure 1	required. A point for the committee.

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				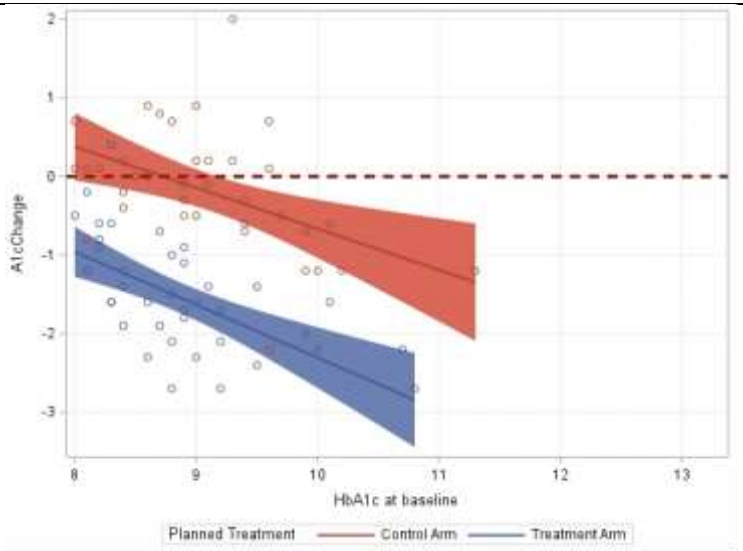	
Medtronic	4	7	2	The MTA assessment methods describe the population for the decision problem as "*people who have T1DM who are having* ***difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring"*** however the comparators were specified as: r*eal time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated)* and *intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.* The current standard of care in NHS England is multiple daily injections (MDI) plus isCGM or rtCGM and these comparators have been excluded from the assessment, despite meeting the population criteria of "***prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring".*** These CGM + multiple daily injection comparators have been included for pregnant women in the PICO on page 61 therefore **we question whether these CGM + MDI comparators been omitted in error for the full Type 1 population?**	Please see earlier response for comparators.

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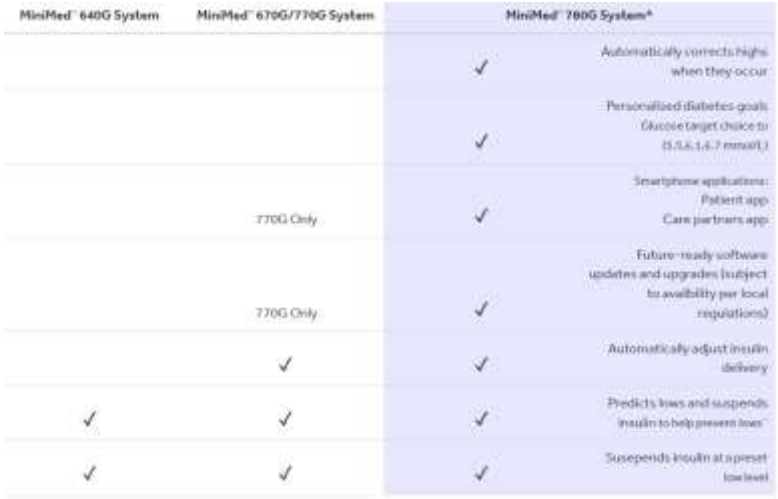
				We are concerned that final guidance will be limited to those already on an insulin pump (CSII) as there is significant inequity of access to insulin pumps currently and this will create further inequity of access to HCL technology. The current inequity of access to insulin pumps has been highlighted in the 2018 NHS England Diabetes Pump Audit[18], which found an unexplained ten-fold variation in pump use by people with Type 1 diabetes.	
Medtronic	5	7	2	All integrated HCL systems have been analysed together however HCL algorithms are evolving very fast and performance has improved with each new generation of the technology e.g. the performance of MiniMed™670G and MiniMed™ 780G has been assumed to be the same in the assessment report however there are significant differences in the performance of two algorithms and the clinical outcomes depending on types and versions of the technology.[8] The updated features in 780G are listed as an example below: 1. Automation level progressively increases from 640G to 780G[9]  1. Ease of use: comparison of closed loop (HCL) exits, and alarm frequency with the standard HCL (HCL 670G) versus enhanced HCL (e-HCL 780G) Medtronic system show the following differences:	This assessment looked at HCL system as a whole rather than specific models.

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				a. Automode exit rate 3.5 VS 0.5 n/week[10] b. alarm frequency decreased from8.6 (5.8) to 3.9 (2.8)[11] 2. Total Daily insulin dose & insulin sensitivity factor is adapted every 24hrs to user requirements based on previous actual insulin delivery and glucose levels.[8] 3. Ease of use: To initiate the system the clinician has to select with the patient 3 choices to make for the settings with several options[9]:  4. Training support to align expectations around automated insulin delivery (AID) benefits and system benefits is essential as outlined: Medtronic's Start right program covers all the points.[12] [13]	
Medtronic	6	13	1	In the independent economic assessment section, it states: "*The published model validation papers suggest that an earlier version of the iQVIA CDM tended to overestimate the incidences of the complications of diabetes, this being particularly important for severe visual loss and ESRD. Medium term modelling of overall survival appeared good, but there was uncertainty about its longer-term modelling. It is not known whether these issues persist in the current iQVIA CDM".* **The published validation papers referred to are the 2004 and 2014 manuscripts. The latest one was published in 2014 and was done in 2013, using model version 8.5. iQVIA is now at version 9.5 Plus. The following reference may provide further information.**	The EAG has not considered the poster presentation and assumes it has not been peer reviewed and is not an externally set validation exercise such as the Mt Hood challenge.

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				Martins L, Ramos M, et al. Contrasting 4 different mortality predictions in patients with type 1 diabetes using the IQVIA Core patients with type 1 diabetes using the IQVIA Core Diabetes Model. ISPOR Congress, November 6-9, 2022, Vienna, Austria. Poster EE649.	
Medtronic	7	156	3	*"The ERG is unable to source the annual SHE rates not requiring medical assistance and requiring medical assistance of 0.65 and 0.25 from Östenson et al who reported a mean annual SHE rate of 0.7 among those with T1DM".* **The overall event rate of SHEs was sourced from Swedish data from a multinational study, wherein the total event rate in people with T1D was 90 per 100 patient years.** **Of these it was assumed that 28% of events (i.e. 25 events per 100 patient years) would require medical assistance, based on the findings of a Canadian study by Leiter et al. (2005).**	The EAG thanks the company for the clarification.
Medtronic	8	3	3	There is a typo here "….but did not significantly affect % time **within** range (<3.9 mmol/L)" should be replaced with "time **below** range".	Thank you, noted. Typo.
Medtronic	9	13	2	The EAG assesses the cost effectiveness of HCL, PLGS and CSII+CGM. "PLGS is extendedly dominated throughout and for this summary the EAG does not consider it further". **We question why this analysis on PLGS was done as it was not in scope and therefore question the need for a network meta-analysis.**	Please see earlier comments on SAP/PLGS
Medtronic	10	41	3	*"The most advanced system is the iLet from BetaBionics which is a dual pump which infuses insulin if blood glucose is too high, and glucagon if it is too low".* **It is unclear why this device is described here as it was not in the scope and is not commercially available.**	From the literature. No response required.
Medtronic	11	66	2	… "*publication bias is present if the funnel plot is asymmetrical"*… **this funnel plot is missing from the assessment report.**	The EAG can provide the funnel plot under supplementary material.
Medtronic	12	66	3	*"Statistical analyses were performed using RStudio version 4.1.0".* **Information on this package is missing from the assessment report.**	The version of the statistical software is reported. It is not academic practice to describe the statistical software.
Medtronic	13	80	1	Figure 1: The numbers reported in this figure are not matching the numbers in table 3 - see for example Thabit net effect -0.3 (-0.5, -0.1) therefore it is unclear where these numbers come from. Another example from McAuley being the range being 0.0-0.7 - when McAuley has no SD.	The ES for HbA1c is the same as the ES in table 3
Medtronic	14	77	2	The Kariyawasam 2022 study is in table 3 but not included in figure 1, in addition the heterogeneity analysis to assess the consistency and coherence of the included studies is missing	Kariyawasam 2022 provided baseline HbA1c

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					only therefore cannot be plotted.
Medtronic	15	91	1	*"Most observational studies employed similar inclusion criteria to those used in the RCTs".* **We suggest that this is not correct, observational studies have a higher baseline HbA1c as illustrated by Castaneda J. et al. 2022**	Point of view, no response required.
Medtronic	16	152	2	*"This inference was, however, subjective as the studies chose arbitrary willingness to pay thresholds".* **We ask the Committee to note that the willingness to pay thresholds used in the cost effectiveness studies referenced here were not chosen arbitrarily; they are chosen based on the willingness to pay in the country where the studies took place, which is on average around €50,000 across Europe, including indirect costs.** The 2019 study applied a willingness-to-pay threshold of SEK 300,000 per QALY and also added a cost-effectiveness acceptability curve for 670G to allow more thresholds to be considered. The 2021 study applied a willingness-to-pay threshold of SEK 500,000 per QALY gained in Sweden (as recommended by the Swedish Agency for Health Technology Assessment [SBU] for high-cost interventions)," The 500,000 SEK is based on Socialstyrelsen (National Board of Welfare) stating that low cost is < 100,000 SEK/QALY, high is > 500,000 SEK/QALY and very high is > 1,000,000 SEK/QALY so below 500.000SEK is totally aligned with the studies. This corresponds to about 50.000 Euros (average threshold across Europe) and is considered cost effective.	Points for the committee, no response required.
Medtronic	17	117	4	"It is not clear whether they used the Guardian™ 4 System (Guardian™ 4 sensor plus Guardian™ 4 transmitter) or just the Guardian™ 4 sensor". **We can confirm that the sensor is always matched with a transmitter and that the Vigersky study is now published.** https://pubmed.ncbi.nlm.nih.gov/36125605/	Thank you for clarifying
Medtronic	18	118	1	*"The main issue with Arrieta et al., 2022 it is not clear whether patients with T1DM were on different previous treatments". The only treatment information that was available is the percentage of MiniMedTM 780G system users, for two different age groups of people".* **There were 12 870 users with at least 10 days of SG data post-AHCL initiation who were included in the analysis. The mean ± SD and median (IQR) of the observation period for this group was 112 ± 69 and 102 (54-160) days, respectively.**	Thank you for clarifying

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				There were 3211 (27%) users who reported to be aged 15 years or younger, and for whom the observation period was a mean ± SD of 120 ± 71 days and median (IQR) of 113 (61-170) days. **There were 8874 users who reported to be aged older than 15 years, and for whom the mean ± SD and median (IQR) of the observation period was 110 ± 68 and 110 (52-156) days, respectively.** **There were 785 users who did not report their age.**	
Medtronic	Bibliography			1. Choudhary P, Kolassa R, Keuthage W, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. *Lancet Diabetes Endocrinol*. 2022;10(10):720-731. doi:10.1016/S2213-8587(22)00212-1 2. Arrieta A, Battelino T, Scaramuzza AE, et al. Comparison of MINIMED ™ 780G system performance in users aged below and above 15 years: Evidence from 12,870 real-world users. *Diabetes Obes Metab*. Published online April 11, 2022:dom.14714. doi:10.1111/dom.14714 3. Ekhlaspour L, Town M, Raghinaru D, Lum JW, Brown SA, Buckingham BA. Glycemic Outcomes in Baseline Hemoglobin A1C Subgroups in the International Diabetes Closed-Loop Trial. *Diabetes Technol Ther*. 2022;24(8):588-591. doi:10.1089/dia.2021.0524 4. Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. *Diabetes Technol Ther*. 2021;23(9):601-608. doi:10.1089/dia.2021.0097 5. Castañeda J, Mathieu C, Aanstoot HJ, et al. Predictors of time in target glucose range in real-world users of the MiniMed 780G system. *Diabetes Obes Metab*. 2022;24(11):2212-2221. doi:10.1111/dom.14807 6. Crabtree T, Griffin T, Lum J. View of Protocol for the Diabetes Technology Network UK and Association of British Clinical Diabetologists' closed-loop insulin delivery audit programme | British Journal of Diabetes. Published 2021. Accessed November 8, 2022. https://bjd-abcd.com/index.php/bjd/article/view/897/1135 7. NICE. Overview | Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) | Guidance | NICE. Published 2016. Accessed November 8, 2022. https://www.nice.org.uk/guidance/dg21 8. Grosman B, Parikh N, Roy A, et al. In Silico Evaluation of the Medtronic 780G System While Using the GS3 and Its Calibration-Free Successor, the G4S Sensor. *Ann Biomed Eng*. Published online September 20, 2022. doi:10.1007/s10439-022-03079-9 9. MiniMed™ 780G system AUS. Medtronic Diabetes. Accessed November 2, 2022. https://www.medtronic-diabetes.com/en-gb/insulin-pump-therapy/minimed-780g-system 10. Matejko B, Juza A, Kieć-Wilk B, et al. Transitioning of People With T1D From Multiple Daily Injections and Self-Monitoring of Blood Glucose directly to MiniMed 780G Advanced Hybrid Closed Loop System: A Two-Center, Randomized, Controlled Study. *Diabetes Care*. Published online September 14, 2022:dc220470. doi:10.2337/dc22-0470	No response required.

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				11. Paldus B, Lee MH, Jones HM, et al. Glucose Control Using a Standard Versus an Enhanced Hybrid Closed Loop System: A Randomized Crossover Study. *Diabetes Technol Ther*. 2019;21(1):56-58. doi:10.1089/dia.2018.0279 12. Boughton CK, Hartnell S, Allen JM, Fuchs J, Hovorka R. Training and Support for Hybrid Closed-Loop Therapy. *J Diabetes Sci Technol*. 2022;16(1):218-223. doi:10.1177/1932296820955168 13. minimed_780g_training_guide.pdf. Accessed October 22, 2022. https://resources.cloud.medtronic-diabetes.com/sites/prd/files/documents/2022-03/minimed_780g_training_guide.pdf 14. Oral presentation Diabetes Technology Network meeting, September 2022 15. Medtronic data on file. Accessed November 7th, 2022 16. Da Silva J, et al. "Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4'120 Users." DiabetesTechnology & Therapeutics, September 15, 2021, dia.2021.0203. https://doi.org/10.1089/dia.2021.0203. 17. Pickup et al. The Evidence Base for Diabetes Technology: Appropriate and Inappropriate Meta-Analysis. Journal of Diabetes Science and Technology Volume 7, Issue 6, November 2013 18. National Diabetes Insulin Pump Audit 2017-18. NHS Digital	
NHSE	1			In this health economics analysis, the cost-effectiveness of hybrid close loops has been assessed compared to a Pump & CGM with clinical benefit associated with Hybrid closed loop systems but with the costs of intermittently scanned (isCGM). *The RCTs quoted do not use isCGM*. There are errors in the document throughout about nomenclature of TIR, TAR and TBR. Both TBR and TAR has been labelled as TIR. The terminology "CGM" is used interchangeably (throughout document) between rTCGM and iCGM. *The cost between the 2 are different.* The studies use rtCGM -yet the economic valuation or difference of £1500 quoted (between CSII/CGM and HCL) is based on iCGM prices- which isn't what the RCTs were done on. In short? Economic analysis takes HbA1c difference from studies with CSII+rtCGM as comparator but use a cost from CSII + IsCGM. That makes the analysis flawed.	The EAG agrees that the main cost difference for CSII+CGM arises from most NHS patients using CSII+rtCGM.

	Comment no.	Page no.	Section no.	Comment	EAG response
NHSE	2			To track journey of a Type 1 Diabetes patient- as per present NICE guidance- NG 17/ NG18 (published 2022) and TA 151 (Published 2008): **a)** A person can get Flash or CGM at diagnosis- **deemed to be cost effective (NG17 & NG18)** **b)** They can have a Pump at A1c>8.5% (and disabling hypo)- **deemed to be cost effective (TA151)** c) As per this data analysis- however, **its not cost effective** when the 2 above are connected via an algorithm (which has no extra cost) That -from a clinical perspective- does not make sense.	No response required
NHSE	3			The studies looked at (RCTs) have an average HbA1c- at baseline around 7.5%. Improvements on that will be low- but importantly- ***about 65% of population in the UK Type 1 Diabetes population have A1c >7.5%*** thus making these studies of lesser real-world value- compared to the Real-world data which shows significant drop & thus cost effectiveness. This is a big issue from a policy perspective as we look at use of technology to target those with higher A1c- which skews with **deprivation and ethnicity.** Looking at studies which don't take deprivation & (thus higher A1c) into account (which the NHSE real world study does) would be inappropriate	Point of view, no response required.
NHSE	4			The evaluation states that they have NOT considered hypos or -more importantly- quality of life metrics. In today's era of diabetes care- and in line with NICE use of quality of life in assessing diabetes technology to update NG17 and NG18- not doing so is ignoring a fundamental part of improving health in those with Type 1 Diabetes	This is incorrect. The lack of direct evidence around hypoglycaemia
NHSE	5			There is a clear discrepancy between the cost effectiveness value of the RCT (179k) and the Real-world data (12 K). RCTs are set to establish safety and show benefit (as it has in HbA1c) while real world data is about its application beyond issues of deprivation, in settings of workforce pressures etc.	Point of view, no response required.

	Comment no.	Page no.	Section no.	Comment	EAG response
				This needs to form a fundamental plank of the final assessment (similar to the case in Flash Glucose Monitoring as used by NICE for NG17 & NG18)-on grounds of consistency- to help in judgment of use of this technology with undoubted potential to improve lives- but across all deprivation quartiles	
NHSE	6			**In summary?** a) The data analysis appears to be flawed b) It ignores the Real-World Data- which is a fundamental plank of work done by NICE jointly with NHS England c) It ignores the fact that RCTs are not representative of vast majority of those living with Type 1 Diabetes- and more importantly the issues of representation from those of more deprived quartiles d) Non consideration of hypos and quality of life is ignoring fundamentals of Type 1 Diabetes care- and thus health economics ***NHS England would appreciate all these significant factors being taken into consideration by the committee – and not simply take a flawed analysis as the only guide to the overall decision process.***	The RCT data forms the economic base case. The NHS pilot data and NHSE/SHE event rates inferred from TBR are considered in scenario analyses of the economics.
Expert (Sufyan Hussain)	1	3	Result	In technology the drop in HbA1c and improvement of TIR is always proportional to the starting HbA1c or TiR – ie higher the starting HbA1c, bigger the drop and vice versa for TIR. In such estimations the absolute change therefore does not convey the power to improve glycaemia. The drop in HbA1c or improvement in TIR should be divided into groups/ ranges to demonstrate the potential. This would also impact on cost effectiveness. i.e the cost effectiveness improves the higher the HbA1c or lower TIR allowing the economic evaluation to determine the optimal threshold for starting hba1c/TIRfor considering HCL This is also in keeping with NHSE pilot data in adults and explains the larger drop given the baseline population with high hbA1c and low TIR	This subgroup analysis was not considered in the protocol. Point for the committee.
Expert (Sufyan Hussain)	2	4		It is unclear how the current pricing of “an annual average £1500 more expensive” has been calculated. Given that majority of the people with T1D on CSII will be considered for rt-CGM if on a HCL enabled pump, the cost will be negligible (ranging from £0 – £800 over 4 years, for systems requiring a one off payment, the cost of the overall system is offset by a lower pump cost).	The costs are provided by NHS Supply Chain at current list prices and assume that CSII+CGM is 10% CSII+rtCGM and 90% CSII+isCGM. The cost difference mainly arises due to the current prevalence of CSII+isCGM in the NHS.
Expert	3	4		Cost effectiveness could therefore be incorrect due to above	Please see point above

	Comment no.	Page no.	Section no.	Comment	EAG response
(Sufyan Hussain)					
Expert (Sufyan Hussain)	4	7		The comparator needs to include is-CGM or rt-CGM on Multiple daily injections (still using one of the technology) This is critical for NHS population cohorts especially after the updates in NICE clinical guidance for type 1 diabetes where all people with T1D will be offered an is or rt CGM. Given comment 2, all on pumps will eventually have a system that is capable of an HCL at a negligible cost. Hence, the comparator of isCGM/rtCGM + MDI is critical in reviewing the cost-effectiveness of CSII/HCL and enabling a meaningful clinical impact .	NHSE did not include MDI. The NICE scope did not list MDI as an eligible prior intervention.
Expert (Sufyan Hussain)	5	10	Systematic review	In the summary of RCT, the average baseline HbA1c (starting) is critical in interpreting the findings – see comment 1. This needs to be highlighted here please.	No response required
Expert (Sufyan Hussain)	6	10		Real-world data from NHSE pilot is included. However real-world data from other peer-reviewed publications has not been fully included at this point. (I note page 90) Whilst the assessment focuses on RCT data which is understandable, the use of technology and associated outcomes from real-world evidence provides demonstrable benefits in clinical environments and allows larger data sets to be used for the purposes of evidence. They also do not have the bias of having people with t1d with high self-management skills and engaged/ motivated behaviours in industry supported trials. In keeping with this Klonoff et al provide a similar rationale in their article: https://pubmed.ncbi.nlm.nih.gov/30943790/ Similarly, pivotal studies may also need to be considered, which are important for safety and efficacy assessment in diabetes technologies	The EAG did assess a number of observational studies along with the NHSE study.
Expert (Sufyan Hussain)	7	12	Camdiab submission	The cost of this system is now reduced using a different pump system (Ypsomed ypsopump) that has a reduced cost as a pump and reduced cost for the cam aps fx app. This will alter the cost effectiveness calculations.	The costs are provided by NHS Supply Chain at current list prices.
Expert (Sufyan Hussain)	8	13	Current prices	See point 2	Please see response for point 2
Expert (Sufyan Hussain)	9	13	EAG base case applies	EAG RCT NMA estimate of -0.29% HbA1c for HCL relative to CSII+CGM - see comment1, this grossly underestimates the utility of HCL and further reinforced by adult NHSE data which demonstrates the point made in comment 2. If data is reviewed as per comment 1, it can be analysed against NDA data to provide a more effective model for potential benefits. Eg segregating in to baseline HbA1c (<6.5%, <7.5%, <8.5%) /baseline TIR (>30% , >40%, >50% etc)	Please see response above
Expert (Sufyan Hussain)	10	15		The paediatric NHSE pilot data again reinforces comment 1 as they had a lower starting HbA1c and therefore smaller improvements	Point of view, no response required.
Expert (Sufyan	11	37	*Conclusions on hypoglycaemia*	Use of rt-CGM is not mentioned as a way to reduce severity of hypos.	Point of view, no response required.

	Comment no.	Page no.	Section no.	Comment	EAG response
Hussain)				Associations with symptoms of anxiety and depression may also need to be highlighted *Diabetes Care* 2022;45(10):2456–2460 https://doi.org/10.2337/dc21-2482	
Expert (Sufyan Hussain)	12	44	**Advanced HCL**	I strongly discourage the use of the term and explanation of it. I would advise removing this as it is incorrect. Classifying the HCL as "advanced" on the basis of ability to deliver correction bolus has no clinical basis. I note this is a term imposed by industry. (The citation is from an industry funded study). If classification is desired it needs to be on the basis of the algorithm and how it operates. These details have largely been kept proprietary by industry hence it is very difficult to classify algorithms other than potentially designate them as MPC, fuzzy logic, PID or mixed etc. Hence it is not possible to claim "advanced" or superior designation based on the rationale detailed.	This term was used in the published evidence.
Expert (Sufyan Hussain)	14	45	***CamAPS FX***	This system can be used with ypsopump by ypsomed as well.	No response required.
Expert (Sufyan Hussain)	15	46	**Identification of important sub-groups**	Vulnerable subgroups missed: elderly, low socio-economic status, ethnic minority, individuals with severe mental health illnesses. To ensure political correctness, this could be mentioned as out of scope due to paucity in the literature at this stage.	No response required.
Expert (Sufyan Hussain)	16	50	***rtCGM***	This section needs to be updated in view of recent NICE CG update	Please see earlier response on figure 1
Expert (Sufyan Hussain)	17	53	***3.1.1***	"There are several hybrid closed loop systems available in the UK such as MiniMed 670G and MiniMed 780G" – why are only Medtronic systems mentioned as examples? 670G is no longer available for new patients.	Additional systems were provided in the NICE scope
Expert (Sufyan Hussain)	18	80	***4.2.2***	See comment 1 which needs to be detailed if evaluating evidence of this nature	
Expert (Sufyan Hussain)	19	69		ADAPT study missing . This is a key study given the need for comparator detailed in comment 4. I would suggest inclusion of this as offers: MDI vs HCL comparison People with type 1 with higher HbA1c than most RCTs This additional data along with NHSE data may allow further analysis with baseline hbA1c/TIR as per comment 1 and 9. https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00212-1/fulltext	The comparators as per NICE scope were: Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated).

	Comment no.	Page no.	Section no.	Comment	EAG response
					Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.
Expert (Sufyan Hussain)	20	90	***4.2.1***	Have some studies been omitted from observational data? Below is from 2021 https://onlinelibrary.wiley.com/doi/epdf/10.1111/dme.14741	Thank you for sharing the systematic review.
Expert (Sufyan Hussain)	21	General		Suggest removal of data related to 670G as this is a first generation HCL system no longer used. The efficacy of this is much lower compared to second generation HCL systems currently available.	Point of view, no response required.
Expert (Sufyan Hussain)	22	General		This is a very comprehensive evaluation on a complex topic where evidence is still emerging, and technology is constantly improving. The issues highlighted hopefully will enable it to offer meaningful benefit to the whole system and patients, as well as future proof aspects whilst recognising the limitations in current evidence base. I am happy to discuss any points if needed.	Thank you

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Assessment

Hybrid Closed Loop Systems for Managing Blood Glucose Levels in Type 1 Diabetes [ID3957 (DAP55)]

Document A

CamDiab evidence submission summary for committee

CamDiab confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

November 2022

File name	Version	Contains confidential information	Date
Appendix A - Company evidence submission summary CamDiab 2022-11-19	**1.0**	**No**	**19 Nov 2022**

Contents

Tables and figures

Submission summary

A.1 Health condition

Type 1 diabetes including very young children and pregnant women.

A.2 Clinical pathway of care

Figure 1 Overview of treatment pathway (Figure 1, Main Submission, page 13)

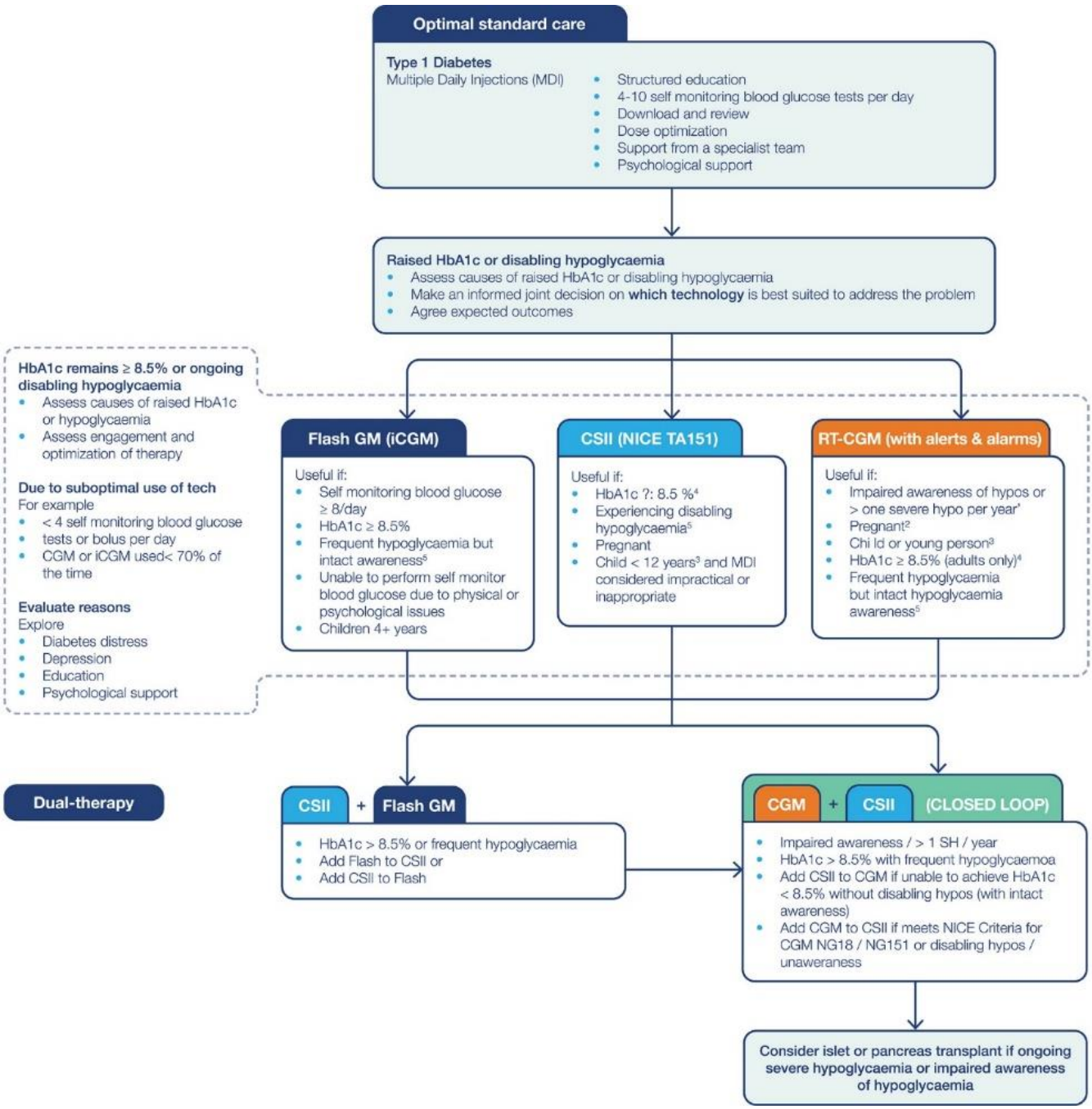
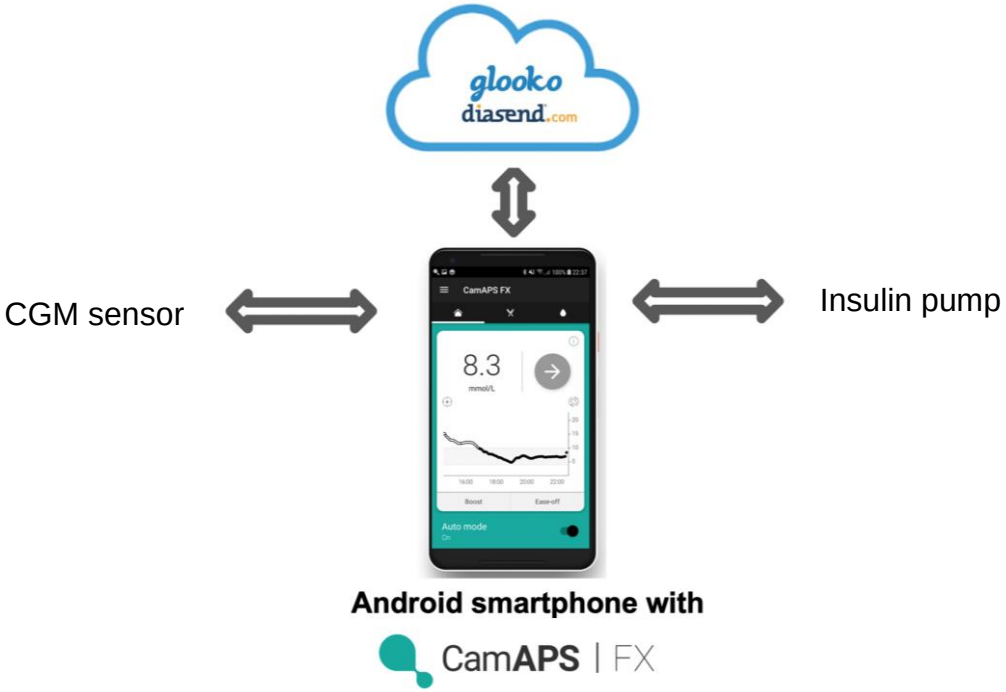


Figure 2 The CamAPS FX hybrid closed loop app (Figure 2, Main Submission, page 14)



A.3 The technology

Table 1 Technology being appraised – B.1.2 (page 12)

UK approved name and brand name	UK approved name: FlorenceX, variant FX Brand name: CamAPS FX
Mechanism of action	Hybrid closed loop app directing insulin delivery based on glucose sensor values
Marketing authorisation/CE mark status	The CamAPS FX app received its CE mark as a class IIb active medical device (MDD) in March 2020
Indications and any restriction(s) as described in the summary of product characteristics	The CamAPS FX app is intended to manage glucose levels in people with type 1 diabetes, aged 1 year and older including pregnancy, using a hybrid closed-loop approach.
Method of administration and dosage	CamAPS is an **interoperable** app, running on a smartphone, receiving data from a compatible continuous glucose monitoring device (currently Dexcom G6, Dexcom, USA, but connectivity to other CGM systems such as Libre 3 [Abbott Diabetes Care, Alameda, CA, USA] is underway or is being explored), directing insulin delivery by a compatible insulin pump (currently mylife YpsoPump, Dana RS and Dana-i, Sooil, South Korea but connectivity to other insulin pump is being explored), and streaming data to a compatible diabetes data portal/ecosystem (currently Diasend/Glooko, Sweden, but connectivity to other data ecosystem is being explored).
Additional tests or investigations	NA
List price and average cost of a course of treatment	Individual license £840 per annum with Dana pumps (Sooil, South Korea), £800 per four year use with YpsoPump (Ypsomed, Switzerland),
Patient access scheme (if applicable)	NA

A.4 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication.

Table 2 The decision problem – B.1.1 (page 8)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with type 1 diabetes who are having difficulty managing their condition. These difficulties may include: - not maintaining HbA1c levels of 6.5% or below or - not maintaining at least 70% time in range of 3.9 -10 mmol/l or - ongoing disabling hypoglycaemia	As per scope	NA
Intervention	Hybrid closed loop systems	As per scope	NA
Comparator(s)	• Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated) Intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion	As per scope	NA
Outcomes	Intermediate measures for consideration may include: • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below target range • Time above target range • Change in HbA1c • Rate of glycaemic variability • Fear of hypoglycaemia • Rate of severe hypoglycaemic events • Rate of severe hyperglycaemic events • Episodes of diabetic ketoacidosis	As per scope	NA

	• Rate of ambulance call outs • Rate of hospital out-patient visits • Rate of weight gain		
Subgroups to be considered	If evidence permits the following subpopulations should be included: • Women with type 1 diabetes who are pregnant and those planning pregnancy (not including gestational diabetes) • Children with type 1 diabetes. If possible, evidence should be analysed based on the following age groups: - 5 years and under - 6 - 11 years - 12 -19 years • People with extreme fear of hypoglycaemia People with diabetes related complications that are at risk of deterioration	As per scope	NA

A.5 Clinical effectiveness evidence

Study	APCam11 [1]				
Study design	Randomised, parallel, multicentre				
Population	Age **6 years and older (n=86**); CSII ≥3M; HbA1c 58 to 86 mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 12 weeks				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				
Reported outcomes specified in the decision problem	The proportion of time that glucose concentration was within the target range was significantly higher in the closed-loop group (65%, SD 8) compared with the control group (54%, SD 9; mean difference in change 10·8 percentage points, 95% CI 8·2 to 13·5; p<0·0001). Reductions in HbA1c percentages were significantly greater in the closed-loop group compared with the control group (mean difference in change 0·36%, 95% CI 0·19 to 0·53; p<0·0001) [1].				
All other reported outcomes	Improved psychosocial outcomes [2]				

Study	Dan04 [3]				
Study design	Randomised, crossover				
Population	Age 10 to 18 years (n=12); HbA1c 53 to 97mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 7 days				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x

Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data
Reported outcomes specified in the decision problem	The proportion of time when the sensor glucose level was in the target range (3.9-10 mmol/L) was increased during closed-loop insulin delivery compared with sensor-augmented pump therapy (72 vs. 53%, P < 0.001; primary end point), the mean glucose concentration was lowered (8.7 vs. 10.1 mmol/L, P = 0.028), and the time spent above the target level was reduced (P = 0.005) without changing the total daily insulin amount (P = 0.55) [3]
All other reported outcomes	NA

Study	Dan04 extension [4]				
Study design	Randomised, crossover				
Population	Age 10 to 18 years (n=12); HbA1c 53 to 97mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 21 days				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				
Reported outcomes specified in the decision problem	The proportion of time that sensor glucose was in the target range (3.9-10 mmol/L; primary end point) was increased during the closed-loop intervention compared with sensor-augmented insulin pump therapy by 18.8 ± 9.8 percentage points (mean ± SD; P < 0.001), the mean sensor glucose level was reduced by 1.8 ± 1.3 mmol/L (P = 0.001), and the time spent above target was reduced by 19.3 ± 11.3 percentage points (P < 0.001). The time spent with sensor glucose levels below 3.9 mmol/L was low and comparable between interventions (median difference 0.4 [interquartile range -2.2 to 1.3] percentage points; P = 0.33) [4]				
All other reported outcomes	NA				

Study	AP@home02 [5]				
Study design	Randomised crossover, multicentre				
Population	Age 18 years and older (n=17); HbA1c < 86 mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 7 days				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				
Reported outcomes specified in the decision problem	During the home phase, the percentage of time when glucose was in target range was significantly higher during closed-loop compared with SAP (median 75% [interquartile range 61-79] vs. 62% [53-70], P = 0.005). Mean glucose (8.1 vs. 8.8 mmol/L, P = 0.027) and time spent above target (P = 0.013) were lower during closed loop, while time spent below target was comparable (P = 0.339). Increased time in target was observed during both daytime (P = 0.017) and nighttime (P = 0.013) [5]				
All other reported outcomes	NA				

Study	AP@home04 [6]				
Study design	Randomised crossover, multicentre				
Population	Age 18 years and older (n=33); CSII ≥6M; HbA1c 58 to 86 mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 12 weeks				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				

Reported outcomes specified in the decision problem	The proportion of time that the glucose level was in the target range was 11.0 percentage points (95% confidence interval [CI], 8.1 to 13.8) greater with the use of the closed-loop system day and night than with control therapy (P<0.001). The mean glucose level was lower during the closed-loop phase than during the control phase (difference, -11 mg per deciliter; 95% CI, -17 to -6; P<0.001), as were the area under the curve for the period when the glucose level was less than 63 mg per deciliter (39% lower; 95% CI, 24 to 51; P<0.001) and the mean glycated haemoglobin level (difference, -0.3%; 95% CI, -0.5 to -0.1; P=0.002) [6]
All other reported outcomes	Improved psychosocial outcomes [7]

Study	AP@home04 phase 2 [8]				
Study design	Randomised crossover, multicentre				
Population	Age 18 years and older (n=29); HbA1c < 58 mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 28 days				
Comparator(s)	Usual pump therapy				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				
Reported outcomes specified in the decision problem	The proportion of time when sensor glucose concentration was in target range was 10·5 percentage points higher (95% CI 7·6-13·4; p<0·0001) during closed-loop delivery compared with usual pump therapy (65·6% [SD 8·1] when participants used usual pump therapy vs 76·2% [6·4] when they used closed-loop). Compared with usual pump therapy, closed-loop delivery also reduced the proportion of time spent in hypoglycaemia: the proportion of time with glucose concentration below 3·5 mmol/L was reduced by 65% (53-74, p<0·0001) and below 2·8 mmol/L by 76% (59-86, p<0·0001) [8].				
All other reported outcomes	NA				

Study	Clip24/7 [9]				
Study design	Randomised crossover, multicentre				
Population	Pregnancy complicated by T1D (n=16); Pregnant 8-24 weeks gest; HbA1c 48 to 86mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 28 days				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No			No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				
Reported outcomes specified in the decision problem	The proportion of time with glucose levels within target was comparable during closed-loop and SAP insulin delivery (62.3 vs. 60.1% [95% CI -4.1 to 8.3]; P = 0.47). Mean glucose and time spent hyperglycaemic >140 mg/dL also did not differ (131.4 vs. 131.4 mg/dL [P = 0.85] and 36.6 vs. 36.1% [P = 0.86], respectively). During closed-loop, fewer hypoglycaemic episodes occurred (median 8 [range 1-17] vs. 12.5 [1-53] over 28 days; P = 0.04) and less time at <63 mg/dL (1.6 vs. 2.7%; P = 0.02). Hypoglycaemia <50 mg/dL (0.24 vs. 0.47%; P = 0.03) and low blood glucose index (1.0 vs. 1.4; P = 0.01) were lower. Less nocturnal hypoglycaemia (2300-0700 h) during closed-loop therapy (1.1 vs. 2.7%; P = 0.008) and a trend toward higher overnight time in target (67.7 vs. 60.6%; P = 0.06) were found [9].				
All other reported outcomes	Improved psychosocial outcomes [10]				

Study	Dan05 [11]				
Study design	Randomised, parallel, multicentre				
Population	Age 6 to 18 years (n=133); CSII ≥3M; HbA1c 58 to 86 mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 6 months				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application	Yes		**Indicate if trial used in the economic model**	Yes	*x*
	No	*X*		No	

for marketing authorisation					
Rationale for use/non-use in the model	Economic analysis funded as part of grant by NIDDK				
Reported outcomes specified in the decision problem	We randomised 133 participants, 65 to closed-loop and 68 to control (mean±SD baseline HbA1c 8.2±0.7% vs 8.3±0.7%). At 6 months mean HbA1c was 0.32% lower with closed-loop compared to control (95%CI 0.04 to 0.59; p=0.02). Closed-loop usage was low with FlorenceM (40% [26, 53]; median [IQR]), and consistently high with CamAPS FX (93% [88, 96]). In post-hoc analysis, **HbA1c in the CamAPS FX cohort (n=21) was 1.05% lower (95%CI 0.67 to 1.43; p<0.0001)** and time in target range 3.9 10.0mmol/L 15.0 percentage points higher (95%CI 8.0 to 22.1; p=0.0001) compared to control (n=25), without increasing hypoglycaemia (p=0.15) [11]				
All other reported outcomes	NA				

Study	Dan06 [12]				
Study design	Randomised crossover, multicentre				
Population	Age 60 years and above (n=37); CSII ≥12M; HbA1c <86mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 16 weeks				
Comparator(s)	Sensor augmented therapy over 16 weeks				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	
	No	***x***		No	x
Rationale for use/non-use in the model	Economic analysis not carried at the time of publication of the data				
Reported outcomes specified in the decision problem	The proportion of time with glucose in target range was 8.6 percentage points (95% CI 6.3 to 11.0) higher during closed-loop compared to control period (p<0.001). Time with glucose >10.0mmol/L was 8.5 percentage points lower (95% CI 6.1 to 10.9; p<0.001), mean glucose was 0.7mmol/L lower (95% CI 0.5 to 0.9; p<0.001), **and glycated haemoglobin 2.7mmol/L ([0.2%], 95% CI 1.2 to 4.2 [0.1 to 0.4]; p<0.001) lower with closed-loop than with control therapy**. Time in hypoglycaemia (<3.9mmol/L) was similar between periods (p=0.74). Mean closed-loop usage was 97% over 16-weeks. [11]				
All other reported outcomes	Improved psychosocial outcomes [not included in the present submission]				

Study	KidsAP02 [11]				
Study design	Randomised crossover, multicentre				
Population	Age 1 to 7 years (n=74); CSII ≥3M; HbA1c < 97 mmol/mol				
Intervention(s)	CamAPS FX hybrid closed loop algorithm over 16 weeks				
Comparator(s)	Sensor augmented pump therapy (SAP)				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	*x*
	No	*x*		No	
Rationale for use/non-use in the model	Economic analysis carried out as part of the project funded by H2020 grant				
Reported outcomes specified in the decision problem	The proportion of time with glucose in target range was 8.7 percentage points (95% CI 7.4 to 9.9) higher during closed-loop compared to control period (p<0.001). Time with glucose >10.0mmol/L was 8.5 percentage points lower (95% CI 7.1 to 9.9; p<0.001), mean glucose was 0.7mmol/L lower (95% CI 0.5 to 0.8; p<0.001), **and glycated haemoglobin 3.9mmol/L ([0.4%], 95% CI 2.9 to 4.9 [0.3 to 0.5]; p<0.001) lower with closed-loop than with control therapy**. Time in hypoglycaemia (<3.9mmol/L) was similar between periods (p=0.74). Mean closed-loop usage was 93±8% over 16-weeks. [11]				
All other reported outcomes	Improved psychosocial outcomes [13, 14]				

Studies APCam11, Dan04, Dan04 extension, AP@home02, AP@home04, AP@home04 phase 2, Clip24/7, and Dan06 were not used to populate the economic model but are included in sections 2.2 to 2.6. The results of these studies support the benefits of closed-loop vs comparator, and/or improved psychosocial outcomes. These studies were not included in the economic model because the grant funding bodies did not fund the economic model.

A.6 Key results of the clinical effectiveness evidence

A.6.1 *Improved glucose control and reduced risk of hypoglycaemia*

The proportion of time when the sensor glucose level was in the target range was increased during closed-loop insulin delivery compared with sensor-augmented pump therapy, the mean glucose concentration was lowered, and the time spent above the target level was reduced without changing the total daily insulin amount. In studies lasting 3 month and longer, glycated haemoglobin was reduced. In some studies, time spent hypoglycaemia was reduced.

A.6.2 *Improved psychosocial outcomes*

Using a hybrid closed-loop system with the CamAPS FX app can have potentially life-changing consequences and may result in a lessened demand for health professionals' input.

A.7 Evidence synthesis

No meta-analysis or indirect and mixed treatment comparisons were carried out.

A.8 Key clinical issues

- Clinical trials are limited in duration to 3 months (crossover study design) or 6 months (parallel study design)
- Ethnic minorities may be underrepresented (this is a common issue in clinical trials of diabetes technology) potentially limiting generalizability
- We recruited research participants already using insulin pump potentially limiting generalizability
- Some studies recruited people with suboptimally controlled type 1 diabetes
- Research participants in closed-loop studies tend to be highly motivated potentially limiting generalizability

A.9 Overview of the economic analysis

Cost-effectiveness analyses of two completed studies Dan05 and KidsAP02 are included in the present submission. These analyses have been completed prior to the deadline of the present MTA submission.

Patient population

- Dan05: children and adolescents aged 6 to 18 years with suboptimally controlled type 1 diabetes. Further details are included in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: young children aged 1 to 7 years. Further details are included in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

Model structure

- Dan05: the Sheffield type 1 diabetes policy model. Further details are included in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: IQVIA CORE Diabetes Model (CDM, v9.5 E360). Further details are included in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

Intervention technology and comparators

- Dan05:
    - Intervention technology: hybrid closed loop using the CamAPS FX app. Please note that data collected using the FlorenceM system alongside the CamAPS FX app in the Dan05 study were not used as the FlorenceM prototype used unreliable hardware causing low usage of auto-mode. These FlorenceM-related hardware issues are not relevant to the commercially available CamAPS FX app, connected pumps, and connected continuous glucose monitoring systems.
    - Comparator: usual pump therapy with/without flash glucose monitoring or continuous glucose monitoring

- KidsAP02
    - Intervention technology: hybrid closed loop using the CamAPS FX app.
    - Comparator: sensor augmented pump therapy

A.10 Incorporating clinical evidence into the model

- Dan05: The key clinical variable was the change of HbA1c from baseline. Further details are included in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: The key clinical variable was the change of HbA1c from baseline. Further details are included in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

A.11 Key model assumptions and inputs

Summary of base-case analysis inputs

- Dan05: Summary of base-case analysis inputs is described in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: Summary of base-case analysis inputs is described in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

Assumptions

- Dan05: Assumptions are described in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: Assumptions are described in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

A.12 Base-case ICER (deterministic)

Table 3 Base-case results (deterministic) – B.3.7 (page 123)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
CamAPS FX (Dan05 study)				22,182	5.36	1.148		19,342
CamAPS FX (KidsAP02 study)				10,303		0.482		21,384
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

A.13 Probabilistic sensitivity analysis

- Dan05: Details are provided in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: Details are provided in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

A.14 Key sensitivity and scenario analyses

Deterministic sensitivity analysis

- Dan05: Details are provided in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"
- KidsAP02: Details are provided in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

Scenario analysis

Scenario analyses were not run.

Summary of sensitivity analyses results

- Dan05: The probabilistic sensitivity analysis showed a tight cost-effectiveness acceptability curve, even assuming substantial parameter uncertainties. One-way sensitivity analysis suggested robust results; even if the sustained HbA1c treatment effect were 60% of the observed value, the algorithm remains cost-effective for patients already using a CGM, see details in the accompanying document "*UK CEA DAN05 CEA Manuscript 2022-05-27*"

- KidsAP02: Results are robust under a range of sensitivity analysis, see details in the accompanying document "*UK CEA KidsAP02 CEA final report 06-13-2022*"

A.15 Innovation

The CamAPS FX is first interoperable app to support the management of type 1 diabetes using the hybrid closed loop approach. The following innovative features apply:

- Extensive clinical data to demonstrate safety and efficacy across all age groups, population groups, and levels of glucose control
- Interoperable design to support user's choice; connectivity to other pumps and continuous glucose monitoring devices is being explored
- "Ease-off", "Boost", personal glucose target support personalisation, and reduce the risk of hypo- and hyperglycaemia (see user manual for details of these features)
- Data streaming to diabetes data ecosystems (Diasend/Glooko; Dexcom Clarity/Follow planned in 2022) to ease data management burden and support monitoring by parents/guardians and data review by health care professionals
- SMS alerting for added peace of mind for parents/guardians
- Bolusing from phone for added privacy and convenience
- "Slowly absorbed meals" feature allowing to manage more effectively slowly absorbed high-fat/high-protein meals such as pizza
- Approved for use with rapid and ultra-rapid insulin analogues
- Wide total daily dose between 5 and 350U/day.

A.16 Budget impact

Budget impact analysis was not done as part of the submission.

A.17 Interpretation and conclusions of the evidence

Dan05 study

The key study conclusion is that the Cambridge hybrid closed-loop algorithm, which safely generated significant sustained improvements in glycaemic control, is cost effective below a £20,000/QALY threshold (this is based on CamAPS FX cost of £840 pa; note that when used with YpsoPump, the CamAPS FX cost **is £200 pa** and thus **much more cost effective**), when compared to usual care for children and adolescents with type 1 diabetes on metered dose insulin. For those already using continuous glucose monitoring, the algorithm appears cost-effect near a £10,000/QALY threshold (**again these cost will be substantially lower when used with YpsoPump**).

KidsAP02 study

In the KidsAP02 population included in the analysis, the interventions utilizing closed loop are cost-effective in the UK compared to sensor augmented pump therapy. Results are robust under a range of sensitivity analysis too. Reduction in HbA1c was the main driver. Varying estimates of treatment effect in reduction of HbA1c, time horizon, and complication costs were not excessively sensitive to the analysis. The IQVIA Core Diabetes Model has not been validated in paediatric populations as such. This is due to the nature of available diabetes long-term studies providing risk equations to predict diabetes related complications not including very young patients.

The current cost-effectiveness analysis is likely conservative as there are uncaptured quality of life (QoL) benefits associated with patients, parents, and caregivers.

Overall conclusions

Clinical data collected using CamAPS FX Cambridge control algorithm are the most comprehensive and serve as a reference for other researchers and manufacturers in the field of closed-loop insulin delivery. The control algorithm have been assessed systematically initially in clinical research centre studies (data on file) and then during free-living studies. The clinical evaluations consistently applied the randomised controlled study design that allowed making justifiable assessments about safety as well as efficacy.

The clinic research studies documented safety during short terms evaluations and included stress tests such as exercise of various intensity, mismatched or missed meal boluses, and alcohol intake (adults only, data on file). The free-living studies expanded on these evaluation and documented safety of the CamAPS FX closed-loop algorithm from the age of 1 years to adulthood including pregnancy. No safety issues have been raised in any of our studies. We have documented efficacy in terms of improved glucose control and reduced burden of hypoglycaemia.

It should be acknowledged that even with our closed-loop system people with type 1 diabetes are at risk of severe hypoglycaemia and diabetic ketoacidosis.

In conclusion, the clinical evaluations demonstrated safety and clinical efficacy of the CamAPS FX closed loop algorithm in people with type 1 diabetes as young as 1-year-old including pregnant women. The studies documented improved glucose control and reduced hypoglycaemia burden, the latter in those aged 6 years and older.

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Executive Summary

Introduction

Dexcom thanks the National Institute for Health and Care Excellence (NICE) for its decision to update its published guidance (DG21) on the use of integrated sensor-augmented pump therapy (SAP) systems for managing blood glucose levels in type 1 diabetes mellitus (T1D).

Dexcom recognises the relevance for the therapy pathway of the final scope set out for this guidance. As with the recommendations in the new NICE Guidelines for T1D (NG17), the final scope of this assessment establishes continuous glucose monitoring (CGM) as the standard of care for people with T1D, and hybrid closed loop (HCL) systems as second line intervention for patients who do not reach treatment targets with CGM (or insulin pumps) alone. This is an important recognition of the extensive clinical- and health economic evidence base for CGM, as shown in appendix C.

Health condition, access and equality aspects

Diabetes is a highly prevalent chronic disease that effects more than 3.9 million people across the United Kingdom (UK) (Diabetes UK). There is a high need to provide evidence-based therapy to people with T1D, since poor glycaemic control is associated with an increased risk of debilitating long-term complications such as blindness, kidney failure, premature heart disease, stroke, and death.

However, access to technologies such as CGM which have been shown to improve haemoglobin A1c (HbA1c), reduce hypoglycaemia and improve quality of life (QoL) is very limited in England (Choudary 2022). Recent data show that only half of Clinical Commissioning Groups (CCGs) have a funding policy for CGM, and among those, only one funded more than 20% of patients and the majority funded CGM for only 5% of their T1D population. A large proportion of patients are still unable to achieve glycaemic control. Data from England and Wales show that only a third of patients achieved a HbA1C target of <7.5% in 2016–2017 (Mair, 2019).

Furthermore, equality in access to diabetes technology is poor. Underserved communities have been shown to have lower access to both CGM and insulin pump,

with access to CGM nearly twice as high for white children and young people compared to black children. Similarly, access to insulin pumps has been shown to be nearly 10% higher in the least deprived areas as compared to the most deprived areas.

Clinical care pathway

With the newly published NICE guidelines for T1D, NICE established CGM as standard of care for adults with T1D, by recommending CGM (either real-time or intermittent) for all adults with T1D. For children and adolescents, NICE has recognised the evidence base for real-time (rt)-CGM, in recommending specifically rt-CGM (and not intermittent CGM) to all children with T1D.

Insulin pumps (e.g., Continuous Subcutaneous Insulin Infusion [CSII]) are recommended for adults and children over 12 years with T1D if attempts to achieve target HbA1c levels with multiple daily injections (MDIs) result in disabling hypoglycaemia or HbA1c levels have remained high despite a high level of care. The guidelines currently under review in this present NG21 recommended SAP for people with T1D only if they have episodes of disabling hypoglycemia despite optimal management with CSII.

It should be noted that the scope of this assessment for HCL highlights a gap in funding of the treatment pathway in the NHS. The newly published NICE guidelines for T1D (NG17) establish CGM as the standard of care for all adults with T1D, and specifically rt-CGM to children and adolescents with T1D, and the scope of the present HCL TA is in line with that, in positioning HCL for patients who cannot reach treatment targets based on CGM (or insulin pump) alone. Should this TA recommend in favor of HCL, there would be mandated funding provided for a second line therapy but not for the intervention recognised as standard of care, since there is as yet no mandated funding for CGM, despite the overwhelming clinical and health economic evidence which led NICE to the new recommendations.

Hybrid closed loop systems

The technology of focus for DG21, HCL systems, are systems able to automatically adjust insulin delivery and address hyperglycaemia while minimising the risk of hypoglycaemia. HCL systems consist of an insulin pump, a glucose sensor, and an algorithm that continuously modifies the rate of insulin infusion on the basis of input

from the sensor. Sensors may need fingerstick calibration or may be factory-calibrated (Dexcom sensors only).

Clinical evidence

Several high quality randomised clinical trials (RCTs) on HCL systems including Dexcom G5 or G6 have assessed the benefit of closed loop systems vs. SAP therapy in children, adolescents and adults with T1D (Brown, 2019; Breton, 2020; Ware, 2022a; Brenton, 2017; Ekhlaspour, 2019; Forlenza, 2019; Ware, 2022b; Boughton, 2022).

Overall, the high-quality evidence from these RCTs demonstrate improved outcomes with respect to change in HbA1c (%), time in range (TIR) (70−180 mg/dL) and QoL for patients with T1D using HCL systems compared to SAP. In particular, studies of Dexcom-based HCL systems have demonstrated a significant benefit over SAP for HbA1c and TIR, with a treatment benefit that exceeds the 0.3% which is considered to be clinically meaningful (Lind, 2008; Lind, 2010).

Health economic evidence

As for the health economic impact of HCL compared to SAP systems, a new analysis was performed by Dexcom for the purposes of the NG 21 update. The analysis used the CORE Diabetes model, which was equally used by NICE for the economic assessments in the Guidelines NG 17 and NG 21.

This analysis demonstrates that, assuming that the algorithm has no incremental cost, HCL is dominant compared to SAP, that is, it provides better clinical results at no extra cost.

The analysis also shows that at a price at or below £1,171 for the algorithm, the incremental cost-effectiveness ratio of HCL remains below the NICE willingness to pay (WTP) threshold of £20,000 (NICE, 2013).

Conclusions

This report lays out that there is still a significant unmet need for people with T1D, with many people not able to reach treatment targets. Overall access to technology has been shown to be limited, and equality of access failing. The report has pointed to the

incongruence of the lack of funding for continuous glucose monitoring, which NICE has established as standard of care for adults with T1D, and specifically rt-CGM for children and adolescents with T1D, whilst a funding mandate following this present assessment would provide funding for hybrid closed loop system as second line intervention.

Dexcom based HCL systems have been found to be supported by several randomised clinical trials which have demonstrated better results on HbA1c, hypoglycaemia and QoL compared to SAP. A health economic analysis performed specifically for this assessment has shown HCL to be dominant compared to SAP.

Mandated funding for continuous glucose monitoring for all people with T1D as well as for HCL systems for people who do not reach treatment targets with CGM alone would help improve access to evidence based, cost-effective technology, and improve chances for people with T1D to reach treatment targets and improve health related quality of life (HRQoL).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Assessment

Hybrid Closed Loop Systems for Managing Blood Glucose Levels in Type 1 Diabetes [ID3957 (DAP55)]

Document A

Medtronic evidence submission summary for committee

MiniMed™ 670G System and MiniMed™ 780G Systems

Medtronic confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

June 2022

File name	Version	Contains confidential information	Date
NICE_MTA_ID3957 (DAP55)_ Document_A_Hybrid_Closed_Loop_ Systems_Medtronic Submission_MiniMed™ 670G	**1.0**	**Yes**	**20/6/22**

Contents

Tables and figures

Table 1: ICER results for the whole analysis (base case + sensitivity analysis)

Submission summary

A.1 Health condition

Type 1 diabetes is characterised by the chronic immune-mediated destruction of the pancreatic insulin-producing beta-cells. The aetiology of type 1 diabetes is multifactorial, with environmental factors, genetic factors, and immune alterations leading to beta-cell destruction and chronic insulin deficiency.

A.2 Clinical pathway of care

In 2016, ***NICE Diagnostic Guidance DG21**: **Integrated sensor augmented pump (SAP) therapy systems for managing blood glucose levels in people with type 1 diabetes***, recommended the MiniMed™ Paradigm Veo system as an option for managing blood glucose levels in people with type 1 diabetes if they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion pump.

There have been significant developments in hybrid closed loop technology since this guidance was published in 2016 and the MiniMed™ Paradigm Veo system has been superseded by MiniMed™ 670G hybrid closed loop system and MiniMed™ 780G advanced hybrid closed loop system and other hybrid closed loop technologies therefore the pathway is likely to change as an outcome of the recommendations from this DAP 55 MTA.

A.3 The technologies

MiniMed™ 780G advanced hybrid closed loop system (AHCL) and MiniMed™ 670G Hybrid closed loop system (HCL) are both interventions in the scope of this MTA [DAP55]. NB: As not all MiniMed™ 670G pump users currently have access to funded CGM, the MiniMed™ 670G hybrid closed loop system is retained in the scope of the MTA to allow “in warranty” MiniMed™ 670G patients access to closed loop therapy, using their existing 670G pump, in line with final MTA recommendations, in the “in warranty” years prior to their upgrade to the 780G system.

MiniMed™ 780G is an advanced hybrid closed loop system that automatically adjusts both basal and bolus insulin delivery to achieve TIR (Time in Range) and HbA1c targets. The MiniMed™ 780G system is the latest development in the evolution of Medtronic integrated insulin pump systems. All MiniMed™ integrated insulin pump systems incorporate CGM technology and are therefore sensor-augmented pumps (SAPs (Sensor Augmented Pump). With each advancement, MiniMed™ integrated insulin pump systems have added new features to help patients with T1D manage their condition. Additional features include:

Low glucose suspend (LGS), first introduced in MiniMed™ Paradigm™ Veo™system. LGS automatically suspends insulin delivery when sensor glucose levels reach a low glycaemic limit and resumes delivery when sensor glucose levels recover.

Predictive low glucose suspend (PLGM (Predictive Low Glucose Management)), first introduced in MiniMed™ 640G system. PLGM automatically suspends insulin delivery when sensor glucose is predicted to approach a low glycaemic limit and resumes delivery when sensor glucose levels recover.

Hybrid closed loop (HCL) with SmartGuard™ technology, first introduced in the MiniMed™ 670G system. HCL automatically adjusts basal insulin delivery.

MiniMed™ 670G was the first approved, commercially available self-adjusting insulin delivery **hybrid closed loop (HCL) system**. Introduced in 2016, it represented the next step in automation with an additional “automode” feature that **automatically adjusts basal insulin delivery.** The system will continuously and automatically adjust the amount of insulin delivered to regulate glucose levels to a target sensor glucose (SG) amount. Auto Mode uses a fixed target SG of 120 mg/dL(6.7mmol/L) and the target can be set temporarily to 150 mg/dL for exercise and other events. The automated basal insulin delivery system is based on inputs from the sensor, which measures glucose levels up to 288 times per day and responds with adjustments to the insulin administration up to every 5 minutes.

The "hybrid" label is due to the requirements of meal announcement. The user is still required to enter carbs before the meal and blood glucose (BG) readings to calibrate the sensor. (Bergenstal et al., 2016).

A.4 Clinical effectiveness evidence

A.4.1 *A.4.1 The MiniMed™ 780G HCL system*

The initial pivotal trial of the MiniMed™ 780G has demonstrated improved clinical and safety outcomes in adolescent and adult cohorts (Carlson et al., 2022) The safety and outcomes results of this on-going trial (NCT03959423, 2019) was confirmed by real world evidence: 80% of the first 4120 AHCL users have reached glycaemic targets, i.e., TIR >70% and a GMI (Glucose Management Indicator) <7.0%, representing a significant improvement over standard of care. (Da Silva et al., 2022) The consistent effectiveness results of this automated insulin delivery device in the current users (over 20’000 in June 2022) confirms its performance, safety and improved usability compared to MiniMed™ 670G reducing the burden of people living with T1D.

Additional effectiveness and usability results of the MiniMed 780G system with Guardian 4 sensor (G4S) have been published earlier this year from the extension study phase of the US pivotal trial. (Vigersky et al., 2022) Safety and effectiveness outcomes were evaluated following transition of participants to the MiniMed™ 780G system with the Guardian™ 4 sensor (NCT03959423, 2019). The results show that participants with T1D (N = 176, aged 7-75 years), regardless of age, safely achieved glycaemic targets using the MiniMed™ 780G system with the G4S, similar to that observed in the pivotal trial of the AHCL system with Guardian 3 Sensor (GS3).

(Arrieta et al., 2022) demonstrate that more than 75% of users with T1D aged 15 years or younger using the MiniMed 780G system achieved international consensus-recommended glycaemic control, mirroring the achievements of the population aged older than 15 years.

A.4.2 The MiniMed™ 670G HCL system

The primary advantage of the 670G HCL system is the automated delivery of basal insulin while the system is in auto mode. This feature may aid users in improving overall glucose control. The glucose target is set by default at 120 mg/dL. Adults and children (7 and 13 years) may benefit from the system to reduce hypoglycaemia and spend more time in the glucose target range. (Saunders et al., 2019)

The safety of the MiniMedTM 670G system was established with the following studies: phase 1 established the safety and feasibility (Steil et al., 2006), the study results found no occurrences of severe hypoglycaemia, users reaching ~75% in target range with stable overnight glucose levels, and fasting glucose levels close to the target. Overall, this study concluded that using an automated insulin delivery system to improve glycaemic control is achievable. The Phase 2 safety and efficacy study was conducted by (Ruiz et al., 2012) to assess the effect of the insulin feedback feature of 670G algorithm on the glycaemic control of closed-loop users. The overall result and benefit of incorporating insulin feedback into the algorithm for the MiniMed™ 670G system was that it enhanced the timing of insulin delivery at meals preventing postprandial hypoglycaemia which is vital to maintaining good glycaemic control. Two phase 3 large scale safety and efficacy clinical trials (Garg et al., 2017) (Forlenza et al., 2019) were conducted prior to the commercial approval and launch of the system in the US and Europe.

Phase IV real-world data on the MiniMed™ 670G system have been published since the launch of the MiniMed™ 670G device. Da Silva et al. conducted the most recent analysis in 14 899 users living in 14 different countries, who provided consent for the aggregation of their data to report on glycaemic outcomes of MiniMed™ 670G users. (Da Silva et al., 2021) Data were extracted from the CareLink™ system which is the database to which Medtronic users upload their pump and/or CGM data to view their diabetes management history over a given time period. After analysing the CareLink data, the study showed increased time in range from an average across all age groups: TIR was 72.0% ± 9.7%. Time spent at <70 mg/dL, and >180 mg/dL was 2.4%± 2.1, and 25.7% ± 10%, respectively. Prior to initiating Auto Mode, TIR was 62.1%, ranging from 57.7% to 66.6%. Users spent an average of 81.4% of the time in Auto Mode.

A.5 Safety / adverse reactions

The two prospective clinical studies confirmed device safety with no device related serious adverse events during the AHCL treatment period of the studies. (MiniMed™ 670G 4.0 insulin pump equivalent to the MiniMed™ 780G insulin pump (running in AHCL also referred to as Auto Mode).

The clinical precaution section in the Instructions for Use (IFU) identifies populations which may be more at risk for hyperglycaemia or hypoglycaemia with the use of the MiniMed™ 780G system. Additionally, the IFU discusses clinical management of these risks (e.g., such as glucose intake when glucose is low) in order to assist in prevention of these risks from occurring

The MiniMed™ 780G insulin pump includes numerous safety features that mitigate these risks and the results of a prospective clinical investigation demonstrate that these risk controls are effective in adequately mitigating the risk of over and under-delivery.

A.6 Overview of the economic analysis

Intervention technology and comparators

The intervention and comparator technologies considered in the cost-effectiveness model were aligned with the decision problem described in Table 5 (Document B).

This economic analysis will focus on the MiniMed ™ 780G Advanced Hybrid Closed Loop system, as a cost-effectiveness analysis of the MiniMed™670G in UK has been previously published. (Roze et al., 2021)

Comparators

- Real-time continuous glucose monitoring with continuous subcutaneous insulin infusion (MiniMed™ 640G system)

- Continuous Subcutaneous Insulin Infusion (CSII) + Intermittently Scanned Continuous Glucose Monitoring (isCGM).

Results

Minimed™ 780G system vs Minimed™ 640G

For the analysis of 780G vs MiniMed™ 640G (0.8% reduction in HbA1c from the baseline of 7.6%):

MiniMed™ 780G was a dominant treatment option relative to MiniMed™ 640G. The improvement in discounted QALY was 0.21 in favour of 780G compared to MiniMed™ 640G.

Additional treatment costs associated with the MiniMed™ 780G AHCL system were partially offset by the savings due to the reduction in diabetes related complications.

Cost Effectiveness Results

Table 15 represents the results for the different analyses, base case and sensitivity analysis. Both ICER and the details of each intervention appear in the table.

Table 1: ICER results for the whole analysis (base case + sensitivity analysis)

	Intervention	Comparator	Intervention		Comparator		ICER	Incremental costs	Incremental QALYs
			Total costs (£)	Total QALY	Total costs (£)	Total QALY	£/QALY		
Base Case 1: MiniMed™ 780G vs MiniMed™ 640G	**MiniMed™ 780G**	**MiniMed™ 640G**	**253,583**	**13.89**	**259,400**	**13.67**	**Dominant**	**- 5,816**	**0.21**
Base case 2: MiniMed™ 780G vs CSII +isCGM	MiniMed™ 780G	CSII + isCGM	253,583	13.89	240,526	13.19	18,672	13,057	0.69
Sensitivity Analyses									

Sensitivity Analysis - MiniMed™ 780G vs MiniMed™ 640G	**MiniMed ™ 780G**	**MiniMed ™ 640G**	**295,459**	**14.15**	**300,225**	**14.04**	**Dominant**	**- 4,765**	**0.12**
Sensitivity Analysis - MiniMed™ 780G vs CSII+ isCGM	MiniMed TM 780G	CSII + isCGM	295,459	14.15	280,701	13.54	23,873	14,758	0.61

MiniMed™ 780G system vs CSII + isCGM

For the analysis of Minimed™ 780G vs CSII + isCGM (0.8% reduction in HbA1c from the baseline of 7.6%).

The Incremental Cost Effectiveness Ratio (ICER) considering direct costs were £ 18,672 per Quality Adjusted Life Year gained (QALY). The improvement in discounted QALY was 0.69 in favour of 780G compared to CSII + isCGM.

Additional treatment costs associated with the MiniMed™ 780G AHCL System were partially offset by the savings due to the reduction in diabetes related complications

A.7 Interpretation and conclusions of the evidence

Higher acquisition costs for the MiniMed™ 780G system / AHCL are partially offset by reduced complications costs and productivity losses, thanks to the improved clinical and quality-adjusted-life years (QALY) results. (Jendle et al., 2021), (Lambadiari et al., 2022).

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Using Recommended Settings in Youth and Adults with Type 1 Diabetes (T1D) — Minimed 780G System with the Calibration-Free Guardian 4 Sensor Results. Diabetes 71, 100-LB. https://doi.org/10.2337/db22-100-LB

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Assessment

Hybrid Closed Loop Systems for Managing Blood Glucose Levels in Type 1 Diabetes [ID3957 (DAP55)]

Document A

TANDEM DIABETES CARE, INC.

evidence submission summary for committee

Tandem Diabetes Care, Inc. confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

November 2022

File name	Version	Contains confidential information	Date
APPENDIX A – Company evidence submission summary – TANDEM 11202022	**A**	**No**	**11/21/2022**

Contents

Submission summary

A.1 Health condition

The t:slim X2 Insulin Pump with Control-IQ technology is designed for the subcutaneous delivery of insulin for type 1 diabetes mellitus.

A.2 Clinical pathway of care

People living with Type 1 diabetes require insulin to control their blood sugar. The injection of insulin can be managed with the manual injection (syringe or pen) of both of short and long acting insulins or with the use of an insulin pump that delivers a single rapid acting insulin every 5 minutes to meet the physiological needs of the user. Modern advanced hybrid closed loop technology automates basal and correct boluses, minimizing the user burden while improving outcomes. Users do not need to go through earlier treatment modalities to qualify or succeed with advanced hybrid closed loop technology.

A.3 Equality considerations

It has been Tandem Diabetes Care's experience that Control-IQ technology provides positive outcomes to people from all ages, genders, ethnicities, and socioeconomic backgrounds.

A.4 The technology being appraised

UK approved name and brand name	t:slim X2 insulin pump with Control-IQ technology The pump makes an Advanced Hybrid Closed-Loop system when used in combination with Dexcom G6 continuous glucose monitoring (CGM).
Mechanism of action	The Control-IQ automated insulin dosing feature is an algorithm embedded in the t:slim X2 insulin pump's software. This feature enables the t:slim X2 pump to automatically adjust the delivery insulin (basal and correction boluses) based on the current continuous glucose sensor value and predicted glucose values 30 minutes in the future. Control-IQ technology is not a substitute for the patient's active diabetes management.

Marketing authorisation/CE mark status	CE 600498 by BSI (Notified Body # 2797) Issued 2020-07-15 Expiry 2023-04-26 MD 1101 Electronic insulin infusion pumps (Class IIb) MD 0102 Cartridge – accessory for insulin infusion pump MHRA 17761 (09/24/2021)
Indications and any restriction(s) as described in the summary of product characteristics	The t:slim X2 insulin pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The pump is able to reliably and securely communicate with compatible, digitally connected devices. Control-IQ technology is intended for use with a compatible continuous glucose monitor (CGM) and the t:slim X2 insulin pump to automatically increase, decrease, and suspend delivery of basal insulin based on CGM readings and predicted glucose values. It can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold. The pump is indicated for use in persons six years of age and greater. The pump is intended for single patient use. The pump is indicated for use with NovoRapid or Humalog U-100 insulin.
Method of administration and dosage	The t:slim X2 insulin pump with Control-IQ technology delivers insulin every 5 minutes based on an establish patient personal profile consisting of a target glucose, insulin sensitivity factor, correction factor, actual and predicted sensor glucose value, and a metabolic algorithm. The pump also delivers an automatic correction bolus when deemed necessary (once per hour). Finally, the user delivers bolus insulin based on consumed carbohydrates.
Additional tests or investigations	None besides the diagnosis of Type 1 diabetes and the use of a continuous glucose sensor (CGM)
List price and average cost of a course of treatment	Annual cost of therapy including t:slim X2 insulin pump and consumables (cartridges, infusion sets, and continuous glucose sensors) ~ British Pounds 4153.30. Does not include cost of insulin.
Patient access scheme (if applicable)	NHS framework - Insulin Pumps, Continuous Glucose Monitoring, Closed Loop insulin Delivery Systems and Associated Products, managed by NHS Supply Chain and effective January 2022. Refer to Air Liquide Healthcare UK submission

A.5 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication of delivering insulin to people living with Type 1 diabetes.

The company submission is consistent with the final NICE scope and the NICE reference case.

A.6 Clinical effectiveness evidence

The t:slim X2 insulin pump with Control-IQ technology is the first advanced hybrid closed-loop system. It has been commercialized since January 2020 as a combination of the t:slim X2 insulin pump, the Dexcom G6 continuous glucose monitor, and the pump embedded Control-IQ algorithm. It is estimated that over 300,000 people use Control-IQ technology around the world, or about 75% of all patients using an advanced hybrid closed-loop system.

The Control-IQ algorithm was evaluated in two independent multi-center Randomized Clinical Trials conducted by the University of Virginia (Charlottesville, Virginia, USA) and funded by the United States National Institute of Health (NIH) with no involvement from Tandem Diabetes Care, the manufacturer of the system.

The first randomized clinical trial (Brown et al., NEJM 2019) included 168 participants (ages 14 and up) for a 6-month period. Patients 14 years and older were randomized between Control-IQ technology and a Sensor Augmented Pump. The trial showed a significant improvement in Time in Range (3.9-10.0mmol/L), a high rate of therapy adherence, and a high percentage of time spent in closed-loop, factors that were not met in prior closed-loop systems. The mean (±SD) percentage of time that the glucose level was within the target range increased in the closed-loop group from 61±17% at baseline to 71±12% during the 6 months and remained unchanged at 59±14% in the control group (mean adjusted difference, 11 percentage points; 95% confidence interval [CI], 9 to 14; P<0.001).

The second trial (Breton et al., NEJM 2020) in a pediatric population (ages 6 to 13) showed similar glycemic control improvements and adherence to therapy. The mean (±SD) percentage of time that the glucose level was in the target range of 3.9 to 10.0 mmol/L increased from 53±17% at baseline to 67±10% (the mean over 16 weeks of treatment) in the closed-loop group and from 51±16% to 55±13% in the sensor augmented pump group (mean adjusted difference, 11 percentage points [equivalent to 2.6 hours per day]; 95% confidence interval, 7 to 14; P<0.001. In the closed-loop group, the median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95).

Since commercialization, real-world studies and analyses have confirmed the RCTs' results across a large and broad population of users. Breton et al. (DTT 2021) published an analysis of 7813 T1D patients who used the Control-IQ system for at least 12 months after transitioning from the Basal-IQ predictive low glucose suspend (PLGS) system. The authors observed that:

- Median percent time in automation was 94.2% for the entire 12-month duration with no significant changes over time.
- Glycemic control improved rapidly (within 2 weeks) after initiation of Control-IQ
- Glycemic control was maintained for the entirety of the 12 months study period.
- Median percent time in range (TIR) (3.9–10.0 mmol/L) was 63.2% at baseline and increased to 73.5% ($p<0.001$) with no degradation over the 12 months use.
- Median percent time <3.9 mmol/L (hypoglycemia) remained below 1%. No improvement was observed since users where already using a PLGS system.
- Median percent time >10.0 mmol/L (hyperglycemia) decreased from 33.5% at baseline to 24.4% ($p<0.001$).
- Finally, similar glycemic improvements and time in automation were observed in all 4 age categories [children under 13, in adolescents, in adults (18-64), and in seniors (65 and over)].

Table 1 Clinical effectiveness evidence

Study title	Brown et al., NEJM 2019	Breton et al., NEJM 2020	Breton et al. (DTT 2021)
Study design	RCT	RCT	Systematic Review
Population	168 (ages 14 and up)	102 (ages 6-13)	7813 (ages 6 and up)
Intervention(s)	Control-IQ 112	Control-IQ 78	Control-IQ 7813 (12 months)
Comparator(s)	Sensor Augmented Pump 56	Sensor Augment Pump 23	Basal-IQ 7813 (2 weeks prior)
Outcomes specified in the decision problem	Glycemic control (time in range) Time in Automation Adverse Events	Glycemic control (time in range) Time in Automation Adverse Events	Glycemic control (time in range) Time in Automation
Reference to section in submission	Reference 68 in Assessment	Reference 69 in Assessment	Reference 63 in Assessment

Study title	Forlenza et al., DTT 2022		
Study design	Systematic Review		
Population	5075 (ages 6 and up)		
Intervention(s)	Control-IQ (>30 days) 5075		
Comparator(s)	Pre-Control-IQ (>30 days) 5075		
Outcomes specified in the decision problem	Glycemic control (time in range) Time in Automation Adverse Events		
Reference to section in submission	Reference 90 in Assessment		

Additional analysis from Forlenza et al. (DTT 2022) has shown that Control-IQ is effective in “at-risk” populations that qualify for public insurance instead of private insurance coverage in the United States. These public insurance funds include populations of varied ethnicities and socioeconomic backgrounds.

People with the highest HbA1c and the lowest Time in Range experience the best glycemic improvements mostly through a reduction of hyperglycemia. On the other hand, well controlled users also experience improvements by reducing variability and hypoglycemia.

A.7 Key results of the clinical effectiveness evidence

Across all studies, Control-IQ has show to be effective at improving glycemic control across large and broad patient populations. Control-IQ is a great equalizer in terms of giving patients of all walks of life an effective tool to improve their glycemic control and their quality of life while reducing the mental burden associated with diabetes management. Control-IQ technology reduces the severe hypoglycemic and hyperglycemic events that require external interventions and hospitalizations, significant short-term and long-terms costs to healthcare systems.

In summary, the Control-IQ technology has been described by users, their families, and healthcare providers as being “life changing” thanks to its mode of action and its effectiveness. Every five minutes, 288 times per day, the system predicts and doses insulin without user engagement for unprecedented glycemic control improvements.

A.8 Evidence synthesis

NOT AVAILABLE

A.9 Key clinical issues

NOT AVAILABLE

A.10 Overview of the economic analysis

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.11 Incorporating clinical evidence into the model

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.12 Key model assumptions and inputs

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.13 Base-case ICER (deterministic)

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.14 Probabilistic sensitivity analysis

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.15 Key sensitivity and scenario analyses

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.16 Innovation

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.17 End-of-life criteria

NOT APPLICABLE

A.18 Budget impact

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

A.19 Interpretation and conclusions of the evidence

NOT SUBMITTED // PLEASE REFER TO DEXCOM SUBMISSION

Association of British Clinical Diabetologists Diabetes Technology Network UK (ABCD DTN-UK) audit of the NHS England Hybrid Closed-Loop Pilot in Adults with Type 1 Diabetes:

Report for NICE May 2022

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Abstract

Background

Hybrid closed loop (HCL) technology automates insulin delivery and has been shown to improve outcomes in people living with Type 1 diabetes. However, there are limited insights into the real-world benefits. NHS England provided the opportunity for 31 diabetes centres in England to start hybrid closed loop therapy in people with Type 1 diabetes aged 18 and over. Inclusion criteria were use of an insulin pump and flash glucose monitoring and a HbA1c ≥69 mmol/mol. Here we present the results of the ABCD DTN-UK national HCL audit programme which describes the real-world outcome data for those included in the NHS England pilot.

Methods

Routinely collected, anonymised data were submitted to a secure online tool. Data outcomes included in the analysis were those with both baseline and follow-up data available. The primary outcome was HbA1c, other covariates of interest included glucose sensor metrics; diabetes distress; Gold Score; event rates (hospital admission, paramedic callouts and severe hypoglycaemia) and user opinion of HCL.

Results

Follow up data were available for 570 individuals; mean age 40 years, 67% female, mean diabetes duration of 21 years, 84% White British. Baseline HbA1c 78.8±9.0mmol/mol [9.4±0.8%] reduced to 62.6±9.5mmol/mol [7.9±0.8%] by 5.0 (IQR 3.9-6.6) months median follow up. Mean adjusted HbA1c reduced by -17.4mmol/mol (95% CI -15.8, -19.0; P<0.001) [1.59% (95% CI 1.44, 1.74, P<0.001)]. Time in range (3.9-10mmol/l) increased from 34.2% to 62.7% (P<0.001), time below range (<3.9mmol/l) reduced from 2.1% to 1.6% (P<0.001). The proportion reporting diabetes-related distress reduced from 70.8% to 43.1% (P=0.001). Gold score reduced from 2.2 to 1.9 (P<0.001). Almost all (96.7%) would recommend closed-loop insulin therapy to others with diabetes while 95.3% reported that the system had a positive impact on their quality of life. No significant increases in hospital admissions/paramedic callouts were found.

Conclusion

The NHS England pilot of HCL therapy led to substantial improvements in HbA1c, time in range and time below range over 5 months of follow up. The prevalence of diabetes related

distress improved. Almost all reported a positive impact on quality of life and would recommend the use of HCL system to other people living with diabetes.

Introduction

Hybrid closed-loop (HCL) insulin systems combine insulin pump therapy with continuous glucose monitoring to automate insulin delivery to maintain glucose near a pre-specified target level. In randomised controlled trials HCL systems led to improved glucose management measured both by HbA1c and time in range (3.9-10mmol/l) and reduced hypoglycaemia when compared to insulin pump alone, multiple daily injections with continuous glucose monitoring (CGM) and sensor augmented pump therapy(1-3). However, the benefits demonstrated in the clinical trials reflected the outcomes in a group of people motivated to take part in research and often with near target HbA1c levels at baseline. This may limit the generalisability of the findings to the general population with Type 1 diabetes. Real-world evidence exists but is limited to single-system studies in individuals who, again, are at or near target HbA1c at baseline(4-6). In recognition of the disconnect between the evidence and observed clinical experience with HCL systems, NHS England (NHSE) comissioned a real-world pilot of HCL systems in those with high HbA1c levels who were already using an insulin pump and flash glucose monitor. The Association of British Clinical Diabetologists (ABCD) Closed-Loop audit was used to capture routine outcome data from adults who participated in this pilot. Data collection is ongoing; this report describes the available outcome data in May 2022 from individuals included in the pilot.

Methods

The methodology for the ABCD closed loop audit has been published in the British Journal of Diabetes(7). The population included in the NHSE adult HCL pilot were those attending adult services with a clinical diagnosis of Type 1 diabetes managed with an insulin pump and flash glucose monitor with an HbA1c ≥69mmol/mol (8.5%). Overall, 31 adult diabetes centres from across England were included in the pilot. Patients in the pilot were started on HCL between August and December 2021. Anonymised clinical outcome data were collected during routine clinical care, review of clinical systems and electronic health records and submitted to a secure online tool. This analysis therefore reflects the data captured between 5 and 10 months of follow up. The primary outcome was change in laboratory derived HbA1c. The glucose management indicator (GMI) was not used in lieu of laboratory HbA1c; GMI was captured as its own data point. Secondary outcomes include CGM metrics

(time in range 3.9-10mmol/l), time below range (<3.9mmol/l), Diabetes Distress 2 score (DDS2) (8), Gold score (9) (a measure of hypoglycaemia awareness where 1= full awareness and 7= complete loss of awareness), event rates (hospital admission, paramedic callouts and severe hypoglycaemia), weight, body mass index (BMI) and user opinion of HCL. Sensor glucometrics were extracted from the relevant HCL system for the 14-days preceding follow-up. Follow-up frequency was determined by the responsible clinical teams, based on clinical need. The most recently available data for each patient was used for this analysis.

Data were assessed for accuracy and completeness and analysed using Stata SE 16. Analysis utilised paired data from individuals with baseline and follow-up. Data were expressed as mean and standard deviation (SD) for continuous parametric outcomes and median and interquartile range (IQR) for non-parametric outcomes. Paired t-tests were used for the analysis of continuous parametric outcomes. Wilcoxon Signed Rank tests were used to assess non-parametric outcomes. P-value <0.05 was considered statistically significant. Change in HbA1c from baseline was adjusted for baseline characteristics and change in other covariates using a multiple linear regression model to correct for key covariates determined *a priori* as follows: baseline HbA1c and weight, gender, age, duration of diabetes, deprivation level, HCL system and ethnicity.

Ethics

As a clinical audit, this programme only collects anonymised routinely available clinical data. Data or tests not performed routinely were not required to be performed or submitted to our audit. As such there was no requirement for approval by a research ethics committee. The ABCD nationwide audit programme, which includes this audit, has Caldicott Guardian Approval and has also been approved by Confidentiality Advisory Group (10).

Results

Baseline data were available for 634 individuals, with follow up data reported for 570 people. **Figure 1.** Contains the flow-diagrams for this analysis. This includes the numbers with paired data available for assessment of each outcome.

Baseline characteristics

For the 570 individuals with baseline and follow up data the median age was 40 years (IQR 29-50), 67.2% were female with a median diabetes duration of 21 years (IQR 14.4-30.2), 83.9% were White British, 39.0% were from the 2 most deprived quintiles with median index of multiple deprivation decile of 6 (IQR 3-8). The baseline characteristics of the cohort are summarised in **Table 1.** The HCL systems initiated in the NHS England pilot included Medtronic 780G (n=265), Medtronic 670G (n=8), Tandem Control IQ (n=204), CAM APS (n=29), Medtrum closed loop system (n=29); the system was not recorded in 35 individuals. Sensitivity analysis comparing individuals with and without follow-up demonstrates that those with absent follow-up were more likely to be from a more deprived background, more likely to be using ultra-fast acting insulin at baseline and had a different distribution of systems being used. The remainder of the baseline characteristics were similar between the groups.

HbA1c and sensor based outcomes

Across the population HbA1c reduced from 78.8±9.0mmol/mol [9.4±0.8%] at baseline to 62.6±9.5mmol/mol [7.9±0.8%] over a median follow-up of 5.0 months (IQR 3.9-6.6). Using a multivariate linear regression model to correct for key covariates, mean adjusted HbA1c reduced by -17.4mmol/mol (95% CI -15.8, -19.0; P<0.0001) [-1.59% (95% CI -1.44, -1.74, P<0.0001)]. These results are summarised in **Figure 2a.** Users experienced similar improvements in HbA1c irrespective of baseline deprivation status or ethnicity (P=1.00 for both). No individuals were achieving a HbA1c of ≤58mmol/mol at baseline; 28.2% (n=179) of users met this HbA1c target at follow-up; 10.1% of achieved HbA1c ≤53mmol/mol. Pre-HCL,0.8% met the internationally recommended targets of ≥70% time in range and <4% time below range, increasing to 28.2% at follow-up (P=0.04). Time in range (3.9-10mmol/l) increased from 34.2% to 62.7%, a mean increase of 28.5% (95% CI 25.6, 31.5, P<0.001). Time below range (≤3.9mmol/l) reduced from 2.1% to 1.6% (P<0.001), with level 1 hypoglycaemia (3.0-3.9mmol/L) reducing from 1.8% to 1.3% (P<0.001). There was no significant change in level 2 hypoglycaemia (<3.0mmol/L). The changes in CGM derived glucose metrics are displayed in **Table 2 and Figure 2b. Figure 3** demonstrates the proportion of the cohort achieving recognised glycaemic targets before and after closed-loop therapy. 92.6% had a

HbA1c drop of 5mmol/mol or greater with 83.8% achieving reductions in excess of 10mmol/mol. Only 15 individuals experienced increases in HbA1c on HCL.

Diabetes distress, Gold score and user satisfaction

Improvements in patient reported outcome measures were observed with reductions in Diabetes Distress of from 3.3 to 2.2, mean reduction of -1.1 (95% CI -1.1, -1.2; P<0.0001). The proportion of individuals with high diabetes distress (mean DDS2≥3) reduced from 70.8% baseline to 43.1% (P=0.001). Gold score reduced from 2.2 to 1.9 (P<0.0001). These results are summarised in **Table 3.** Within the NHS England pilot, 96.7% of users would recommend HCL therapy to others with diabetes and 95% rated HCL therapy as having had a positive impact on their quality of life.

Acute and adverse events

Reported hospital admissions related to hypoglycaemia and hyperglycaemia/DKA and paramedic callouts (not resulting in admission) were low in this cohort and no increase in pro-rata rates were observed. These are summarised in **table 4.** One individual with diabetic ketoacidosis sadly died. An anonymised report detailing the death is available through NHS England.

A total of 37 adverse events were reported. The majority (24/37) of these adverse events were related to either pump or cannula issues (n=11) or sensor failures, inaccuracies, and skin reactions (n=13). A total of 57 users discontinued closed-loop therapy either temporarily or permanently. Twenty individuals have at least some follow-up data available for inclusion despite a short duration of therapy or erratic usage. Of these 20 users, 6 discontinued use of the Medtrum system due to concerns within the team about the safety of this device and reliability of the CGM data – these individuals were subsequently commenced on alternative systems. Reasons given for permanent discontinuation (n=37) included: lack of trust in the system/anxiety (n=4), erratic glucose levels (n=5), issues with cannulas/skin site reactions (n=6), early problems in adjusting to closed-loop (n=6), and failing to attend follow up appointments so discontinued by the clinical team (n=5). No reasons were provided for discontinuation in the remaining cases.

Discussion

This real-world evaluation of the NHS England pilot of HCL system use in people living with type 1 diabetes has demonstrated substantial improvements in HbA1c, time in range, time below range and the proportion of users achieving recognised glucose targets over 5 months of follow up. The observed HbA1c reductions in the NHS England pilot were greater than those reported in both randomised control trials and existing real-world studies, which describe HbA1c reductions between 5 and 8mmol/mol between baseline and follow-up(1-3, 6). Furthermore, the population captured by this analysis is unique in the current literature, with significantly elevated HbA1c levels at baseline despite optimal care, pump therapy and intermittently scanned CGM usage. The reductions observed and the HbA1c levels achieved are therefore likely to translate in to significant reductions in complications in the long-term providing a significant net health economic benefit with use of this technology. The proportion of people achieving HbA1c targets ≤58mmol/mol in the NHS England pilot increased from 0 to 28.2%, a similar proportion to that reported in the National Diabetes Audit (28.6% in NDA) (11). Although the pilot follow-up glucose time in range (62.7% in 3.9-10mmol/l) was lower than in many existing HCL studies, our audit population had much lower time-in-range at baseline (34.2%) and the change in time in range, an increase of 28.5%, was much greater(1-3, 6, 12).

There was a significant reduction in the prevalence of diabetes-related distress, and almost all users reported a positive impact on quality of life and would recommend the use of HCL systems to other people living with diabetes. This is consistent with existing qualitative evidence supporting the use of closed-loop insulin systems(13, 14).

Whilst average Gold score decreased, the percentage of individuals scoring 4 (therefore meeting definition for impaired awareness of hypoglycaemia) or more increased. This may be indicative of some individuals detecting a greater proportion of hypoglycaemia with real-time CGM compared to intermittently scanned CGM, which may have led to reporting bias.

The main strength of this analysis is the real-world nature of the data captured in a large number of HCL users. It is the first real-world closed-loop study performed independently of device companies, covering a range of systems in individuals with higher HbA1c levels at

baseline. The results are therefore likely to be generalisable not just within an NHS context but may have implications for other healthcare systems. The variety of systems used will allow for later comparison. Although the clinical audit design allows for collection of real-world data it remains reliant on clinicians inputting data into the secure online tool and on the data for certain outcomes being available. Missing data is a limitation. In addition, the nature of a clinical audit approach and the necessary emphasis on anonymised outcome data is such that a more detailed analysis of adverse events is not feasible. Whilst this analysis is novel as it focuses on individuals with a HbA1c ≥69mmol/mol at baseline, this may also be viewed as a limitation as it may limit the applicability of the findings to those groups with high HbA1c values.

Conclusion

Among adults with Type 1 diabetes and high HbA1c, HCL resulted in significantly lower HbA1c levels, improved CGM derived outcomes, reduced diabetes related distress and a reported positive impact on quality of life. These findings support wider access to hybrid closed loop therapy in people living with Type 1 diabetes.

Figure 1. Flow diagram showing the numbers included in this analysis

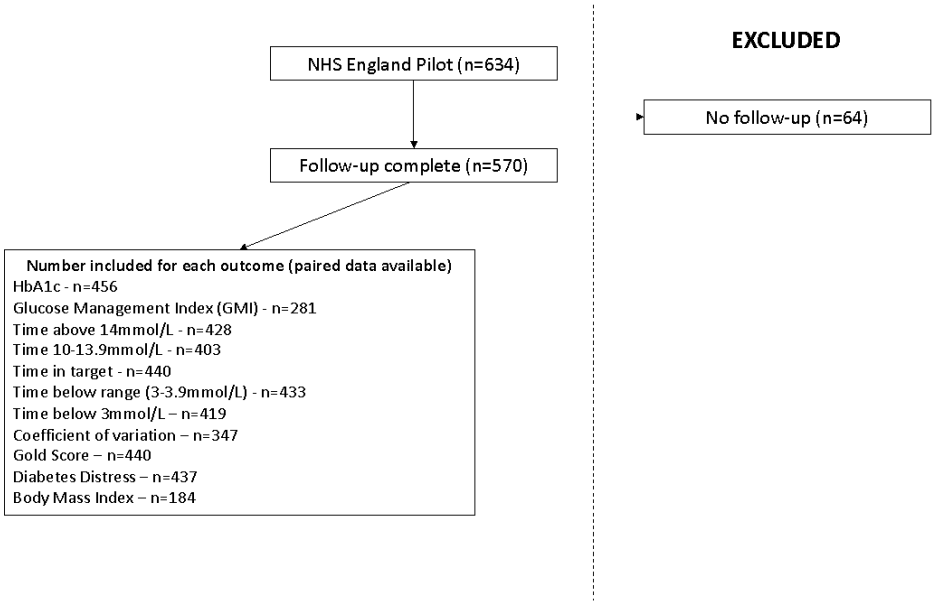

Table 1. Baseline characteristics including sensitivity analysis of those with missing vs complete follow-up

Baseline Characteristics		All n= 634	Follow-up Complete n= 570	Follow-up Missing n= 64	P-Value - Complete vs missing
Age, Years	*median (IQR)*	39 (28-50)	40 (29-50)	38 (28-45.5)	0.233
Gender, Female	*%*	67	67.2	65.6	0.800
Diabetes Duration, Years	*median (IQR)*	21 (14.4-30.3)	21 (14.4-30.2)	21 (13.7-31.8)	0.684
Pump Duration, Year	*median (IQR)*	7 (4.5-10.9)	7 (4.6-11)	7 (3.2-9.9)	0.807
Weight, kg	*mean (±SD)*	81 ±17.6	81 ±17.8	82 ±15.8	0.701
Body Mass Index, kg/m²	*mean (±SD)*	29 ±6	29 ±6.1	29 ±5.6	0.954
Median index of multiple deprivation	*median (IQR)*	6 (3-8)	6 (3-8)	5 (2-7)	0.040
Ultra-fast acting insulin use	*%*	4.2	3.3	13	0.001
Presence of retinopathy at baseline	*%*	48	49	41	0.307
Ethnicity					
White - British	*%*	84.7	83.9	92.2	
Asian	*%*	2.5	2.6	1.6	
Black	*%*	1.1	1.2	0	0.691
Mixed	*%*	1.6	1.8	0	
Other	*%*	0.8	0.7	1.6	
Whte - Other	*%*	2.2	2.1	3.1	
Unknown	*%*	7.1	7.7	1.6	
HbA1c/CGM Metrics					
Mean HbA1c, mmol/mol	*mean (±SD)*	78.8 ±9.6	78.9 ±9.6	77.5 ±10.2	0.277
Total Daily Insulin Dose, units	*mean (±SD)*	49.9 ±29.7	50.2 ±30.6	46.9 ±18.4	0.481
Glucose Management Indicator, mmol/mol	*mean (±SD)*	71.6 ±12.1	71.6 ±12.1	72.4 ±11.9	0.767
Time above range (≥14mmol/L), %	*mean (±SD)*	38.5 ±20	38.1 ±19.7	43.9 ±22.9	0.065
Time above range (10.1-13.9mmol/L), %	*mean (±SD)*	26 ±11.2	26.3 ±11.1	22.7 ±11.9	0.068
Time in range (3.9-10mmol/L, %	*mean (±SD)*	33.8 ±15	33.8 ±14.8	32.8 ±16.8	0.650
Time below range (3-3.8mmol/L), %	*mean (±SD)*	1.7 ±2.3	1.7 ±2.4	2 ±1.9	0.417
Time below range (<3mmol/L), %	*mean (±SD)*	0.4 ±1.3	0.4 ±1.3	0.5 ±1.1	0.678
Number of scans per day	*mean (±SD)*	7.2 ±5.8	7.2 ±5.8	7.6 ±6.3	0.707
Coefficient of variation	*mean (±SD)*	37.8 ±7.2	37.9 ±7.3	37.2 ±5.1	0.644
Insulin Pump/Closed-Loop System					
Medtronic 780G	*%*	47.8	46.5	59.4	
Tandem Control IQ	*%*	34.2	35.8	20.3	
Not recorded	*%*	6.9	6.1	14.1	0.006
CAMAPS FX	*%*	4.9	5.1	3.1	
Medtrum	*%*	4.9	5.1	3.1	
Medtronic 670G	*%*	1.3	1.4	0	
Gold/DDS Scores					
Gold Score	*mean (±SD)*	2.2 ±1.4	2.2 ±1.4	2.3 ±1.5	0.818
DDS1 Score	*mean (±SD)*	3.1 ±1.3	3.1 ±1.3	3.3 ±1.6	0.489
DDS2 Score	*mean (±SD)*	3.5 ±1.4	3.5 ±1.4	3.6 ±1.4	0.634
DDS Mean Combined Score	*mean (±SD)*	3.3 ±1.3	3.3 ±1.3	3.4 ±1.4	0.478

Figure 2a. Boxplot demonstrating HbA1c at baseline and follow-up

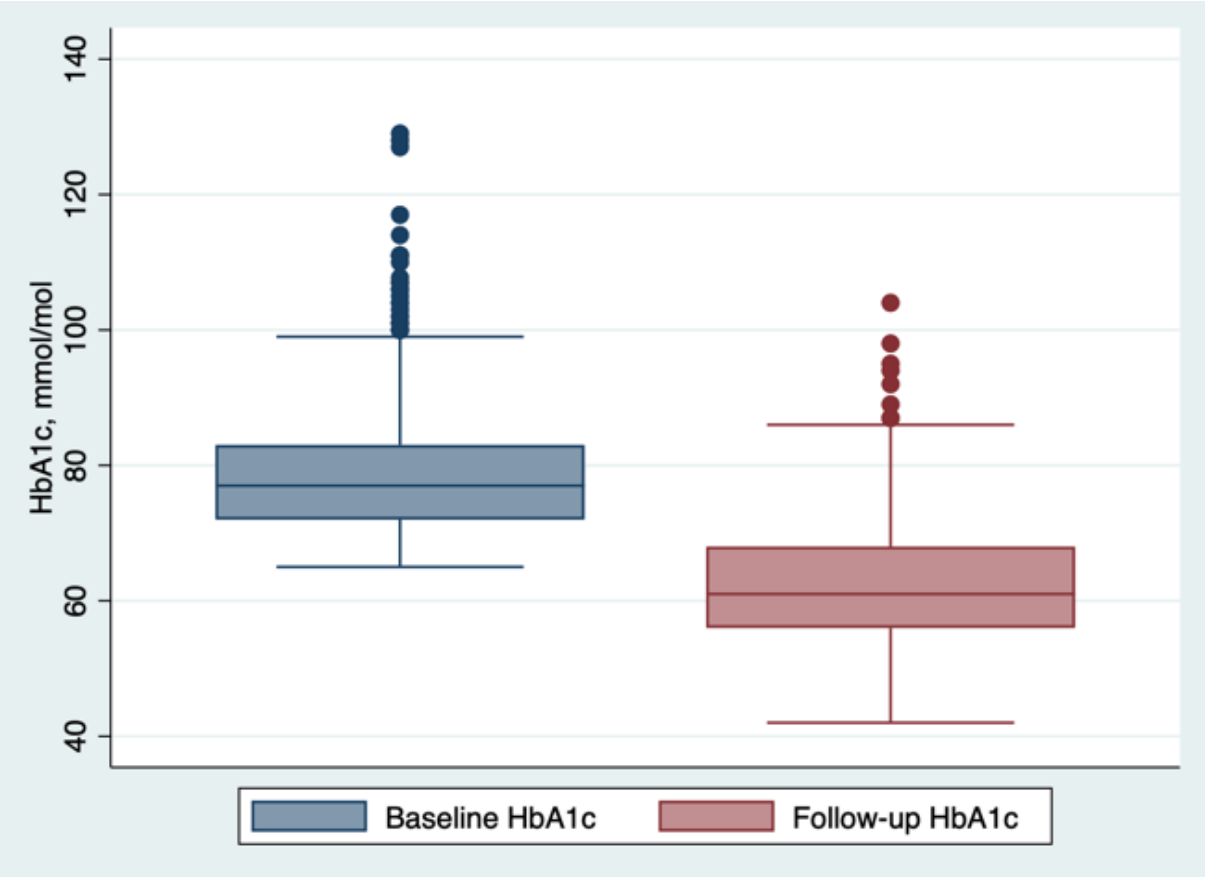

Figure 2b. Stacked bar chart demonstrating time-in-glucose ranges at baseline and follow-up

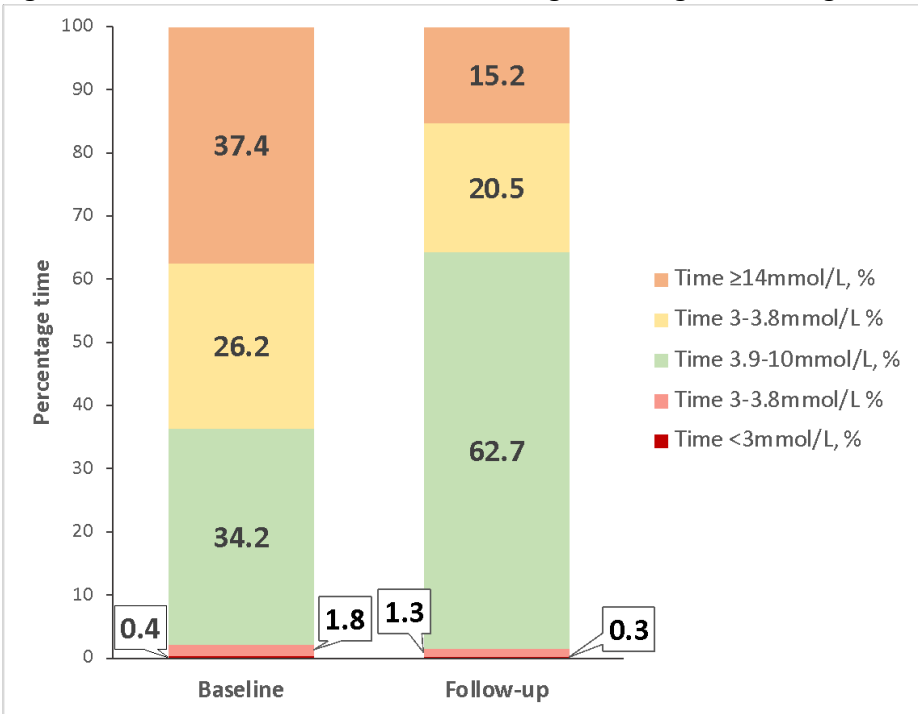

Table 2. Baseline and follow-up HbA1c and CGM derived glucose metrics (uncorrected changes)

	Baseline	Follow-up	Change (95% CI)	P-Value
HbA1c, mmol/mol	78.8	62.6	-16.2 (-15.3, -17.1)	<0.0001
HbA1c, %	9.4	7.9	-1.5 (-1.4, -1.6)	<0.0001
GMI, mmol/mol	71.2	56.2	-15.0 (-13.2, -16.7)	<0.0001
Time ≥14mmol/L, %	37.4	15.2	-22.2 (-20.4, -24.0)	<0.0001
Time 10.1-13.9mmol/L, %	26.6	22.6	-4.0 (-2.4, -5.5)	<0.0001
Time 3.9-10mmol/L, %	34.2	62.7	28.5 (25.6, 31.5)	<0.0001
Time 3-3.8mmol/L %	1.8	1.3	-0.5 (0.2, 0.7)	0.0003
Time <3mmol/L, %	0.36	0.34	-0.02 (-0.1, 0.2)	0.794
Coeffieicent of variation	37.8	34.6	-3.2 (-2.2, -4.3)	<0.0001

Figure 3. Proportion of individuals achieving targets for HbA1c, glucose management indicator (GMI), time-in-target range (TIR) and a composite outcome of TIR and time-below-range (TBR) at baseline and follow-up

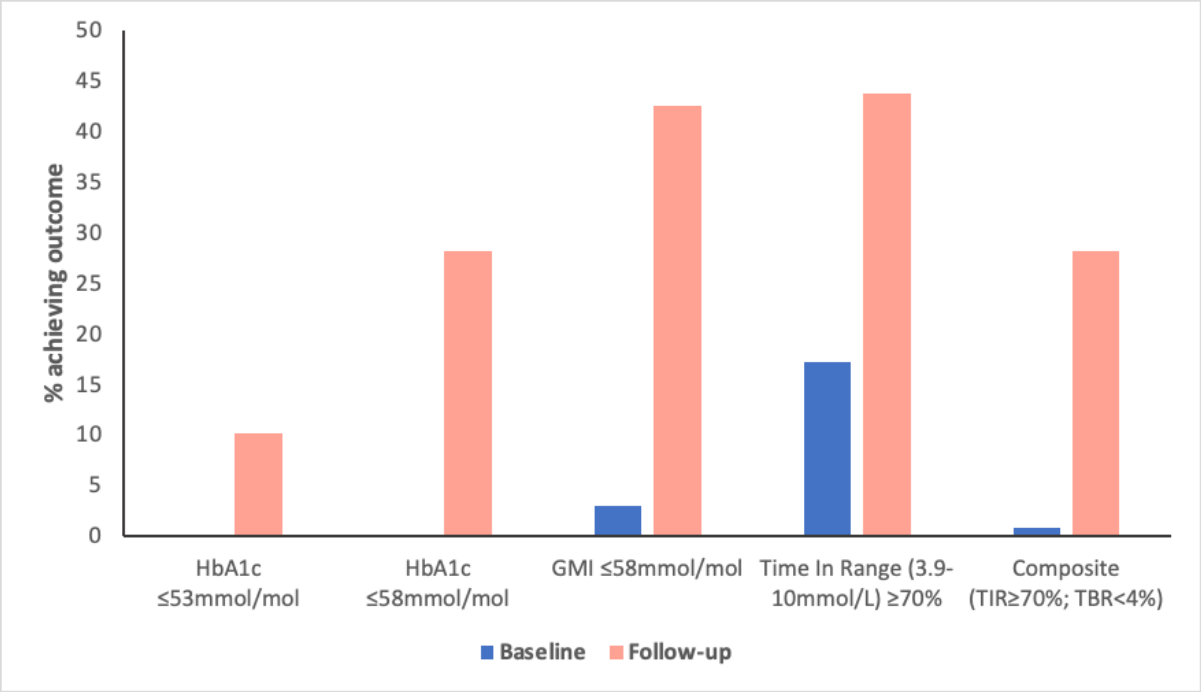

Table 3. Patient reported outcome measures at baseline and follow-up

	Baseline	Follow-up	Change (95% CI)	P-Value
Gold Score	2.2	1.9	-0.3 (-0.2, -0.5)	<0.0001
Diabetes Distress	3.3	2.2	-1.1 (-1.0, 1.2)	<0.0001
Diabetes Distress (Average Score ≥3), %	70.8	43.1	-18.9	0.001
Impaired Awareness of hypoglycaemia (Gold ≥4), %	26.0	31.7	5.7	<0.0001

Table 4. Event rates at baseline and follow-up

		Rate per person per year		
		Baseline	**Follow-up**	**P-Value**
Admission	Hyperglycaemia/DKA	0.07	0.11	0.458
	Severe Hypoglycaemia	0.02	0.01	0.483
	Other (Diabetes related)	0.01	0.02	0.209
	Other (Any)	0.10	0.07	0.009
Paramedic call-out	Hyperglycaemia/DKA	0.02	0.00	0.005
	Severe Hypoglycaemia	0.03	0.07	0.581
	Other (Diabetes related)	0.01	0.00	0.564
	Other (Any)	0.03	0.01	0.02
Severe hypoglycaemia		0.34	0.21	0.380

Conflicts of interest

TSJC has received speaker fees and/or support to attend conferences from NovoNordisk, Sanofi and Abbott Diabetes Care

TPG has received personal fees from NovoNordisk, Sanofi Aventis, Mundipharma Pharmaceuticals, Abbott Diabetes Care and Eli Lilly.

REJR has received speaker fees, and/or consultancy fees and/or educational sponsorships from BioQuest, GI Dynamics and Novo Nordisk.

PC has received personal fees from Abbott diabetes care, Dexcom, Eli Lilly, Insulet, Medtronic, Novo Nordisk, Sanofi Aventis, Glooko.

EGW has received personal fees from Abbott Diabetes Care, Dexcom, Eli Lilly, Glooko, Insulet, Medtronic, Novo Nordisk, Sanofi Aventis.

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NHS England Closed Loop Study in Children and Young People: Report for NHS England and NICE

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Consortium

Paediatric Centres n=251 recruited	Named Lead for Closed-Loop Study
Southport and Ormskirk Hospital n=45	Sze May Ng
Nottingham Hospital n=44	Tabitha Randell
Alder Hey Children's Hospital n=39	Atrayee Ghatak
Leeds Children's Hospital n= 38	Fiona Campbell
University College London Hospital n=28	Peter Hindmarsh
Oxford University Hospital n=24	Diana Yardley
Southampton Hospital n=22	Nicola Trevelyan
Sheffield Children's Hospital n=11	Neil Wright

Introduction

Hybrid closed-loop (HCL) systems are characterised by automated insulin delivery systems that are algorithm-driven to automate insulin delivery combined with manual mealtime blousing. It uses real-time continuous glucose monitoring (CGM) to inform algorithm-directed insulin delivery via an insulin pump.[1] HCLs are associate with better blood glucose management and reduced risk of hypoglycaemia, and currently represent the most advanced form of insulin delivery available for people with type 1 diabetes today[2 3 4]. The use of HCL systems have been reported to increase the time sensor-measured blood glucose to near-normoglycaemia range while reducing the risk of time in hyperglycaemia and hypoglycaemia[5 6 7 8].

Objective

The aim of the study was to evaluate the real-world data and effectiveness of hybrid closed loop (HCL) systems on glycated haaemoglobin A1c (HbA1c), time-in-range (TIR), hypoglycaemia frequency (%), fear of hypoglycaemia, sleep and quality of life measure in children and young people (CYP) with Type 1 diabetes (T1D) and their carers.

Setting

Patients were recruited into the NHS England real-world hybrid closed loop observational study from the 1st of August 2021 to the 10th of December 2022 from eight paediatric diabetes centres in England prospectively.

Methodology

This is a prospective real-world observational study of CYP (1-18 years of age) with T1D commencing on HCL. Criteria for recruitment were any CYP age under 19 years with T1D with at least one year duration and had a minimum of two HbA1c measurements prior to commencing the HCL. Exclusion criteria were any other medical conditions that may impact on glucose metabolism or wearing of devices and participation in other current diabetes technology trials or trials that delay onset of T1D.

Data on HbA1c, TIR and hypoglycaemia frequency were reviewed at baseline prior to starting HCL, and at 3 and 6 months after commencement of the HCL. Data on HbA1c, TIR and time in hypoglycaemia was collected prior to starting the HCL and 3 months after HCL was started. CYP aged 12 years and above independently completed the validated hypoglycaemia fear survey (HFS)[9]. The HFS is a validated questionnaire of behaviour and worry related to hypoglycaemia and its negative consequence. Parents of patients <12 years old were asked to complete a modified version of the HFS-Parent survey (HFS-P)[10 11]. The HFS-P is a reliable and valid measure of fear of hypoglycaemia adapted from an existing adult validated questionnaire[6]. The HFS-P is designed to assess fear, anxieties, avoidance behaviours, and worry associated with hypoglycaemia in parents and carers of younger children with diabetes[12].

HbA1c, TIR (defined as blood glucose levels between 3.9-10mmol/L or 70-180 mg/dL) and time in hypoglycaemia (%) , where hypoglycaemia was defined by less than 3.9mmol/L were reviewed as metrics for blood glucose control[13 14] using several downloading platforms that the unit was using such as Diasend® system (Glooko Inc, Mountain View, CA, USA)., Tidepool (Tidepool.org), Dexcom Clarity™ (Dexcom, Inc., San Diego, CA, USA) and the Carelink™ ((Medtronic, Northridge, CA) uploader systems which allow analytic reports that can be accessed through a web interface.

CYP aged 12 years and above independently completed the validated Hypoglycaemia Fear Survey (HFS). Parents of patients less than 12 years of age completed a modified version of the HFS-Parent survey. To assess the quality of sleep, the Patient Reported Outcomes Measurement Information System (PROMIS) for Sleep-Related Impairment (SRI) questionnaire was used for CYP aged 8 years and above who independently completed the PROMIS-Sleep Related Impairment questionnaire short form[15 16]. Parents of patients less than 8 years of age completed the PROMIS-Parent Proxy Sleep Disturbance questionnaire[16]. The 8-item PROMIS Paediatric SRI short form assesses daytime sleepiness, sleep offset, impact of sleepiness on cognitive functioning, effect on behaviours and daily activities. Raw to T-score conversions were established based on a large general population sample[16]. PROMIS item-banks are freely available for use in for both research studies and clinical practice

Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences 21.0 (version 23; SPSS Inc.,Chicago, IL, USA). Distributions of continuous outcomes were checked. Data were expressed as mean and standard deviation (SD) for continuous parametric outcomes and median and interquartile range (IQR) for non-parametric outcomes. Student t-test for analysis of continuous parametric outcomes. Mann-Whitney Wilcoxon test for non-parametric outcomes. P-value <0.05 was considered statistically significant.

Ethics statement

It was not deemed necessary by NHS England to gain ethical approval for this study as this study was undertaken as part of a service evaluation for CGM and HCL use within the organisations and did not affect patient care or direction of management. Data collection and QoL surveys were evaluated and did not alter the course of patient care.

Results

There were 251 CYP (147 males, 58%) with T1D recruited with a mean age of recruitment at 12.3 ± 3.5 SD (range 2-19 years) at commencement of HCL. 89% of all CYP were of white ethnicity, 3% Asian ethnicity, 3% black ethnicity and 3% mixed ethnicity, 1% as other. Overall duration of diabetes were 6.6 years ± 3.7 SD (range 1.0 to 15.7 years). Age of recruitment was

12.4 years ± 3.6 SD (range 2.0 to 18.9 years) The demographics from each of the 8 centres are shown in Table 1.

The HCL systems used in the study were: 1) Tandem Control-IQ AP system, which uses the Tandem t:slim X2 insulin pump (Tandem Diabetes Care, San Diego, CA) with the Dexcom G6® CGM (Dexcom, San Diego, CA) sensor; 2) Medtronic MiniMed™ 780G (Medtronic, Northridge, CA) and 3) CamAPS FX (CamDiab, Cambridge, UK.) which uses the insulin pump Dana Diabecare RS (DANA-i; Sooil, Seoul, South Korea) with Dexcom G6® CGM. Our results showed that 78% (n=196) of all patients were on Tandem Control-IQ AP, 11% (n=27) were on the CamAPS FX (11%) and 11% (n=28) on the Medtronic 780G (11%).

HCL use demonstrated significant improvements after 3 months and 6 months of use in HbA1c, TIR, frequency of hypoglycaemia compared 3 months prior to starting HCL (Table 2).

Conclusions

The NHS England Closed Loop Study in Children and Young People showed improvements in glycaemic control, TIR, frequency of hypoglycaemia, hypoglycaemia fear and quality of sleep for children and young people when using HCL for 6 months. Hypoglycaemia fear and quality of sleep were also improved for their parents and carers at 6 months.

Table 1. Recruitment centres and demographics

Centre	Number recruited (N=251)	Gender Male:Female	Age at start of HCL (years)	Duration of T1D (years)
Southport and Ormskirk Hospital	45	32:13	12.5 ± 3.5	4.3 ± 2.1
Nottingham Hospital	44	24:20	12.4 ± 3.8	6.7 ± 3.8
Alder Hey Children's Hospital	39	22:17	11.1 ± 4.4	7.2 ± 3.4
Leeds Children's Hospital	38	17:21	13.0 ±3.3	5.0 ± 3.0
University College London Hospital	28	13:15	13.1 ± 3.3	7.9 ± 3.8
Oxford University Hospital	24	19:5	13.4 ±2.8	7.8 ± 3.2
Southampton Hospital	22	13:9	11.7 ± 3.9	7.1 ± 3.6
Sheffield Children's Hospital	11	7:4	12.1 ± 2.6	5.0 ± 3.0

HCL, hybrid closed loop; T1D, Type 1 diabetes
Data are shown in years as mean ± standard deviation

Table 2. Comparison of variables pre HCL vs post HCL commencement at 3 months

Variables	Before HCL	3 months after HCL	Difference (95% Confidence interval)	P value
HbA1c (mmol/mol)	61.8 ± 11.2	54.1 ± 7.9	7.7 (6.5 to 8.9)	P< 0.001
TIR (%)	48.9 ± 15.1	64.7 ± 11.8	-15.8 (-17.6 to -14.1)	P< 0.001
Hypoglycaemia (%)	3.7 ± 3.1	2.4 ± 2.7	-1.3 (0.7 to 1.74)	P< 0.001

HCL, hybrid closed loop; TIR, time-in-range
Data are shown as mean ± standard deviation

Table 3. Comparison of variables pre HCL vs post HCL commencement at 6 months

Variables	Before HCL	6 months after HCL	Difference (95% Confidence interval)	P value
HbA1c (mmol/mol)	62.3 ± 12.1	55.3 ± 9.3	7.0 (5.8 to 8.2)	P< 0.001
TIR (%)	48.7 ± 15.3	63.0 ± 12.4	-14.3 (-15.9 to -12.4)	P< 0.001
Hypoglycaemia (%)	3.6 ± 3.8	2.4 ± 2.2	1.2 (0.82 to 1.74)	P< 0.001

HCL, hybrid closed loop; TIR, time-in-range
Data are shown as mean ± standard deviation

Table 4. Fear of hypoglycaemia before and after HCL commencement at 6 months

	HFS Scores	Before HCL	6 months after HCL	Difference (95% Confidence interval	P-value
Parent/carers	Mean behaviour score	27.0 ± 6.9	22.6 ± 7.6	4.4 (3.1 to 5.7)	P< 0.001
	Mean Worry Score	29.6 ± 12.0	23.1 ± 11.4	6.5 (4.7 to 8.3)	P< 0.001
	Mean Total Score	56.5 ± 16.7	45.2 ± 16.9	11.3 (8.5 to 14.1)	P< 0.001
Patients (aged >12yrs)	Mean behaviour score	31.5 ± 6.0	28.6 ± 6.1	2..9 (1.7 to 4.0)	P< 0.001
	Mean Worry Score	33.7 ± 12.7	29.1 ± 9.7	4.6 2.7 to 6.5)	P< 0.001

	Mean Total Score	64.9 ± 15.3	57.5 ±12.7	7.4 (4.8 to 9.9)	P< 0.001

HCL, hybrid closed loop; HFS, Hypoglycaemia Fear Score
Data are shown as mean ± standard deviation

Table 5. Sleep T-scores before and after HCL commencement at 6 months

	PROMIS Scores	Before HCL	6 months after HCL	Difference (95% Confidence interval	P-value
Patients (aged >8yrs)	PROMIS-Sleep Related Impairment T-score	56.6 ± 9.1	54.9 ± 9.3	1.7 (0.3 to 3.0)	P=0.017
Parent/carers	PROMIS-Parent Proxy Sleep Disturbance T-score	60.1 ± 10.4	56.1 ± 10.5	4.0 (2.2 to 5.6)	P< 0.001

HCL, hybrid closed loop; PROMIS, Patient Reported Outcomes Measurement Information System; Data are shown in as mean ± standard deviation

A. Supplementary analyses

1. Comparison of variables pre HCL vs post HCL commencement at 6 months by unit

Southport and Ormskirk (n=46)			
Variables	**Before HCL**	**6 months after HCL**	
HbA1c (mmol/mol)	64.5 ± 15.4	59.4 ± 12.4	
TIR (%)	50.7 ± 16.8	61.5 ± 14.4	
Hypoglycaemia (%)	3.0 ± 3.7	2.1 ± 1.5	
Nottingham Hospital (n=45)			
Variables	**Before HCL**	**6 months after HCL**	
HbA1c (mmol/mol)	57.8 ± 7.0	52.4 ± 6.2	
TIR (%)	53.4 ± 13.3	64.4 ± 12.3	
Hypoglycaemia (%)	3.7 ± 3.6	2.7 ± 3.6	
Alder Hey Hospital (n=39)			

Variables	Before HCL	6 months after HCL
HbA1c (mmol/mol)	62.2 ± 11.9	54.6 ± 9.0
TIR (%)	47.7 ± 16.7	63.9 ± 11.7
Hypoglycaemia (%)	3.7 ± 4.6	2.0 ± 2.0
Leeds Children Hospital (n=38)		
Variables	**Before HCL**	**6 months after HCL**
HbA1c (mmol/mol)	60.8 ± 9.2	54.5 ± 7.8
TIR (%)	47.4 ± 13.5	68.5 ± 11.5
Hypoglycaemia (%)	3.8 ± 3.0	2.5 ± 1.5
University College London Hospital (n=28)		
Variables	**Before HCL**	**6 months after HCL**
HbA1c (mmol/mol)	63.3 ± 12.5	53.2 ± 9.7
TIR (%)	46.7 ± 12.9	69.3 ± 10.9
Hypoglycaemia (%)	4.2 ± 3.2	2.8 ± 1.9
Oxford Hospital (n=24)		
Variables	**Before HCL**	**6 months after HCL**
HbA1c (mmol/mol)	70.3 ± 12.2	56.9 ± 7.2
TIR (%)	40.1 ± 11.5	60.0 ± 10.9
Hypoglycaemia (%)	2.5 ± 2.4	1.7 ± 1.7
Southamptom Hospital (n=22)		
Variables	**Before HCL**	**6 months after HCL**
HbA1c (mmol/mol)	63.0 ± 10.4	55.6 ± 9.2
TIR (%)	44.6 ± 17.3	56.8 ± 13.5
Hypoglycaemia (%)	3.3 ± 2.6	2.3 ± 1.9
Sheffield Hospital (n=11)		
Variables	**Before HCL**	**6 months after HCL**
HbA1c (mmol/mol)	55.8 ± 7.2	54.4 ± 6.3
TIR (%)	51.7 ± 11.6	63.4 ± 5.7
Hypoglycaemia (%)	5.7 ± 3.7	3.0 ± 1.4

HCL, hybrid closed loop; TIR, time-in-range
Data are shown as mean ± standard deviation

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Hybrid Closed Loop Systems, Insulin Pumps, and Continuous Glucose Monitors for People with Type 1 Diabetes in the NHS: A Rapid Review of Enablers and Barriers affecting adoption of diabetic technologies as part of the NHS England Pilot.

Matthew Robinson, Dr Helena Teague, Sharon de Sa and Caitriona Lacy

Key Points

- Advances in Medical Technology (Med-Tech) continue to improve how people with Type 1 Diabetes (T1D) manage their condition. Greater usage and reduced variation in access of diabetic technologies has long been advocated as a way of easing NHS pressures for clinicians, improving patient outcomes and experience, reducing health inequalities, and delivering benefits for the wider economy.
- In June 2021, NHS England announced funding worth £2 million for a pilot roll-out of hybrid closed-loop technology in order to gain real-world evidence of this novel class of technology. There are three parts to a hybrid closed loop system (HCLs): a continuous glucose monitor which continuously monitors blood glucose readings, an insulin pump which automatically releases insulin into the body, and an algorithm which is a computer programme that reads the blood sugar info and works out how much insulin needs to be released by the insulin pump.
- The pilot was undertaken from June 2021 till June 2022, with 32 number of Trusts taking part across England. In total, 644 adults and 250 children were provided with HCLs as part of the pilot. A clinical audit by the Diabetes Technology Network (DTN) is capturing clinical data on the impact of HCLs on patient outcomes and the analysis will be submitted to the National Institute for Health and Care Excellence (NICE) in June 2022 to support their decision making as part of the Multiple Technology Assessment (GID-TA 10845).
- In addition to the clinical audit, the Innovation, Research and Life Sciences (IRLS) Team at NHS England, which is part of the Accelerated Access Collaborative (AAC), were asked by the Diabetes Team at NHS England to conduct an qualitative review of the pilot, in order to identify enablers and barriers affecting adoption and uptake of HCLs as well as other diabetic technologies in general, i.e. continuous glucose monitors and insulin pumps. This included Trusts who had not taken part in the pilot. This real-world qualitative information will also be submitted to NICE in June to guide the model inputs. The primary aims of the findings is to support the development of a toolkit for Trusts, apply to future programmes of work, inform ongoing adoption and spread strategy development, and better support future working relationships between the NHS and private companies. This toolkit of course will only be distributed if NICE recommends it for wider use.

- This review comprised of a rapid desktop literature review of the identified enablers and barriers to Continuous glucose monitors (CGMs), Insulin Pumps and HCLs. The findings of this research then informed the development of the reviews' research tools. Research was gathered through a combination of: (I) bespoke surveys shared with a combination of patients and clinicians; (ii) semi-structured consultations that were conducted with a purposive sample of key stakeholders, including clinicians, commissioners and manufacturers; and (iii) two focus groups with people who have T1D.

Key Findings

- Nearly all of the healthcare professionals we spoke with were positive about HCLs. Key enablers described included the availability and use of dedicated administrative support, strong communications between Trust staff, commissioners, and manufacturers, and use of DAFNE (Dose Adjustment For Normal Eating) training (and other training) before onboarding onto HCLs.
- Barriers included the capacity, capability and timescales required to train staff members on all the different HCLs, which in some cases meant many Trusts relied heavily on industry support and in some cases resulted in Trusts not offering all of the clinical onboarding and support that were normally provided. Some clinicians expressed frustration that the variety of different products can prove time consuming to master, including the need to log in with different apps and data platforms.
- Manufacturers that ran onboarding themselves described that variation in patient activation was a significant issue. This variation in some cases increased the level of risk a company had to manage which they felt should have been managed before patients were referred to the company for onboarding on the HCLs. Local procurement infrastructure and decisions can also affect adoption of the products. Another barrier raised by manufacturers what the use of local pump lists to exclude devices on national procurement frameworks.
- Digital exclusion remains the highest risk of exacerbating health inequalities, however several other risks were identified, including an existing bias towards white, more socioeconomically active patients who gain access to an insulin pump, a risk against those with poor numerical literacy due to the calculations requires for carbohydrates, and overall younger age groups also face additional barriers in understanding the devices, and require more support from parents, carers and teachers. The onboarding process was also in some places inequitable and inaccessible to some, as for example the need for patients to make specific times and dates also favours those in more flexible and better paid jobs.
- Clinicians should be aware of the prevalence amongst their patients of "DIY Looping" which is the process by which someone with diabetes "hacks" their existing insulin pump with a single-board computer, and consider the implications for the adoption and uptake of endorsed hybrid closed loop systems in this group, should they become recommended across the NHS.
- Concerns were raised about the increasing numbers of patients on HCLs presenting at A&E and the uncertainty of A&E staff knowing how to manage patients on the technology. Policymakers should be aware of this risk and consider firstly how the introduction of HCLs will require existing guidelines on diabetic technologies in inpatient settings to be updated, and secondly how to ensure processes in A&E reflect the best practice outlined in these documents.

The full list of Implications and Recommendations are listed on page 16.

About the Accelerated Access Collaborative

The Accelerated Access Collaborative (AAC) brings together industry, government, regulators, patients and the NHS to remove barriers and accelerate the introduction of ground-breaking new treatments and diagnostics which can transform care. Our ambition is to help make the UK one of the most pro-innovation health systems in the world. We do this by bringing decision-makers from across the health service together with innovators from industry to accelerate impactful and cost-effective products in a way that hasn't happened before. The AAC supports all Types of innovations: medicines, diagnostics, devices, digital products, pathway changes and new workforce models.

Background

Med-Tech has always been and continues to be an important part of how many people with diabetes manage their condition. There are currently dozens of research projects exploring different types of diabetes technologies and the benefits they can have for people with diabetes, all in various stages of clinical testing. Across all areas of illness, patients rightly expect that the NHS will provide emerging, transformational innovations as soon as they become available, and for our health outcomes to keep pace with those of other countries. They also expect adoption of technology will allow more efficient NHS delivery of care and create benefits for the wider economy.

In June 2021, The NHS announced funding worth £2 million for a pilot roll-out of HCLs. This meant that up to 1,000 people who live with T1D in England, who met certain eligibility criteria (Box 1), would be able to access this technology on the NHS. HCLs, sometimes referred to as artificial pancreas technology, have the potential to transform the lives of people with T1D, improving both their quality of life and clinical outcomes. The objective of the pilot was to gain insight into the real-world benefits HCLs offer to patients and the healthcare system. There are three components to HCLs:

- Continuous glucose monitor (CGM): A small sensor that sits under the skin. It continuously sends blood sugar readings to a separate device like a mobile phone or direct to your insulin pump.
- An insulin pump: The pump, which is worn on the body, automatically releases insulin into the body whenever a person needs it based on your blood sugar readings (except for mealtimes when the pump still needs information about carbohydrates amounts in the food consumed). To work as a HCLs, it needs to be able to communicate with a CGM sensor, sometimes called a looping, sensor augmented, or an integrated pump.
- The algorithm: A computer programme that reads the blood sugar info and works out how much insulin is needed. The algorithm can be part of an app on a separate device like a mobile phone or may be part of the insulin pump itself.

Not all types of commercially available continuous glucose monitors and insulin pumps can work together, due to proprietary and interoperability issues. HCL systems are not a cure and requires a significant commitment from patients to excel in their diabetes management.

In less technical terms, a HCLs allows a person's insulin pump to 'talk' to their CGM. It continuously monitors blood glucose levels and calculates the amount of insulin required. Then, it automatically adjusts the background (or basal) insulin based on the blood sugar readings. The doses of insulin the body needs through the day and night to help keep the blood sugar levels stable are released via the pump. Some of these are adjusted automatically in response to the blood sugar levels which are monitored all the time by the CGM.

Box 1: Eligibility Criteria for Pilot

Adult Criteria:
- Have Type 1 Diabetes
- Be using an insulin pump and Freestyle Libre for more than 3 months
- Have a recent (within 3 months) HbA1c blood test that is more than 8.5% (70 mmol/mol)

Paediatric Criteria:
- Age under 19 years with Type 1 Diabetes of more one 1-year duration
- Must not be participating in any current diabetes trials including trials to delay onset of diabetes.
- Eligible for funding for insulin pump therapy as per NICE TA151, or already on a pump but not on HCL
- Willing to complete study requirements' surveys i.e. sleep questions, HFS
- Willing to share their data for trial purposes
- At least 2 HbA1c measures over the previous 1 year prior to HCL
- No other medical conditions that might impact on glucose metabolism or wearing of devices

The NHS England Hybrid Closed Loop Pilot

Following the pilot announcement in June 2021, NHS England and NHS Supply Chain negotiated bespoke arrangements and discounts for CGMs and insulin pumps with several of the companies that supply HCLs. Successful companies were required to develop a programme of support in training and assisting with the 'onboarding' of patients for participating Trusts. NHS Trusts with an interest in taking part were required to submit Expression of Interest to the NHS England Diabetes Programme. 32 Trusts over England took part in the pilot.

NHS England reimbursed £1,500 to each Trust for each eligible patient that were moved on to a HCLs as part of this pilot; this was comprised of £1,200 to cover the additional cost of CGM sensors, and £300 to contribute to implementation and support costs as part of the pilot. Patients already benefitting from a HCLs system did not qualify for this national reimbursement scheme. Trusts were encouraged to take advantage of the discounts by signing and returning the Memorandums of Agreement to NHS Supply Chain or other frameworks that reflected the negotiated discounts.

In total, 644 adults and 250 children have been provided with a HCLs system as part of the real-world pilot of this new technology. A clinical audit conducted by the DTN is capturing clinical data on the impact of HCLs on this cohort of people and the analysis will be submitted to NICE in June help guide the model inputs of the Multiple Technology Assessment.

Approach to this Qualitative Review of the Pilot

In addition to the clinical audit conducted by the DTN, the IRLS Team at NHS England, which is part of the AAC, were asked by the Diabetes Team at NHS England to conduct a qualitative review of the HCLs pilot study, in order to identify **enablers and barriers affecting adoption and uptake of Hybrid Closed Loop Systems and other diabetic technologies in the NHS**. This real-world qualitative data, in the form of this report, will also be submitted to NICE in June to help guide the model inputs they use for the Health Technology Assessment (HTA). The review also considered the enablers and barriers to constituent diabetic technologies, namely continuous glucose monitors and insulin pumps, in Trusts that had not taken part in the pilot.

Aside from the aim of collecting data to inform NICE's decision making, a primary ambition of this report was to create a series of recommendations that will drive the creation of a toolkit that will support roll out across the wider NHS. This will ensure faster patient access, and reduced burden on local systems rolling out the technology. This toolkit, if developed, will only be distributed if NICE recommends the technology for wider use.

The review also aimed to specifically support the commitment by the NHS to support the reduction of health inequalities at both a national and system level, demonstrated through its Core20PLUS5 approach. The approach defined a target population cohort – the most deprived 20% of the national population, plus other groups experiencing poor health access – and identified '5' focus clinical areas requiring accelerated improvement including maternity services, severe mental illness, chronic respiratory disease, early cancer diagnosis and finding hypertension to reduce cardiovascular disease (CVD) and stroke. Therefore, this review and its recommendations also focuses on the reduction of health inequalities.

We also conducted the NHS England Equality and Health Inequalities Assessment.

Methods

A mixed methods approach was chosen, in which interviews, online surveys and focus groups were used to answer review questions. As a study into enablers and barriers, the methodological orientation used to underpin the study were based on phenomenological methods. Our approach to this study has comprised a series of core evidence sources as set out below:

- **Rapid desktop review:** A review of available literature that provided insights into identified enablers and barriers to CGMs, Insulin Pumps and HCLs. This review included a complexity adoption assessment of HCLs, which is based on Professor Greenhalgh NASSS framework for technology adoption in healthcare[1].

[1] Beyond Adoption: A New Framework for Theorizing and Evaluating Non-adoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies https://www.jmir.org/2017/11/e367/

This review informed the generation of a list of themes that informed the development of further research tools (survey and interview question design) and has also informed the structure of the findings in this report.

- **Monitoring data:** Monitoring data from the NHS Diabetes Programme Audit was made available on the uptake of Insulin Pumps by Trusts nationally, as well as some further, more detailed data, for trusts engaged in the HCL Pilot. This data provided information on the proportion of the population with Type 1 diabetes, uptake of insulin pumps, and success in onboarding patients to the HCL Pilot as a proportion of patients that were offered or forecast to have been prescribed. This data was then manually supplemented with nationally available data on populations local demographics (inc. levels of deprivation, proportion of ethnic minorities), level of rurality, membership of Trusts to the Shelford Group, geographic locations etc. This data was analysed to inform shortlist targets for surveys and consultations and study resource was being used effectively. Further detail on this analysis and shortlisting process is included in Appendix A.
- **Survey design and delivery:** Surveys were designed for patients benefitting from diabetes technologies (pilot and non-pilot participants) and clinicians. These were delivered through CitizenSpace, and survey analysis was undertaken and integrated with core monitoring data where relevant. The surveys from the activity ran from 24/05/2022 to 06/06/2022. Data was downloaded into Microsoft Word and Excel.
- **Stakeholder consultations**: A series of virtual stakeholder consultations were undertaken with a purposive sample of key stakeholders, including people with type 1 diabetes, frontline clinicians, commissioners and finance managers, procurement experts, and manufacturers.
- Consultations were semi-structured and a standardised set of interview questions for each interviewee type was used as an interview prompt. All interviews were transcribed verbatim, and anonymised. The interviews were from March to June, 2022. Only participants and interviewers were present.
- **Patient focus groups:** Two virtual patient focus groups with patients on HCLs, either through the pilot or otherwise, to talk about their experience. The focus groups enabled further collection of rich data and an opportunity to build upon findings from the online surveys and interviews. The surveys were held in May, 2022. The focus groups were recorded, and field notes made afterwards. Only participants and interviewers were present.

All participants were made aware of the reasons for this study in written invitations, and verbally at the start of interviews and focus groups. No assumptions or biases were declared or identified in discussions with the interviewers. No repeat interviews were carried out, and transcripts were not returned to participants for comment.

The review themes focussed on the following areas:

- The narrative around the perceived benefits or disadvantages of HCLs and other diabetic technologies
- Barriers and enablers, context and relationships encountered during onboarding and the wider pilot
- Lessons learned including unexpected benefits/dis-benefits, and implications for the generic spread and adoption of innovations.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of information and recommendations developed for this document, we have:

- Given due regard to the need to eliminate discrimination, harassment, and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Results

Our desktop research of the literature reviewed 34 articles and reports and resulted in three separate analyses of the enablers and barriers previously identified for CGM, Insulin Pumps, and HCLs. systems respectively. We conducted 18 interviews with stakeholders across the NHS, which included commissioners, consultants, nurses, and manufacturers. We also conducted two virtual focus groups, facilitated with our PPI lead, with 14 participants.

Due to significant delays in the NHS England publishing approvals process, we were only able to publish our surveys in mid-May with a deadline of 6th June. This, along with limited preparation and use of channels to get the published surveys to clinicians and patients meant that the survey responses were not as wide reaching as we would have liked. Across 8 different surveys we analysed survey responses from 52 participants and 4 clinicians. Of these responses, 4 patients and 2 clinicians were involved in the pilot, The survey results therefore are not significantly representative, but their inclusion aims to support the stakeholder interviews and focus groups.

Due to the limited time-period of the work, the authors do not believe the data had reached saturation, but several major and minor themes were identified.

Perspectives of People with T1D and their Parents.

Adults with T1D on their Experience of using Hybrid-Closed Loop Systems as part of the Pilot

Unfortunately, only two survey responses were received, both white females aged 25-35. In terms of concerns before starting, one respondent stated that they had some concerns about the system making decisions for her and how this would make her feel. She stated that she had anxiety relating to hypos and was concerned whether the system would keep her safe. These concerns were addressed by the education that was provided and helped a lot. Both respondents were satisfied with the process of getting started on HCLs and felt the in-person sessions were helpful. One respondent stated that the regular calls and input from clinical team at the start was helpful. Both respondents were positive about the effect of the technology:

> Respondent 1*: "Completely changed my life around for the better. I don't have to think about my diabetes half as much as I did and I feel much more confident with doing things I may not have done before."*
>
> Respondent 2: *"I feel overall my lifestyle has improved. I get better sleep as I no longer worry about missing a hypo overnight. I feel more able to be more active and still stay in control and generally feel like it has made diabetes a smaller aspect of my life.*

In terms of issues, 1 respondent stated that sensor failures had caused problems but then knowing when to change sensors had helped. The respondent that was previously using a Flash glucose monitor stated that one downside was the amount of calibration that was needed which meant that she had to finger prick which was not required whilst using Flash.

Parents and Children and Young People (13-17) with T1D on their Experience of using Hybrid-Closed Loop Systems as part of the Pilot

Only one person responded to this survey, who said they declined to be part of the HCL pilot. Their reason for doing so was they didn't know enough about HCLs. They would have been more attracted to try the device if they had been offered a shorter trial period rather than a more permanent move away from their previous method of diabetes management. They would also appreciate better management of expectations versus reality of using a HCL.

Parents and Carers of Children (<13) with T1D on their Experience of using Hybrid-Closed Loop Systems as part of the Pilot

Unfortunately, only three parents of children under 13 who were part of the pilot responded to the survey. They described wanting to take part in the pilot as it was an amazing opportunity to develop future technology and had no concerns. All three described benefits of the product for them and their child, with excellent blood glucose results in range and better control. Benefits included improved life due to less anxiety, better sleep, and ability to have the care overseen by the parent when they're not with them. The support they found most useful; was reported by all three as the sessions with the company's representative, and ongoing company support. In terms of suggested improvement for the onboarding process, the parents said they would prefer a group start to enable a buddy system to support each other with new tech, or signposting to peer or group support, as well as more information on troubleshooting and guidance specifically for parents, from the NHS and the company.

Parents and Carers of Children (<13) with T1D on their Experience of using Diabetic Technologies.

There were twenty-five respondents to this survey, with a good geographical spread, and age and gender mix. They were using a variety of existing diabetic technologies, highlighted in the table below.

	Total
They are using a continuous glucose monitor only	9
They are using a flash glucose monitor and an insulin pump	5
They are using a continuous glucose monitor and an insulin pump	9
They are using a hybrid closed loop system	3
Not Answered	0

Continuous Glucose Monitors

Nearly all respondents found that CGMs have improved their child's management of T1D. In general, most highlighted that CGMs have improved their and their child's life. They cited better blood glucose control, reduced anxiety for everyone, improved sleep, and improved a child's confidence and independence. However, some respondents highlighted there were a variety of small issues they had found using CGM.

	Total
There have been no problems	6
It hurts or is difficult to insert the sensor	6
It is uncomfortable to wear their monitor because of the needle	2
It is uncomfortable to wear their monitor because it makes their skin irritated	4
It is hard to find a new place to insert the sensor every time	3
It is hard to use the reader device or app to read their glucose levels	0
It is hard to use the software needed to track their glucose levels for example FreeStyle LibreLink or Dexcom Clarity	0
They don't like how the monitor looks when they wear it	1
The monitor gets in the way or falls off	1
I don't trust the readings the monitor gives	2
The alarms on the monitor are annoying	2
I need to change the sensor for the monitor too often	0
I am more worried about their blood glucose levels because I am more aware of them	3
I have not had enough training in how to use the continuous glucose monitor, app, or software	0
There is not enough support with using the monitor after the first training	1
There is not enough support from other people or families with type 1 diabetes using a continuous glucose monitor	1
Other (please provide details in the text box below)	4
Not Answered	8

A few comments highlighted concerns around the Dexcom performance:

> *"The Dexcom often becomes erratic towards the end of its 10 day cycle."*
> *"There are sometimes large vertical jumps in reading's which we and school have seen...according to Dexcom...these do not happen and have declined to help with an answer."*
> *"The Dexcom can have inaccurate readings and data loss on slim children which is frustrating. The sensor is still quite large and uncomfortable for children which makes them more aware of it."*

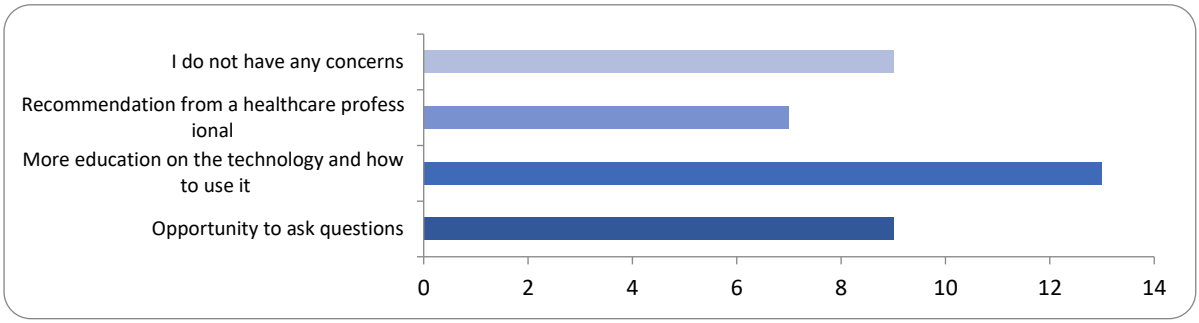
Insulin Pumps

Parents and carers left some free text comments about insulin pumps. Some of the benefits include greater control, less injections, less intrusive, easier to adjust insulin pumps. Participation in sports and exercise were seen as a

particular game changing benefit. Making it easier to eat a snack was a benefit for children. Some parents thought it would be complicated to use and found that it was better than expected.

Approach to Hybrid Closed Loop

The respondents showed a mix amount of awareness of HCLs before completing the survey, but were interested in the technology, with some potential concerns that could be rectified in the following areas.



In free comments, respondents said they would like more information around how the device is used, full details of success rates, support and training offered, and any implications and issues that could hinder it working currently. Some were interested in the research about it, and others would be keen to hear about patient testimonials.

Adults not part of the Pilot provided Insight about their Experience of Diabetic Technologies in General

Thirty-five adults (43% Male, 57% female) responded to the survey from centres across the UK to tell us about their experience of using diabetic technologies. In general, all respondents found that use of CGM has increased the overall quality of life as well overall diabetes management due to both physical and psychological benefits. Of those that used an insulin pump, the benefits cited included more control of their diabetes, more freedom and freedom of food choice and benefits that come with not pricking finger.

A majority said they would be keen to try HCLs but said they would like more education on the technology and how to use it, as well as the opportunity to ask questions, and more understanding of pro's and con's.

Focus Groups provided Additional Insight about their Experience of HCLs

We received a variety of insight from our focus groups. Firstly, in terms of awareness of HCLs and other diabetic technologies, younger participants highlighted that social media/Twitter was for them the key channel they use to gain knowledge about new technologies and about the HCL pilot. One participant that they had found peer support on Twitter that they had never had in real life. By contrast, several participants told us that having a motivated and engaged member of their clinical care team, which was usually their DSN, was how they found out about new innovations and was the reason they were invited to be part of the pilot. Some participants expressed frustration at what they perceived to be a lack of a pro-innovation ethos by their clinical team, relating they had never been proactively told in clinics about new technologies.

On the HCLs, the overall consensus by participants was that HCLs had made a significant difference to the management of their glucose levels, with several saying it had been better than any other device they had tried. For example, one participant described having for the first-time overnight blood glucose levels which were in range, which allowed them to have freedoms which were previously restricted, such as having a snack.

"As well as better blood sugars, it has done wonders for my emotional wellbeing, and there's been so much mental bandwidth freed up" – Focus Group Participant.

The onboarding processes the participants had experienced were generally well received. Many had had virtual onboarding and found the company and clinical staff were excellent, with the follow-up calls by companies helpful. - Participants reflected that choice is still important, and some people would benefit from in person, especially if a clinician has to physically touch someone's body, but that many valued the time-saving benefits of virtual onboarding. One participant had an in-person onboarding session, and said it helped with the sense of community wellbeing. - One of the challenges identified with the Medtronic virtual clinic was the difficulty of uploading results so clinicians could see them, as the Medtronic app does not work with every phone, including recently released models.

Several improvements were suggested to improve the onboarding and experience. Some felt that counselling could have been helpful. One described a 'honeymoon phase' followed by a difficult period where you have to adjust to a

situation where you are less directly managing your diabetes and feel like you are giving up control to the device. Learning to trust the HCL takes some adjustment, and some participants described they were in the early days trying to overcompensate.

"If I'm not completely comfortable going to sleep, I have to tell myself, let the pump do its job." – Focus Group Participant.

Some participants found that they had to relearn skills, especially around "carb counting," with participants saying that they had to become stricter and more aware about the nutritional mix of food. One option suggested was option of 'refresher' DAFNE training. Others had issues with keeping the sensors stuck on the body.

One of the largest frustrations, for those on the Medtronic system, was the need to recharge the device every week. The cleaning associated with this was a particular frustration. Participants on the Medtronic system expressed surprise that the t:slim device lasts for several months before a new battery was required and may be a deciding factor in patient choice.

Finally, in a discussion on health inequalities, the participants were aware that they were a generally more digitally and health literate group, and worried that those less aware would be less likely to advocate for themselves, and therefore gain access to new technologies. They also expressed views that they thought there was a risk that older people may not be offered the technology as they might be perceived as less digitally capable. One participant said she was aware of inequality of access for those from minority ethnic backgrounds. Finally, some expressed concerns around inequality of access for those who were trying hard to manage their diabetes, and therefore had glucose levels that were 'too good' for the technology.

A Variety of Methods were Used for Onboarding Patients.

The methods by which Med-Tech products are presented to patients can affect adoption rates, and in the pilot Trusts and manufacturers used several different methods to onboard patients. Trusts identified eligible patients on their patient lists and wrote out to them, inviting them to be part of the pilot. To support and increase participation, some offered 'Pump Demo' days, which were in groups and facilitated peer support, which acted as an enabling function. Participants were reported to find them useful and clinicians said this helped increase participation. Some Trusts offered individually tailored 1-1 education for patients who choose to use a HCLs. Several companies and Trusts offered virtual online clinics to explain the pilot.

The choice and flexibility of methods used to onboard patients can be a key enabler in encouraging participation in the pilot and familiarity with the technology. Methods that afford flexibility, such as virtual engagement, and ones that facilitate peer support were cited as particularly useful methods. However, use of these methods should consider the impact on those at risk of being digitally excluded.

Perspectives of Healthcare Professionals

Healthcare Professionals keep Abreast of Novel Diabetes Technologies using a Variety of Sources.

Awareness of novel technologies by patients and clinicians can be a significant barrier to the adoption and spread of innovations. Unsurprisingly, healthcare professionals keep abreast of novel diabetes technologies through a variety of sources, with patients themselves identified as a key avenue. In some cases, clinicians advised that patients are better informed than healthcare professionals about certain technologies. Many clinicians described that they had several highly engaged patients who follow technology developments both in the UK and abroad and are keen to drive NHS access to these novel technologies. Clinicians also identified that they receive updates from Med-Tech Supplier representatives, by going to relevant meetings and conferences, following developments online, and finally through press releases and social media/Twitter. Many also said that the DTN was a key source for them to keep up to date with novel technologies.

There is a risk that higher socioeconomic groups are more likely to be more aware of the latest technologies and ask for the latest and best forms of care, therefore driving greater inequalities in care. The JDRF Pathway to Choice Report, a joint partnership programme building awareness of, and access to Type 1 technology choices between JDRF and industry partners (Abbott Diabetes Care, Dexcom, Insulet International Ltd and Roche Diabetes Care Ltd), highlighted that while 18% of people from lower socio-economic groups discussed technology treatments with healthcare professionals, this contrasted with 46% of those from higher socio-economic backgrounds. Healthcare staff should be conscious of this risk when delivering a service.

Healthcare Professionals felt that HCLs had improved Diabetes Management for the Majority of their Patients.

Nearly all of the healthcare professionals we spoke with were positive about HCLs, with several saying that most people who have managed to use them have had the best glucose control that they have had in their lives, including those who have had consistently high glucose levels for many years. The patients were typically considered harder to treat. Clinicians related stories of patients describing HCLs as a tool to allow them to have more headspace and get on with 'normal life.'

Respondent 2: *"They reduce the burden on people living with diabetes and support them to achieve glucose levels which are often not possible or sustainable with pump alone. The improvements and experiences witnessed during the pilot bring you to tears".*

A few clinicians noted that some patients had expressed frustration around eligibility criteria for the pilot. Therefore, patients who had worked very hard to lower their HBA1C levels were ineligible for the pilot, while those who were (perceived to be) less focused and with poorer control being eligible. Policymakers, commissioners, and clinicians should reflect on how to best provide equitable access to novel technologies in a cost-effective manner. NICE could consider this impact in its report, or NHS England could consider how to proactively address this in a toolkit.

Healthcare Professionals Identified Several Enablers that supported Adoption of HCLs by Patients.

One of the most significant and commonly cited enablers for easier access and uptake of HCLs identified in the pilot highlighted by several Trusts was the availability and use of dedicated administrative support. The administrative support staff had responsibilities that included sending out letters to patients, handling ordering issues, ordering supplies, and troubleshooting emails from patients (e.g. issues with delivery, pumps out of warranty etc). Without administrative support, several staff said this would likely be done instead by a diabetes specialist nurse (DSN), impacting on their clinical care time. Some Trusts cautioned that warranty admin can be substantial for insulin pumps. Outside of the pilot, administrators in some Trusts were responsible and essential for reapplying to CCGs for funding and proving patient eligibility when pumps required renewal, which is every four years.

Unsurprisingly strong communications between Trust staff, commissioners, and manufacturers was also described as a key enabler, especially through the use of regular multidisciplinary meetings. In one Trust, clinicians found that having weekly open invitation meetings for staff at Trusts involved in the pilot were very helpful for troubleshooting around problems identified.

Some Trusts highlighted that DAFNE (Dose Adjustment For Normal Eating), which is an educational course for managing T1D by helping give diabetic patients the necessary skills to administer the right amount of insulin for the amount of carbohydrate you choose to eat, was also a key enabler in success on HCLs. Not all diabetic centres offer DAFNE courses, although any diabetes specialist team looking after people with T1D can train to become a DAFNE centre. Patients can discuss with their GP the possibility of transferring their diabetes care to a neighbouring centre where DAFNE is offered. However, DAFNE is a 5-day training course, with a follow-up 8 weeks after the course finishes, and there is a risk that the commitment risks excluding marginalised groups. Their website reports that local DAFNE team can provide people with a letter for their employer explaining why they should be given paid time off work (as a health-related absence), but people in less secure and low paid employment may be more hesitant to ask for paid time off work, or have that option not available to them. A recent TUC poll reported 67% of insecure workers said they receive nothing when off sick compared with 7% of secure workers who reported receiving nothing when off sick.[2]

Remote DAFNE courses are available, which has been created for people with T1D who feel that a face-to-face DAFNE course is not for them and in response to changes in diabetes services as a result of the Covid 19 requirement for shielding and social distancing. The Remote DAFNE course takes 5 weeks to complete and includes online learning from home each week and weekly group video support calls with up to three other participants and a trained Remote DAFNE educator. Policymakers should consider the current availability of remote DAFNE courses, and their potential impact in reducing health inequalities.

Healthcare Professionals Identified Several Barriers for Patients on HCLs Systems.

Clinicians identified several barriers that were experienced by their patients, with commonly cited barriers focusing around patient behaviour and preference. The requirement of finger pricking was one example, with one system in particularl requiring it frequently. Lots of patients are reported to be uncomfortable doing this and had got used to not doing it as frequently on Freestyle Libre. Patients also relayed that, in some cases, they found the alarms hard to deal with.

[2] https://www.tuc.org.uk/research-analysis/reports/covid-19-and-insecure-work

Patients also found themselves uncomfortable spending time with basal levels that are lower than what they were used to, at around 4-5% (which are set by the HCLs devices) and said they associated the levels with being on the way to a 'hypo'. This issue led to over-adjusting or over-eating to compensate when it was not required, and in some cases did lead to some people withdrawing from the pilot scheme. There were also some admissions for diabetic ketoacidosis. Some patients found the need to calibrate the HCLs frustrating. Some clinicians found that patients had to unlearn 'bad habits' in their insulin pump care and retrain to develop new HCLs specific habits.

Managing patient expectations was also cited by many clinicians as a barrier, which was also echoed by manufacturers. Clinician's stressed that although it is a great step forward, HCLs systems are not a cure, and requires a significant commitment from patients to excel in their diabetes management.

In some cases, one of the barriers was patients not attending appointments – *"If offered a place on the pilot but they don't respond and don't attend (or answer the phone) for clinic appointments then we are unable to offer and get them started on closed loop."*

One of the clinician's in the survey felt that insufficient training in using the device was a barrier to uptake. The other respondent stated *"Those who did not take up the opportunity didn't appreciate the potential benefits. Some didn't come to clinic so missed the opportunity to discuss in more detail."*

Barriers Identified for Healthcare Professionals

The capacity, capability and timescales required to train staff members on all the HCLs was described as a significant challenge by many clinicians. This was especially pertinent for novel technologies in the Trust. Clinicians highlighted that the onboarding effort is front-loaded. For example, one clinician described a typical patient journey in their Trust for onboarding requires a:

- Device Choice Meeting – to choose the HCLs Device
- CGM Onboarding Meeting
- New Insulin Pump Start Meeting (if required)
- Period of using CGM and an Insulin Pump Independently
- Meeting to set up the Hybrid Closed Loop System
- 0.5/1/2/4/8-week follow up meetings.

Many Trusts relied heavily on industry support due to the high number on onboardings. The short timescales in some cases meant that not all clinical onboarding and support that were normally provided in some Trusts were offered, for example more intense psychological support. Clinicians reported that in some cases, this reduction in support offered led to negative clinical implications for some patients (i.e. diabetes ketoacidosis). To compound this issue, in some cases patients were onboarded by clinicians who were not their usual clinicians, and therefore were less likely to know their background. In some cases, this led to some onboarding problems as existing issues/complications weren't known or addressed. Healthcare professionals and clinicians should consider how to achieve continuity of care with differing levels of device expertise amongst staff members, by either producing supporting guidance or through development of a knowledge sharing network to enable all staff members to support on all types of HCLs available.

"We were one of the largest centres in the pilot and if HCL is more widely recommended we will be in a strong position to deliver as we already have the expertise in house. The main challenge we will face is having enough staffing to deliver. The pilot was easy because the people included were already on pump. Getting people started on the pump is the most labour-intensive part and this will be difficult to deliver at scale on current staffing."

Some Trusts also highlighted that they did not want to neglect other patients due to the pilot, and said that resources must be fairly prioritised in doing what is right for the whole population seen at clinics, i.e. the very young, vulnerable cases, and people with Type 2 Diabetes with complex needs. Many Trusts highlighted that they were dealing with a large COVID-19 induced backlog of patients who are using out-of-warranty pumps, with the risk that if they break, they will need to go back onto injections. This meant balancing resource to ensure people were onboarded onto the pilot, against those who just needed insulin pump renewal.

Some healthcare Trusts expressed frustration that the variety of different products can take a lot of time to master and learn about in order to provide expert support. In particular, issues that came up included the need to change different sensors after different lengths of times and logging in with different apps and data platforms. Clinicians also said that to keep staff happy, they staff often had to spend a significant amount of time on small alternations to the technology, which they often consider to be unnecessary.

Presentation at A&E

Some clinicians told us that there have been cases when patients on HCLs had presented at A&E and the staff were unsure how to manage the patient.

"A patient on a HCL arrived at A&E unconscious, and so a member of the A&E ward staff rang the Diabetes Department for advice as they were unsure what to do. The person who answered was not trained on that specific technology and had to ring the appropriate staff member at home for advice."

The growing impact of managing patients with insulin pumps, CGMs, and HCLs in the hospital, either at A&E or in elective care, has already led the creation of committees to consider the issue and produce recommendations. In the US, in April 2020, the "Continuous Glucose Monitors and Automated Insulin Dosing Systems in the Hospital Consensus Guideline Panel" convened and met virtually to develop recommendations and guidelines. The consensus recommendations are published here, Continuous Glucose Monitors and Automated Insulin Dosing Systems in the Hospital Consensus Guideline. In the UK, the 'Joint British Diabetes Societies - Inpatient Care Group' (JBDS-IP) updated their 'Self-Management of Diabetes In Hospital in August 2021. The guiding principle of the document is that people with diabetes should manage their condition on a day to day basis when out of hospital and therefore should continue to self-manage during a hospital admission unless there is a specific reason why they cannot.

Policymakers should be aware of this risk around A&E and inpatient attendance and consider firstly how the introduction of HCLs will require these guidelines to be updated, and secondly how to ensure processes in A&E reflect the best practice outlined in these documents. Manufacturers could support this issue by providing specific advice for their systems for these scenarios which are easily available from their websites.

The Impact of 'DIY Looping' – DIY Hybrid Closed Loop Systems.

DIY Looping is the process by which someone with diabetes "hacks" their existing insulin pump with a single-board computer. *"Looping is part of the larger Open Artificial Pancreas System (OpenAPS) movement where advocates in the diabetes community are developing opensource platforms, code, and apps to essentially reserve-engineer existing durable medical equipment (like older insulin pumps) to help people living with diabetes achieve better health outcomes when FDA-approved devices have proven inadequate."*

A few clinicians told us that several of their patients were doing DIY Looping and have either self-funded their CGM or insulin pump, or both. These patients tend to be more technologically savvy. Clinicians described to us how user groups self-regulate by controlling access to the software and releasing the software to users in a controlled fashion. Users have to produce evidence they are successfully using the initial "slice" of software before getting access to next 'slice'. There are six steps, or slices with ascending functionality. The patients that engage in this practice have a large community and a lot of peer support, with the role of a clinician often to 'quality check' the outputs and provide further support to then.

Clinicians should be aware which of their patients are DIY Looping and consider the implications for the adoption and uptake of endorsed HCLs, should they become recommended across the NHS.

Perspectives of Manufacturers

Manufacturers Perspectives – Enablers

Several of the manufacturers involved in the pilot also shared with us their perspectives. The greatest enabler for adoption identified by manufacturers was having a Trust with enthusiastic teams who have the interest and capacity to try new things and do the best for their patients. They also identified patient demand as an increasingly powerful enabler, especially with more routine use of social media, with both companies and NHS Trusts disclosing they were often approached by patients who asked to be part of the trial. The publication and news of the pilot in the national press also helped increase interest in the trial and the technology. In terms of enabling wider access to the technology, some companies have been conducting online HCLs onboarding in different languages, which is helping access in underserved populations.

Manufacturers Perspectives – Barriers

Several barriers were identified from the manufacturers. One of the inevitable barriers in access is that some centres were more familiar with one type of technology, which either meant clinicians favoured the incumbent technology, or struggled to master the new technology.

There was variation in how centres prefer patients to be onboarded onto the technology. Some NHS Trusts take a very active role in onboarding and managing patients themselves, others prefer the company themselves does the

onboarding. There did not seem to be a strong consensus on the best approach, but this variation has an impact on the capacity and timescales for onboarding patients.

Companies that ran onboarding themselves described that variation in patient activation was a significant issue (we define patient activation as a measure of a person's skills, confidence, and knowledge to manage their own health). Some companies expressed concerns about large knowledge gaps in patients; in some cases, patients thought they were just going for a pump upgrade. This variation increased the level of risk a company had to manage. In one case a company representative had to work through a significant fear of hypoglycaemia with a patient, which they felt should have been managed by a clinician before being referred to the company for onboarding. Manufacturers reflected that it might have been better for patients to get used to the constituent components of the HCLs sequentially, rather than all at once.

Any toolkit developed to support the rollout of HCLs should address these barriers by suggesting a suite of options by which Trusts could onboard patients. Manufacturers could also have clear options for onboarding, and include collaborative methods.

Perspective of a company yet to launch their HCL

We were contacted by an insulin pump manufacturer proactively who had heard about our study and who have FDA approval for their product to act as a HCL with the Dexcom 6 in the USA, but they have not yet launched in the UK. We felt it was useful to understand their perspective's and existing experience of working with the NHS. In terms of barriers faced, they cited an ageing and reducing workforce with high turnover, resulting in a limited insulin pump service across the NHS. They also believed that clinician's often use cost as an excuse not to engage with the manufacturer and as a company struggle to engage with the right commissioners. In terms of enablers, their offer of virtual or in person training for staff and patients was reported to be well received.

Their ideas for improvement included more awareness and transparency on who the right people were to engage with on their products, understand commissioning objectives, and ensuring that patient make an informed choice about the type of technology that works best for them.

Health Inequalities

Digital Exclusion is still the Greatest Health Inequality Risk

Digital exclusion was identified throughout the review as highest health inequality, and companies and Trusts were at a loss at how to mitigate this. Patients must have skills, access, and confidence/trust in ability to use digitally enabled technology (including smartphone app/digital tools), all of which are at risk for older populations. Wider rollout of technology may increase the inequality access gap due to digital exclusion. Manufacturers noted that from a market access perspective, digital exclusion also reduces awareness of product and therefore patient demand for novel technology. There is currently no national plan for addressing digital exclusion, however a recent Briefing Paper on Digital Exclusions and Health Inequalities by the Good Things Foundation, supported by the Health Foundation, outlines policy and practical responses we have seen and future proposals. Policymakers should consider these resources in addressing the digital exclusion risk of HCLs, and the development of a toolkit could have one focus on mitigating digital exclusion.

Respondent 2 of HCL Clinical Survey *: "This cannot be used to move everything virtual. We need to be cognisant of widening the divide between those who can access health remotely (either due to costs or internet/devices or technical ability) and establish a model of care which takes the technology to those who most need it"*

Several other risks of exacerbation of health inequalities were identified. The eligibility criteria for the pilot required patients to already be on an insulin pump. There is already an existing bias towards white, more socioeconomically active patients who gain access to an insulin pump, especially in regard to large racial-ethnic disparities in diabetes technology (especially insulin pump) use, with lower uptake in those from Black and Asian background with drivers unknown beyond socio-economic status[3]. Some participants expressed the view that there is a clinical mindset that patients have to be 'worthy' of an insulin pump through optimal care, and by passing a lot of training and learning lots of information.

The onboarding process was also in some places inequitable and inaccessible to some. The letter inviting people to be part of the pilot relied on those who can read English. The need for patients to make specific times and dates also

[3] Agarwal et al., 2021.. Racial-ethnic disparities in diabetes technology use among young adults with Type I Diabetes. *Diabetes Technol. Ther*

favours those in more flexible and better paid jobs. In some cases, training procedures, such as DAFNE training previously highlighted, required time off work. For people who are less socioeconomically active or in insecure employment, this can be a significant hurdle. Some Trusts admitted in some cases they were more relaxed about the training guidelines but noted there were safety implications of people starting on diabetic technologies with minimal training. Some clinicians expressed frustration that those will benefit the most from online or in person training are the ones who are the least likely to do it.

Some cultural barriers to access to the technology were identified, with some people not wanting to tell their families that they have diabetes. Fasting during Ramadan dramatically affects management of diabetes for those observing, with increased risk for severe hypoglycaemia, hyperglycaemia, and higher glycaemic variability. Fasting during Ramadan may also affect their decision to use the technology during that period, however this was not considered as part of this review. Evidence in this area is developing, and Diabetes UK have a section of their website that specifically covers Ramadan and Diabetes and have already done some engagement with the Muslim community. A small trial recently demonstrated automated insulin dosing systems showed a safe and effective management strategy to support prolonged and consecutive fasting.[4] Policymakers should consider the impact of fasting during Ramadan during onboarding, improving population outcomes, and in reducing health inequalities.

A risk against those with poor numerical literacy, due to the calculations requires for carbohydrates and other measures, was also identified. Younger age groups also face additional barriers in understanding the devices, and require more support from parents, carers, and teachers. Teachers were specifically cited as a group where support resources and guidance for HCLs could be developed further.

Healthcare Professionals Highlighted Specific Cases of HCLs Reducing Health Inequalities

Respondents were able to tell us of specific cases of successfully onboarding patients with additional considerations onto HCLs, including people with learning disabilities, people who were blind, and in one person who had Down's Syndrome. It would be helpful to create case studies to celebrate and share this reduction in health inequalities to spread best practice.

Certain Groups who face More Pronounced Health Inequalities face Greater Barriers to Access.

Some groups of people, such as homeless people, people in the criminal justice system, and people with substance misuse issues were hypothesised as part of the review's Equality and Health Impact Assessment to face greater barriers in access to technologies for diabetes management. It was beyond the scope of the work to reach out to these groups due to the time sensitive nature of the work and remains a limitation in our report and as a key area for the NHS to consider conducting research on access. Reasons for increased barriers in these groups include regulations around use of required needles for finger pricking etc in prisons, the need use of technologies that require access to digital technologies (digital reader or app only available on certain smartphones) which need a phone and/or to be able to charge phone/reader to utilise, and that people with addictions are less likely to engage with or utilise the technology. Policymakers should work with Health and Justice and other relevant teams to consider the adoption of novel diabetic technologies in these groups. Diabetes UK have some resources to support diabetes management in prison.

Respondents had innovative ideas to reduce health inequalities.

In terms of reducing health inequalities, a clear theme emerged of the need for clinicians to be aware of the risk of exacerbating health inequalities, and not inadvertently discriminating against those who can't advocate for themselves in terms of technology. One Trust mentioned they were doing an audit of their Type 1 population evaluating protected characteristic and socioeconomic data (by postcode proxy) versus access to diabetic technologies. We recommend all Trusts should consider a similar approach. It was also stressed that care provision should be as holistically as possible, through the inclusion of psychologists, safeguarding, and youth workers.

Structural Barriers

Local Procurement Infrastructure affects Adoption and Uptake

Local procurement infrastructure and decisions can affect adoption of the products. In terms of supply, one manufacturer expressed confusion that although their product was on an NHS Supply Chain National Tender, in which every Trust can join and order through, only around 30-40% are leveraging the opportunity, and are therefore paying more by doing so. They reported that Trusts seem to have no urgency to join.

[4] https://eprints.ncl.ac.uk/file_store/production/279149/340D002F-E7D8-4EBF-85CA-8B62F2B27DC5.pdf

Another barrier raised by manufacturers was the use of local pump lists. One manufacturer expressed frustration that despite already being on a national tender, each ICS have their own preferred pump list. Before the pilot, commissioners of one CCG said they could not procure that manufacturers device as it was not on the CCGs pump list and not on Bluteq, despite being on a national tender. This took close to a year to resolve.

Some stakeholders raised concern that in many cases the money does not follow patients who move to other centres to gain access to technology in a smooth manner. They hoped that with the move to Integrated Care Systems (ICSs), there will be more scope for patients to be able to go to the place that offers the system they want within an ICS with the money flowing more easily.

Data Systems and Interoperability

The systems by which manufacturers allow patients and clinicians to see data can be both an enabler and a barrier. Some clinicians found the web-based viewing platforms useful and clear, however clinician's expressed frustration at the sheer number of different apps/data platforms/logins required for all of the different systems that patients are using.

In some Trusts, NHS servers have been known to block a manufacturers site. In one example, it has taken a year to unblock. Incompatibility with Diasend, the software which allows diabetes data to be submitted to the data audit, is an issue with some devices. Some Trusts have used this incompatibility as a barrier not to engage with certain technology. Manufacturers should ensure their HCLs are compatible with Diasend.

Due to time constraints we were unable to ascertain which companies HCLs have passed, or would pass, the Digital Technology Assessment Criteria for health and social care (DTAC), which gives staff, patients and citizens confidence that the digital health tools they use meet the NHS's clinical safety, data protection, technical security, interoperability and usability and accessibility standards. The DTAC was developed by NHSX. HCLs would be eligible, DTAC criteria is linked to the definition of a Health IT System as defined in DCB0129 and DCB0160 and being a product used to provide electronic information for health or social care purposes where the product may include hardware, software, or a combination of both. As a recommendation, a central NHS England team should work with all the HCL manufacturers to ensure they are compliant with DTAC, and support Trusts to do their DTAC assessments as easily as possible using nationally organised material.

Relationship with Commissioners

Trusts expressed the view that having a good relationship with their local commissioners were key to stronger adoption and usage. One clinician said that having a strong relationship not only with their local CCG, but in neighbourhood CCGs where patients would come from was an enabler. We spoke to fewer commissioners than we would have liked. The enablers for technology adoption cited by commissioners included ensuring their Local Diabetes Board, which ensured plans for the technology was included in their wider programme plan, and clinician enthusiasm for the technology. Barriers at a commissioner level for new technologies included funding, often the requirement for a pilot, and competing priorities. Capacity for adoption in primary and secondary care was also discussed. The views of commissioners remains a weakness of this report.

Implications and Recommendations.

Based on the findings from the surveys, interviews, and focus groups, there are a number of emerging recommendations for NHS England, local commissioners, and others working to improve access and uptake of HCLs and other diabetic technology by enhancing enablers and reducing barriers. Some of these recommendations are shorter term while others may require further system changes or for groundwork to be laid.

Recommendations for NHS England

Development of a Toolkit to Support Trusts. A secondary ambition of this report was to create a series of recommendations that will drive the creation of a toolkit that will support roll out across the wider NHS. The first recommendation is that such as toolkit should be made, to support local Trusts to offer HCLs to patients more easily by simplifying the offer and ensuring that learning from this review and the DTN clinical audit is put to use. Technical information for all of the different suppliers, including FAQs and troubleshooting guides, should be centrally provided for ease of access.

Workforce Planning. A key theme throughout the discussions was the importance of workforce as either a key enabler or barrier to success. Therefore, NHS England needs workforce planning to ensure that Trusts have the appropriate roles where staff have had required training on multiple devices. Each unit should is likely to need a full time "technician" to help in onboarding to HCL. The necessary adjuvant support by staff, including administrative roles and psychological support will also be required.

Funding. NHS England should be conscious that notwithstanding a positive TA recommendation by NICE, there may be additional and better received opportunities to ensure people with T1D have access to HCLs without the risk of funding losses for other people's care. Therefore, a key focus for NHS England should include a strategy for national negotiations with companies to increase the value for the NHS, based on the Freestyle Libre experience. The use of additional levers, such as "Pathway Transformation Funding" for non-recurrent costs could also be explored.

Education. There is a clear need for better assurance that patients are educated around HCLs and how they work, and in particular their limitations. It would help to produce a national training webinar for patients, which is an accredited and safe resource that healthcare professionals can refer patients to for free, which will free up time to support more complex patients. This would include issues such as dealing with the expectation that they would spend more time in basal glucose levels that are lower than what they are used to. A reference and link to this webinar would be included in the toolkit. However, a lack of access to education should never act as barrier to accessing diabetic devices and should be desirable for better results but not mandatory.

Educational Programme and DAFNE Training. Policymakers should consider the added value of centralised, accredited Dose Adjustment For Normal Eating (DAFNE) training, which can be carried out in the evenings and weekends. This will help address health inequalities for those unable to take time off work and reduce burden on centres. Again however, it should be made clear there are other programmes available, and that training should not act as a barrier to access.

DTAC. The Digital Technology Assessment Criteria for health and social care (DTAC), which gives staff, patients and citizens confidence that the digital health tools they use meet the NHS's clinical safety, data protection, technical security, interoperability and usability and accessibility standards. A central NHS England team should work with all the HCLs manufacturers to ensure they are compliant with DTAC, and support Trusts to do their DTAC assessments as easily as possible using nationally organised material available in the toolkit. Furthermore, NHS Digital should work with all Trusts to ensure their IT systems are compatible with all HCLs websites and systems.

A&E Attendance. The toolkit should make Trusts aware of this risk around A&E and inpatient attendance. NHS England should consider how the introduction of HCLs will require existing national guidelines to be updated. Secondly the toolkit should provide advice on how to ensure processes in A&E reflect the best practice outlined in these documents.

Reducing Health Inequalities. NHS England should take learning from the Briefing Paper on Digital Exclusions and Health Inequalities by the Good Things Foundation, and other resources, to develop policy and practical responses to in address the digital exclusion risk of HCLs. As part of the toolkit, NHS England should create case studies to celebrate and share reductions in health inequalities to spread best practice. Further research and engagement is needed on the impact of fasting during Ramadan and the process onboarding and access to HCLs.

Concerns about the Pilot Scheme. Some clinicians expressed concerns about the conduct of the pilot, clinical audit, and impact on the NICE review, highlighting that the question asked should be around whether the use of HCLs has been a success, not how much of a success it has been. Some clinicians expressed the belief and concern that the

pilot had not been properly controlled, adverse events were not being properly reported, and there were limited record of disasters that have been averted with care interventions. This was not a strong theme however. Without this information they expressed concern that as a system we will not learn how to deliver the technology properly and safely. There was also concern expressed by the review run by DTN, who have a stronger incentive to prove that the technologies work. NHS England should proactively address these concerns in proactive communications about the pilot to improve trust.

DIY Looping. NHS England should conduct research into DIY Looping, specifically focusing on any transition issues from patients who are DIY Looping onto endorsed HCLs, should they become recommended across the NHS.

Procurement. NHS England should audit local commissioners pump lists and highlight variation.

Recommendations for NICE

Eligibility. NICE could consider as part of its HTA, the role of occupation as part of the criteria for eligibility, specifically for those in occupations in which regular finger-pricking is unacceptable, e.g. chefs or scientists. There is a risk of an untended consequence of patients who have worked hard to lower their glucose levels and therefore potentially not eligible will deliberately not manage their diabetes as well to become eligible.

Staffing. NICE could consider how many healthcare professionals should be trained on a device to care for a certain cohort of their patient population and the requirement for dedicated roles to support adoption of HCL. In addition, NICE could consider the cost-effectiveness of employing additional administrative staff to support onboarding and ongoing delivery of care.

Recommendations for NHS Trusts

Administrative Staff. Trusts planning to increase insulin pump or HCL usage amongst their population should invest in dedicated administrative roles, with specific roles and responsibilities around diabetic technology management. A toolkit supplied by NHS England could support with draft job applications.

Clinical Team are Trained on all HCLs Offered. Clinics need to have capacity to manage different devices. Smaller Trusts should weigh up the advantages and disadvantages of offering only one technology, to reduce training workload. Such consideration should accommodate patient choice. Trusts and commissioners should consider how best to share learning through regional networks between larger more experienced Trusts and small centres.

Offer flexible Onboarding Processes. Trusts should consider whether to triage onboarding on HCLs systems between a fast-track route, for highlight activated patients who are doing well on an insulin pump, and a more comprehensive route for patients who struggle more and require more behavioural and psychological support. Trusts should also consider how best to work with manufacturers for onboarding processes, as this will have an impact on capacity and timescales. Trusts should also offer onboarding in different languages, which could help access in underserved populations.

Reducing Health Inequalities. Trusts should audit their patient list to identify if usage of diabetic technologies adversely affects any protected group, specifically focusing on people from a black or minority ethnic background, sexual orientation and trans status, and age. Trusts should also try and ascertain whether there is any bias on socioeconomic status if the information is available. Postcodes can be used as a proxy measure. Draft material should be included in the toolkit, as well as draft EHIAs. This should be done for other diabetic technologies, especially insulin pump users.

Procurement. Trusts should review if HCL and other diabetic technologies they order are on NHS Supply Chain and if they are ordering through NHS Supply Chain or a more expensive procurement option. If on a more expensive option, they should move to ordering through NHS Supply Chain.

Recommendations for Manufacturers

Increasing Capacity. All manufacturers should offer 'Train the Trainer' schemes, which enables more people to onboard patients onto the technology.

Education and Support. Manufacturers should produce information that is specifically aimed at teachers caring for children using hybrid closed loop systems. Manufacturers should have available a 24-hour consultant for patients and clinicians to call.

A&E Attendance. Manufacturers could develop resources support this issue by providing specific advice for their systems for these scenarios which are easily available from their websites.

Strengths and Limitations

Strengths

This review has employed a mixed method approach to triangulate findings from quantitative and qualitative research activities. A key advantage of this approach is both analysis of known factors and exploration of unidentified factors can be achieved in the same study, offsetting common disadvantages encountered if quantitative and qualitative methods were used independently. Our analysis includes data from 27 Trusts which were broadly representative of Trusts in England with some exceptions, notably slightly larger proportions of registered patients with white ethnicity and located in more urban areas.

Limitations

As a rapid review, our qualitative research may have excluded people based on digital only methods. We did consider methods such as surveys distributed to diabetes centres in paper form, however the time and capacity limitations prevented us from doing so. The surveys were delivered in English and written in clear accessible language and tested with patient partners, however there is potential adverse effect of no inclusion of those with non-English first language in data collection. The fact that respondents were self-selecting also poses the risk of selection bias: i.e. those with strong positive or negative opinions may have been more likely to respond. The small sample size of respondents for the survey precluded any assessment of statistical significance. As a result, the reported findings illustrate trends.

Acknowledgements

This review was conducted by members of the NHS England Innovation, Research and Life Sciences team. They were Matthew Robinson (m), Senior Policy Manager (MSci), Dr Helena Teague (f), Policy Manager (PhD), Caitriona Lacy (f), Policy Manager (BSc), and Sharon de Sa (f), Project Support Officer (BSc). All authors have had academic and on the job training and experience in qualitative research methods.

We would like to acknowledge the contributions of the following individuals who provided guidance and support as part of our governance group: Professor Partha Kar, National Clinical Director for Diabetes, Mark Brodigan and Ben McGough from NHS Diabetes Programme, Liz Perraudin from Diabetes UK, and Alice Williams and Sophie Parslow from the IRLS Patient and Public Involvement team. We are also grateful for clinical support and advice from Dr Emma Wilmot.

Errors or omissions remain the responsibility of the authors alone.

Glossary

- AAC – Accelerated Access Collaborative
- CGM – Continuous Glucose Monitoring
- DAFNE – Dose Adjustment For Normal Eating
- DTN – Diabetes Technology Network.
- DSN – Diabetes Specialist Nurse
- DUK – Diabetes UK
- EHIA – Equality and Health Impact Assessment
- HBA1C – glycated haemoglobin -- average blood glucose (sugar) levels
- HCLs - Hybrid Closed Loop Systems
- NICE – National Institute of Clinical Excellence.
- Onboarding - the action or process of familiarizing a new patient with a company's product
- PPI – Patient and Public Involvement

Appendix A: Approach to Monitoring Data Assessment and interview/survey shortlisting

As set out in the study approach, monitoring data was made available to the study team on the uptake of Insulin Pumps by Trusts nationally, as well as some further, more detailed data, for trusts engaged in the HCL Pilot. This data provided information on the:

- Proportion of the Trust's population with Type 1 diabetes.
- Uptake of insulin pumps as a proportion of the population with Type 1 diabetes.
- (For HCL Pilot Trusts only) The number of patients Trusts forecast to prescribe HCL, the number of patients they offered prescriptions of HCL, and the number of patients who received prescriptions for HCL.

This data was then manually supplemented with nationally available data on:

- Levels of deprivation (as sourced from the Index of Multiple Deprivation from the Ministry of Housing, Communities & Local Government (MHCLG).
- The proportion of the population from ethnic minorities as calculated through an aggregation on the number of people from Asian and Black ethnic groups (as sourced from the Office of National Statistics (ONS)).
- Levels of rurality as categorised by the Department for Environment, Food & Rural Affairs (DEFRA) Local Authority Districts Rural-Urban classification.
- Membership to the Shelford Group[5]; and
- Regional geography (as categorised by ONS NUTS 3).

This data was analysed to inform shortlist targets for surveys and consultations; ensuring study resource is used effectively. A summary of the approach taken for identifying targets on Insulin Pump uptake and the HCL Pilot are included in turn below.

NB. Analysis was limited by available data and not all Trusts had complete data across all of the above indicators.

Insulin Pump Uptake

For the analysis of Insulin Pump Uptake data, Trusts that were involved in the HCL Pilot were not included in the analysis. Trusts that met the following criteria were identified as of interest for interviewing:

- Low Uptake of Pumps as a % of T1 pop.
- High uptake from non-white ethnic groups.
- High uptake from areas of high deprivation.
- High general uptake but low proportional uptake from non-white ethnic groups; and
- High general uptake but low proportional uptake from areas of high deprivation.

All Trusts were ranked in order for each criterion. The top five highest ranked trusts for each criterion were then longlisted, and the top two trusts ranked against each criterion and any trusts that met multiple criteria (were then shortlisted as targets for interview and/or surveying.

All information was then sense-checked to check for any geographic location, rural/urban classification, and Shelford Group membership bias.

HCL Pilot

Pilot Centres that were involved in the HCL Pilot and met the following criteria were identified as of interest for interviewing:

- High over- or under- performance when comparing the number of patients that were forecast to be prescribed HCL and that were actually prescribed HCL.
- High over- or under- performance when comparing the number of patients that were offered HCL prescriptions and that were actually prescribed HCL.
- A high proportion of ethnic minorities with T1 Diabetes; and
- A high proportion of patients with T1 diabetes living in the most deprived areas.

[5] https://shelfordgroup.org/

All Pilot Centres were scored against this criterion, and the ten highest scoring pilot centres were shortlisted. As with the insulin pump data, this list was then checked against geographic location, rural/urban classification, and Shelford Group membership, to ensure there were no data biases.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Developed from:
Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the inter view or focus group?	Page 18
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Page 18
3. Occupation	What was their occupation at the time of the study?	Page 18
4. Gender	Was the researcher male or female?	Page 18
5. Experience and training	What experience or training did the researcher have?	Page 18
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	n/a .
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Page 5
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Page 5

Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Page 4
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Page 5
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Page 5
12. Sample size	How many participants were in the study?	Page 5
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Page 5
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Page 5, .
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Page 5
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Page 6
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Page 5
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	Page 5
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Page 5
20. Field notes	Were field notes made during and/or after the inter view or focus group?	Page 5
21. Duration	What was the duration of the interviews or focus group?	Page 5
22. Data saturation	Was data saturation discussed?	Page 6
23. Transcripts returned	Were transcripts returned to participants for comment	Page 5

	and/or correction?	
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	n/a
25. Description of the coding tree	Did authors provide a description of the coding tree?	n/a
26. Derivation of themes	Were themes identified in advance or derived from the data?	Page 5
27. Software	What software, if applicable, was used to manage the data?	Page 5
28. Participant checking	Did participants provide feedback on the findings?	n/a
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Page 6 to 15
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Yes, there was. Page 6 to 15
31. Clarity of major themes	Were major themes clearly presented in the findings?	Yes. they were. From page 9 to 15
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Discussion of major and minor themes From page 9 to 15

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Diabetes UK

Your position in the organisation: [redacted]

Brief description of the organisation: *Diabetes UK is the UK's leading charity for people living with, at risk of and affected by all types of diabetes. We fund research into diabetes, drive improvement in care for people living with and at risk of diabetes through policy and campaigning work, and offer direct support to people affected by diabetes through events, our helpline and content on our website.*

Diabetes UK is a membership organisation that supports both people affected by diabetes and healthcare professionals working in diabetes. We have a membership of over 80,000 people.

The majority of Diabetes UK's income is from legacies and donations. We also earn income from activities which support our charitable mission, such as our Diabetes UK Professional Conference. A small percentage of our income is from support for specific programmes of work from the medtech and pharmaceutical industry.

Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?
[Relevant manufacturers are listed in the appraisal matrix.]

Yes

If so, please state the name of manufacturer, amount, and purpose of funding.

Diabetes UK receives some funding from the pharmaceutical and medtech industry to support specific programmes of work and for conferences we run. Please see as follows relevant to this appraisal:

Roche: £100,000 +VAT

Abbott Diabetes Care: £110,914.64

Lilly: £108,100

Insulet International Ltd: £33,000

Medtronic Ltd: £5,000

DexCom International Ltd: £36,000

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: *None*

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Type 1 diabetes can be relentless to live with. It is a serious, life-long condition that requires intensive self-management. Most people living with type 1 diabetes will spend no more than 2-3 hours a year with a diabetes healthcare professional – they spend the other 8757 hours managing their condition alone.

Where people living with diabetes find it a challenge to effectively self-manage their condition they are at risk of developing devastating short- and long-term complications. These include life-threatening diabetic ketoacidosis (DKA), severe hypoglycaemia, blindness, cardiovascular disease and amputations.

Most people living with type 1 diabetes make 180 more health-related decisions a day than someone without diabetes. That's an extraordinary

number of extra decisions to be made – about once every 5 minutes when you are awake.

Self-management of type 1 diabetes includes but is not limited to monitoring of blood glucose levels, carbohydrate counting and intensive insulin therapy. Many factors including stress, menstrual cycle, exercise levels, heat and type of food eaten can all have a significant and sometimes unpredictable impact on ability to effectively self-manage and manage blood sugar levels.

"It's a numbers game- you're always watching what you eat" [person living with type 1 diabetes]

For people living with type 1 diabetes, the demands of the condition can be overwhelming and likewise for parents and carers. A child with type 1 diabetes sleeping over at a friend's house, going out for a family meal or planning a holiday can all cause immense worry, frustration and, at times, anger.

Another key challenge of managing type 1 diabetes is the prevention and treatment of hypoglycaemia (hypos). Hypos can be life threatening but even where they are not they represent a huge issue for people living with diabetes – including having an impact on their working life, their ability to take part in activities at school and whether they are allowed to drive.

The issue of hypos is something that comes up regularly via the Diabetes UK Helpline, in focus groups we run and on our online Forum. We know that to avoid hypos people living with diabetes often test their blood sugar levels excessively or run their blood sugar levels higher than advised which negatively affects quality of life and can increase the risk of developing long-term complications.

"You can't do things on the spur of the moment – for instance if my children want to play football with me- I need to make sure my blood sugars are ok first. You can't be spontaneous." [person living with type 1 diabetes]

For parents and carers of children with type 1 diabetes we often hear about years spent waking up several times in the night to test blood sugar level sin

order to avoid hypos. This has an enormous impact on the lives of parents, carers and families. For parents and carers this can affect their ability to work, eat healthily and exercise – which puts them at risk of developing health problems. For children and young people living with type 1 diabetes their learning at school and college can also be negatively affected.

Unsurprisingly the relentless demands of self-managing type 1 diabetes contribute to people living with the condition being at an increased risk of mental ill health including depression, burnout, suicidal ideation and anxiety. For some the constant need for vigilance can result in disordered eating - including insulin omission for weight loss - with life-threatening consequences.

"For me it's a job in itself (managing type 1 diabetes). I give it my all. Learning to accept that you have this condition is a lifelong thing. It does wear you down. I would love something that took the hard work away" [person living with type 1 diabetes]

The above highlights just some of the reasons type 1 diabetes can be a relentless condition to live with. It also helps underline why people with diabetes and their parents and carers should be able to benefit from therapies that help them to live as well as possible with this long-term and serious health condition.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

There are two key areas that important treatment outcomes for people with diabetes tend to fit under. The first are clinical outcomes – for example, reaching a target HbA1c and time in range, experiencing no or very few hypos, and avoiding the development of long-term complications such as blindness, chronic kidney disease and cardiovascular disease.

The second are quality of life outcomes – for example, less time spent managing diabetes, increased confidence with self-management, and ability to take part in day-to-day activities people living with type 1 diabetes can feel otherwise unable to do.

However, it is an oversimplification to separate these two areas. For example, experiencing fewer hypos will inevitably lead to less time spent managing or 'treating' diabetes and increased confidence with self-management of diabetes will often help people towards reaching their target time in range.

People living with type 1 diabetes and their parents and carers are all different, so prioritising specific treatment outcomes over and above another is a difficult task that will almost inevitably miss out certain individuals and experiences.

Broadly speaking, people living with type 1 diabetes want to live well managing their condition, whether that's in clinical or quality of life terms. The same tends to go for parents and carers of people living with type 1 diabetes too.

For many, the existing available therapeutic options on the NHS do not offer them sufficient support to achieve these important outcomes. We know that at point of diagnosis it is common for people with type 1 diabetes to be told that a cure is fast approaching. While this is contestable, for some hybrid closed-loop artificial pancreas technology represents what is sometimes described as a 'practical cure' for diabetes and it is certainly one of the the best available tools to support people living with type 1 diabetes to reach their individual, desired outcomes.

Diabetes UK sincerely hopes for and supports much wider access to treatments and technologies that will bring people living with diabetes and their parents and carers closer to achieving all the outcomes that are important to them as individuals.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Insulin has been the most important treatment used to manage type 1 diabetes since it was first discovered 100 years ago. The vast majority of people living with type 1 diabetes currently use an insulin pen to administer insulin.

Until recently, most people living with type 1 diabetes have also monitored blood glucose levels using a finger-prick testing device – something we know people living with diabetes often find painful and inconvenient. That's why at Diabetes UK we've been pleased to see significant progress being made in recent years towards Flash glucose monitoring being made available to growing numbers of people living with type 1 diabetes.

"Finger prick tests can hurt and have caused sores on my fingers. This is problematic as I'm a cellist and need to have good sensitivity in order to play" [person living with type 1 diabetes]

A recent update to NICE guidelines NG17 and NG18 should mean that going forward everyone living with type 1 diabetes has the choice of using either Flash or continuous glucose monitoring (CGM).

While significant progress has been made towards more people using wearable technology to monitor their blood glucose levels we are concerned that too few people living with diabetes are able to access an insulin pump. Audit data shows that while around 70,000 people meet the NICE TA 151 criteria for accessing an insulin pump just 20,000 people are actually using one.

Data shows that just 27.6% of people living with type 1 diabetes currently reach an HbA1c level below 58mmol/mol. This suggests that existing treatment does not provide sufficient support for people living with diabetes to reduce their HbA1c and increase their time spent in target glycaemic range.

However, data also shows that individuals using an insulin pump, as opposed to insulin pens, are more likely to have recommended HbA1c levels. Evidence

further shows that individuals using Flash or CGM are more likely to have blood glucose levels falling within their target range – indeed, the reduction in HbA1c seen with the addition of Flash or CGM is comparable to adding another oral hypoglycaemic agent for people living with type 2 diabetes. However, more can be done to improve on this.

There is considerable scope for improvements in outcomes for people living with type 1 diabetes and technologies like hybrid closed-loop technology can support this whilst also reducing inequalities experienced by people who are less able to effectively self-manage their condition.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

The following represent just some of the benefits we know people living with type 1 diabetes and their parents or carers can expect to gain from using hybrid closed-loop technology.

- *Improved HbA1c level*
- *Increased time spent in target glycaemic range*
- *Reduction in time spent below target glycaemic range*
- *Reduction in time spent above target glycaemic range*

- *Reduction in episodes of severe hypoglycaemia*
- *Reduction in episodes of severe hypoglycaemia resulting in hospitalisation*
- *Reduction in episodes of diabetic ketoacidosis*
- *Reduced risk of developing long-term diabetes complications*
- *Reduced time spent managing type 1 diabetes*
- *A better night's sleep*
- *Improved quality of sleep*
- *Less time spent treating low or correcting high blood glucose levels*
- *Reduction in calculations required to administer correct insulin doses*
- *Less worry for parents and carers*
- *Reduced burden of self-management*
- *Greater independence for child or young person living with type 1 diabetes*
- *Reduction in exam stress for children and young people living with type 1 diabetes*

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

The following quotes from people living with type 1 diabetes and their parents or carers highlight the significant impact closed-loop technology can have on the lives of people living with the condition. Key themes from reports of people using this technology are that it significantly reduces the 'mental load' and allows them to spend 'less time' managing their condition and more time in target glycaemic range.

*"Essentially, I've gone from being the 'understudy to a pancreas' to being **the manager of an 'understudy to a pancreas'** where I just input the data and let the system do all the maths every 5 minutes to keep me in range for 90+% of the time and with an HbA1c of a non-diabetic" [Person living with type 1 diabetes]*

*"I am aware that **I'm already thinking less about diabetes** and enjoying a lot more sleep, as well as relying on the pump to sort out any miscalculations in carbs or late snacks" [person living with type 1 diabetes]*

*"I have been using the 780g system for a couple of months (I self fund the CGM) and with the CGM **I have my A1C down to 47**. This includes a months period where my family travelled to America (6 hour time change difference that my body usually struggles with) and a trip to Disney! I have far less low blood glucose, and I no longer have feet on the floor phenomenon. I am excited to say it is looking like, all being well in the next few weeks, **it will be a huge help for baby #2**" [person living with type 1 diabetes]*

"I work full time and I am also in my final year of my MSc (while also running around after a 4 year old and another on the way). Using this system has

*significantly **taken away the "mental load" of constant basal adjustments** and it is hard to explain how much that has made a difference even in such a short amount of time." [person living with type 1 diabetes]*

*"We have 2 daughters using control IQ. It has made a huge difference to QOL, both for them and for us as parents. **Less workload, more sleep**, < 1% hypoglycaemia, no severe hypoglycaemia, improved TIR. Overnight the control is absolutely amazing. " [parent of children living with type 1 diabetes]*

*"We don't have to discuss diabetes so much as the closed loop is doing its job and we see the figures and troubleshoot when necessary. Our interactions with our child are not just about diabetes now. **We are all getting more sleep now**. They (CLS) definitely help to alleviate some of the burden of diabetes. They are an essential part of the solution but not the whole solution." [parent of child living with type 1 diabetes]*

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS

treatments in England.

- *Finger-prick testing is painful and inconvenient*
- *Insulin injections can be painful and inconvenient*
- *Lack of suitable blood-glucose monitoring equipment for people living with visual or hearing impairments*
- *Insulin pens only allow for whole or half-unit measure, meaning it is harder to 'finely-tune' insulin dosing*
- *Access to insulin pumps and Flash or CGM can be difficult – there are too many barriers in place to use one*
- *Difficulty managing exercise with insulin injections and capillary blood glucose monitoring*
- *Inflexibility – if plans change spontaneity can be difficult*
- *Lack of access to healthcare professionals who can support with dosing decisions in a timely manner*

Please list any concerns patients or carers have about the treatment(s) being appraised.

- *The technology is bulky and too visible*
- *The technology and the data it provides can be overwhelming*
- *It can be difficult to trust a 'machine' to do the work people living with diabetes are so used to doing themselves*
- *The technology available on the market and through the NHS doesn't work as well as open-source closed-loop systems some individuals are using*

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

All people living with type 1 diabetes are likely to benefit from this treatment for a number of different reasons.

For individuals who are finding their diabetes is leading to burnout, distress or generally having an impact on their quality of life this technology can be beneficial. This is because we know where people have used it they have

reported spending less time managing their diabetes giving them the freedom to live better with their diabetes.

People for whom numeracy is an issue are also likely to find this technology particularly beneficial. Some of the difficult calculations involved in diabetes self-management can be done by the technology itself meaning the margin of error can be reduced.

For people who struggle to engage with their diabetes self-management in general, this technology can also offer significant benefit. For example, for someone who regularly misses meal-time boluses and does not test their blood glucose levels, time in target glycaemic range is likely to remain low. With this technology whether someone announces a mealtime bolus or not they are likely to see a significant improvement in time in range regardless because the technology is doing a lot of work outside of mealtimes to get blood sugar levels into the target glycaemic range.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.
For some people the idea of wearing this technology constantly may be a barrier to using this technology effectively.

For others, letting go of some of the control could be difficult too. The information provided by this technology could also be overwhelming for some people living with diabetes.

The evidence is clear that this technology can support people living with diabetes to reduce their HbA1c while improving their quality of life. However, we recognise that a number of individual barriers may prevent people from wanting to or being able to use hybrid closed-loop systems.

It is crucial that healthcare professionals have open and honest conversations with people living with diabetes they support about this technology. People living with diabetes need to be supported to make informed decisions about whether this is the right therapy for them and healthcare professionals need to

ensure they avoid making assumptions about who may or may not benefit from its use.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

While time spent with a healthcare professional may exceed what is expected in routine NHS care, broadly speaking the experiences of patients using hybrid closed-loop systems within the NHS do reflect those of individuals using them as part of a clinical trial.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Yes

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

- Diabetes is Serious (Diabetes UK)
- Too often Missing (Diabetes UK)
- Barnard KD, Wysocki T, Thabit H, Evans ML, Amiel S, Heller S, Young A, Hovorka R; Angela Consortium. Psychosocial aspects of closed- and open-loop

insulin delivery: closing the loop in adults with Type 1 diabetes in the home setting. Diabet Med. 2015 May;32(5):601-8. doi: 10.1111/dme.12706. Epub 2015 Feb 20. PMID: 25615888.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Access to diabetes technology can be life-changing and allows for much easier self-management. However, access to these transformative technologies is unequal, with people living in areas of high deprivation and from minority ethnic groups being the least likely to use it.

For example, people living less affluent areas are least likely to have access to an insulin pump – including when they meet the criteria stipulated under NICE TA 151. Children from minority ethnic groups are also significantly less likely to be using an insulin pump.

Geographic inequalities in access to this technology are also important to consider. It is crucial that regardless of where a person lives they have access to trained healthcare professionals who can support them to use hybrid closed-loop systems.

Diabetes UK strongly encourages NICE to make clear recommendations in this appraisal on steps local areas should take to identify and address inequities in access to this technology which may emerge.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

The integration of an insulin pump and continuous glucose monitor, via an algorithm, to automate insulin delivery has been a hugely exciting development in type 1 diabetes care.

For this technology being appraised it is the automation of insulin delivery that makes it particularly important and different from existing treatments for type 1 diabetes. Above we have underlined the relentless nature of self-management of type 1 diabetes and this technology can help to reduce that burden. This is not innovation for innovations sake but a treatment that can truly help people living with type 1 diabetes to live well with their condition both in terms of clinical and quality of life outcomes.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Type 1 diabetes is a relentless condition to live with

- Hybrid closed-loop technology has the potential to positively transform the lives of people living with type 1 diabetes and their parent or carers
- Hybrid closed-loop technology should be available to the widest possible group of people living with type 1 diabetes on the NHS
- Hybrid closed-loop technology can reduce inequalities in care and outcomes for people living with type 1 diabetes
- Hybrid closed-loop technology can help reduce the burden of living with diabetes – improving quality of life and clinical outcomes

……

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Hybrid-closed loop systems for managing blood glucose levels in type 1 diabetes

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted] and [redacted]

Name of your organisation: JDRF, the type 1 diabetes research charity

Your position in the organisation: [redacted] and [redacted]

Brief description of the organisation:

(For example: who funds the organisation? How many members does the organisation have?)

JDRF is the UK's type 1 diabetes charity. We fund research into new treatments and cures for type 1 diabetes. We also provide information to those affected by the condition and engage with decision-makers to advocate for widened access to treatments and technologies. We are not a membership organisation but we have around 22,000 supporters.

Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?

Yes.

If so, please state the name of manufacturer, amount, and purpose of funding.

Medtronic - £10,000 to exhibit at our events (technology events and Discovery Days)

Dexcom - £47,000 to exhibit at our events (Discovery Days and technology events), partner in our Pathway to Choice initiative, advertise in our publications

Tandem - £23,000 to exhibit at our technology and Discovery events and advertise in our publications

Dana - £7,000 to exhibit at four technology events

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition,

or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

There are approximately 250,000 people with type 1 diabetes in England, including 26,000 children. Nearly 10,000 people were newly diagnosed in 2019.[1]

Type 1 diabetes affects people of all ages. Many people experience a diagnosis as a result of diabetic ketoacidosis - a serious event where the blood glucose levels are very high, which requires hospitalisation, and in some circumstances can lead to coma or death. As such this can be highly traumatic for people who are newly diagnosed and their families.

Type 1 diabetes does not impact every person in the same way, and much is reliant upon the individual's lifestyle, for instance how active they are, their diet, BMI, smoking status, as well as issues such as access to technology and frequency of access to healthcare and appointments. However, most people with type 1 tell of their experiences of the difficulties of living with it, where one must constantly think about their condition and act to manage their glucose levels effectively. This includes adjusting insulin doses depending on the amount of carbohydrates in a meal, as well as adjusting for activity levels, for different weather conditions and more.

The toll that type 1 takes on people cannot be understated. It is a condition that can result in “diabetic fatigue” from the burden of managing the condition. Many people with type 1 or their carers face issues with their glucose levels at night, when they are unable to monitor them, and are at risk of highs and lows, which may be fatal. This results in further loss of productivity and missed school for young people, with frequent appointments and fatigue.

Physical symptoms result from hypoglycaemic or hyperglycaemic episodes, where a person’s blood glucose reaches unsafe high or low levels. This can result in fatigue, confusion, dizziness, nausea, sweating, mood swings, blurred vision, headaches and more. The long-term impact of unstable blood glucose is also significant - complications can arise with a person’s eyes,

[1] NHS Digital, National Diabetes Audit Report 1 2020/21

leading to a condition called diabetic retinopathy which can lead to loss of eyesight. Other health complications can develop with a person's heart and blood vessels, nerves, and feet. Type 1 diabetes can impact a person's renal system, thereby the condition can impact a person's whole body over a long period of time, which can be exacerbated through a number of factors relating to sub-optimal glycaemic management.

1. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The outcomes that are important to patients or carers are short, medium and long term.

Short term: staying in safe glucose range so that they can pursue normal life safely including physical activity, deep thought, variations in plans (eg running for a bus, change of meal times) alongside the normal demands of life such as education, work, relationships, and relaxation.

Medium term: relief from the burden of constant decision making to titrate the insulin dose and constant adjustment to deal with deviations from the expected result, reassurance that glucose management is as good as it can be to avoid short term deviations and long term complications. Avoiding psychological burnout.

Long term: avoiding microvasuclar, macrovascular and neurological damage.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Treatment of type 1 diabetes must involve administration of insulin, measurement of glucose and adjustment to the treatment several times per day. The standard treatment is by multiple daily injections (4 or more times per day) and finger prick blood glucose measurement 4 or more times per day).

This condition is very demanding on the patient or carer and there are considered to be 40+ factors which affect glucose levels, not just the carbohydrate consumed.[2] This means that treatment is adjusted by the patient or carer throughout the day – it is not simply a case of following doctor's orders.

People with type 1 diabetes feel burdened by the demands of multiple decisions, injections and finger pricks each day and each one can have an immediate and long-term impact.

People with type 1 often speak of their frustration that despite all the calculations and considerations, their glucose levels do not always show the desired outcome and sometimes it can feel like no matter how hard they try they are doomed to 'get it wrong and suffer the consequences'.

NHS care across England varies in terms of clinical expertise, access to structured education for the person with type 1 diabetes and access to devices recommended by NICE. There is a perceived postcode lottery and some perceive that those who put most time and effort into managing their condition get the least help from the NHS.

As with any long-term condition, people with type 1 diabetes are at greater risk of depression than the general population and depression will also impact glucose management.[3]

Wearable glucose monitoring technologies such as flash glucose monitoring and continuous glucose monitoring have shown to lower average blood glucose levels, which supports overall wellbeing and reduces the risk of developing complications later in life.[4] Many people throughout the COVID pandemic who had access to diabetes technology felt better prepared to manage their type 1 diabetes in the absence of routine NHS support, making those without it more vulnerable and taking a worsened toll on their mental health.[5]

Many people prefer to use technology including flash glucose monitoring, continuous glucose monitoring, insulin pumps and hybrid closed loop systems to help manage their type 1 diabetes as it helps them achieve their desired clinical outcomes and helps to relieve the burden of self care.

[2] 42 factors that affect blood glucose, Diabetes Research Connection https://diabetesresearchconnection.org/42-factors-affect-blood-glucose/

[3] JDRF, Covid and Beyond, 2021

[4] Parkin, C et al., Is Continuous Glucose Monitoring underappreciated in the UK?, 2017

[5] JDRF, Covid and Beyond, 2021

3. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

- Reduced burden on the person with type 1 diabetes or their carer
- Reduced time in dangerously low glucose range
- Reduced time in unsafe high glucose range
- Automated correction of glucose excursions
- Greater overnight safety and therefore more restful sleep
- Greater ability to participate in physical activities even when unplanned
- Greater flexibility of eating times and appetite-appropriate eating
- Fewer skin pricks from injections and finger pricks

The below case studies illustrate some of these points:

One of our supporters told us: “Within days of starting the system I began to notice improvements in my diabetes. Although it wasn’t perfect it was much better than my DIY system, even in the initial three weeks where I was still learning to use the technology. I also began to notice my mood improving too.

After my first week with it my time in range was already better than I had managed to achieve (with a lot of effort) with my DIY version. Things have continued to improve and I’m now spending much less time worrying about my diabetes and just getting on with my life again.

The regular lows have disappeared as have the deep hypos and spikes. The CGM is very accurate and so my confidence in the system grows daily...”

We also heard from parents of a child with type 1 diabetes, aged 5. “We were able to join the study [clinical trial for the artificial pancreas system] which was amazing. Using the app has meant that multiple people can access their child's data at any time, meaning that his care is not in the hands of just one person”. This aspect of the app gives the parents reassurance and support, as well as a greater sense of freedom. Being able to involve people remotely in their son’s care is an “absolute game changer.”

The app has also reduced the impact of monitoring the child’s blood glucose levels at night, and they can now check by looking at the phone app rather than going into the child’s room to do a finger prick blood glucose measurement.

“His HbA1c has been “fantastic” since starting on the system.” They also feel that using the system has helped identify problems before they arise. They expressed that they “knew that it wasn’t going to fix everything, but it was going to help us manage the condition better. I would say that that goal - of better management - is being achieved”.

“With the amount of tech that’s needed for the closed loop system, the more things there are that can go wrong.” But despite occasional issues, the parents are clear they wouldn’t go back. Most importantly, the app has meant that type 1 diabetes doesn’t stop their son getting the most from school and home life. “He’s a very happy, healthy boy and that’s the main thing.”

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Hybrid-closed loop technology has a significantly positive impact on the lives of people with type 1 diabetes and their families or carers. Hybrid-closed loop technology enables the person with type 1 diabetes to not have to think about their condition as often, as they have the reassurance of their technology automatically measuring their glucose levels and adjusting their insulin accordingly. This reduces the need for adjusting for exercise levels and activity, for the weather and other factors that can affect a person's glucose levels and result in potential hypers or hypos. It provides a safety net which enables people to achieve better clinical outcomes with a lower daily burden.

As this technology is much easier to live with than standard treatment for type 1 diabetes self-management, ie finger prick tests and injections, it is particularly suited to a number of groups of people - however it must be acknowledged that almost everyone with type 1 could benefit from this technology being available to them. The reduction in daily decision making and glucose excursions particularly supports people with mental health issues

or learning disabilities, as well as children and young adults beginning to manage their diabetes independently, and people who work in public-facing roles and cannot prick their finger or inject at appropriate times.

People with type 1 diabetes report improved quality of life with hybrid-closed loop technology. They said the technology helps them manage their type 1 diabetes and improve their HBA1c which will improve long term management and reduce long term complications. They tell us the burden of managing the condition is greatly reduced.

Adults tell us of improved sleep quality and subsequent mood and productivity increase. Adults with type 1 diabetes, who have young children to look after, tell us that they are glad their children no longer have to act as informal carers.

We have heard from parents with children as young as one year old that this technology has helped especially as their children cannot express when they are feeling unwell due to high or low glucose levels, and toddlers with or without type 1 diabetes often do not finish their meals. The automatic adjustment of hybrid closed loop systems can thus remove family anxiety around mealtimes.

Parents also report better sleep as they can rely on the system to take on the burden of overnight glucose management when untreated hypos can be fatal and long hours of hyperglycaemia contributes to overall suboptimal glycaemic management.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

JDRF has heard from some people living with type 1 that they are content with their existing methods of treatment and do not feel that technologies are suitable to them and their lifestyle. Others have expressed concern about wearing medical technology, in that the tubes on some insulin pumps could be caught on their clothing or whilst doing physical exercise. Some people avoid wearable medical technologies due to feeling self-conscious about their type 1 diabetes and don't like a visible reminder. There is a perception that the technology can be difficult to access from the NHS and some people are put off of asking to try it for that reason. Some people justify suboptimal outcomes by citing the inaccessibility of the technology being appraised. Some people don't like the idea of increased data available to them or their clinic which is afforded by the technology being appraised.

What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

- The potential of technical errors
- Increased expectations of glucose management by themselves or their clinical team
- Initial worsening of retinopathy due to improved glucose management
- Having to wear two devices which means an invisible condition becomes visible
- Risk of having devices stolen or being lost or broken
- Wearability issues including itchiness, lack of choice of adhesive patch colour, choice of device brands

Please list any concerns patients or carers have about current NHS treatments in England.

- The perceived postcode lottery/inequity of access to current technologies across the country
- Inequity of access across socio-economic levels
- Clinical inertia and/or preference
- Difficulty in accessing even the most basic treatments – for example having to get a new prescription for insulin every month, only being prescribed two months' worth of glucose testing strips at a time, issues with pharmacists questioning prescribing, issues with GPs or their staff questioning the need for ongoing supplies, variation in contaminated sharps disposal policy
- Perception that anything but standard treatment is expensive and the user needs to 'deserve' it and 'failure' to be fully engaged 24/7/365 might result in withdrawal of the treatment and return to injecting and finger pricking.

Please list any concerns patients or carers have about the treatment(s) being appraised.

- Being unable to get it 'in their area'
- Long waiting lists to be trained and started on the system
- Timely tech support
- Timely clinical support
- Inadequate support or training from their team who might not have expertise or has a preconception about the individual's ability to use it
- Being forced to use it against their will
- Being forced to use a particular brand rather than their preference
- Risk of technical fault and having to return to injections and or finger prick glucose measurement
- Will it be more complicated than my current regime?
- The risk of forgetting how to manage with injections in the event of equipment failure.
- The risk of choosing the 'wrong' brand and being 'stuck with it' for 4

years

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

4. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Most people living with type 1 diabetes could benefit from hybrid-closed loop systems, and there is evidence that the technology can regulate glucose levels and therefore reduce HbA1c safely in all users. The hybrid-closed loop system will be especially beneficial for people who fear a severe hypo or hyper and therefore run consistently high or low as a result. The knowledge that their technology is helping to keep their levels stable can help to support them physically and emotionally, lifting much of the psychological burden of making many decisions each day or maintaining suboptimal levels as a safety net.

"Unlike many other chronic conditions, type 1 diabetes places a unique burden of management on the individual with the condition. In addition to complex medication regimens, other behavioural modification is also needed; all of this requires considerable knowledge and skill to navigate between hyper- and hypoglycaemia."[6]

Hybrid-closed loop systems could be particularly beneficial for people living with type 1 who have learning disabilities or mental health problems. Studies show that "people with learning disabilities experience poorer health outcomes than those without LD (Cooper et al, 2018; LeDeR, 2021) and are at increased risk of developing diabetes complications due to barriers accessing healthcare (Macrae et al, 2015; Hanlon et al, 2018)." A hybrid-

[6] The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8481000/

closed loop could reduce this risk, provided the individual is given appropriate skills and education required in using one.

Children may also benefit from hybrid-closed loop systems as it could allow parents to feel more at ease when their child is at school or away from the home. Parents and guardians may also be able to remotely monitor their child's levels, reducing anxiety and allowing greater independence for children and young people.

Hybrid closed loop would also be particularly beneficial to those going through hormonal life stages, such as puberty or menopause, people in public-facing roles such as teachers, checkout assistants, or those who work with their hands, such as mechanics. People who forget to inject will also benefit from hybrid closed loop.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

People who are content with their existing methods of management and do not experience adverse complications may not wish to use an alternate method and would therefore experience less benefit.

5. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☐x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials

Yes, patients who use hybrid closed loop technology as part of their routine

NHS care share similar experiences as those who took part in clinical trials.

We have heard from healthcare professionals that some people with type 1 who would not qualify to be part of a trial (as their management was previously suboptimal, for example) have benefited greatly from using hybrid closed loop technology.

Also, the self-selected people with type 1 diabetes using DIY hybrid closed loop technology demonstrate a wide acceptance of the technology and benefits from its use, sometimes without any clinical input or support.

Patients in clinical trials are often from a specific patient demographic. For example, Professor Barnard-Kelly's research into the effectiveness of automated insulin delivery for pregnant women with type 1 diabetes7http://dx.doi.org/10.1186/s12884-022-04543-z or Professor Roman Hovorka's study on hybrid closed loop technology from very young children.8 As such it is challenging for JDRF to assess if these findings reflect those of the participants in the NHS pilot of hybrid closed loop technology, without access to the full data of this pilot.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Yes, the outcomes measured by trials are the ones that are important to people with type 1 diabetes.

The NHS 2021-2022 pilot of hybrid-closed loop technology required participants to be using an insulin pump and wearable glucose monitoring device in order to be eligible for involvement in the pilot. The wider type 1 diabetes population will potentially see even greater benefit from this technology than those eligible for the pilot.

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[7] Tara Lee., Katharine Barnard Kelly et. al., AiDAPT: automated insulin delivery amongst pregnant women with type 1 diabetes: a multicentre randomized controlled trial – study protocol, 2022

[8] Julia Ware;, Roman Hovorka et al., Error! Hyperlink reference not valid., 2022

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☒ Yes ☐ No

If yes, please provide references to the relevant studies.

In 2020 JDRF carried out market research on access to diabetes technologies, compiled into a report called Pathway to Choice.[9] This report contains qualitative information on perceptions of technologies such as insulin pumps and glucose monitors.

JDRF is also aware of the published research literature referenced in the Scottish Health Technologies Group assessment of closed loop systems for people with type 1 diabetes.[10]

6. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality

[9] JDRF, Pathway to Choice, 2020

[10] https://shtg.scot/our-advice/closed-loop-systems-and-the-artificial-pancreas-for-type-i-diabetes-mellitus-t1dm/

issues that should be considered in this appraisal.

The National Paediatric Diabetes Audit and the National Diabetes Audit showed that uptake of diabetes technology, such as continuous glucose monitoring and insulin pumps is much lower amongst people from a socially deprived area or ethnic minority background. As such if hybrid-closed loop technology is recommended for all with type 1 diabetes, the issue of inequity and inequality will be addressed. It must be ensured that it is accessible not just to those who already possess technology, but to those who do not, especially hardly reached communities.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Some people with type 1 diabetes who also have learning difficulties may have difficulty using currently available treatments due to the complexity of carbohydrate counting and manually administering insulin, as well as recognising when they are experiencing a hypo or hyperglycaemic episode. As such hybrid-closed loop systems would be much easier for this group to self-manage their type 1 diabetes.

People with visual impairments may have difficulty finding the right device that works with their abilities.

People with fine motor skill issues may have difficulty using any aspect of a hybrid closed loop system for example inability to select a meal bolus due to shaking hands. This needs to be worked through with HCPs to find a suitable system and manufacturers may need to address such issues in future developments.

Additionally, those experiencing a digital divide or with lower digital health literacy should receive additional support in accessing and using hybrid-closed loop effectively. For example, they may need access to a smartphone to run the algorithm or computer to upload data.

7. Other issues

Do you consider the treatment(s) being appraised to be innovative?

x☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Hybrid-closed loop systems are a prime example of innovation, given the advancement in improving people's quality of life compared to existing treatment methods.

Managing type 1 diabetes involves administering insulin, checking glucose and adjusting treatment according to outcomes. Some influences on daily management cannot be anticipated or counted. Automating part of the process by allowing a pump and sensor to communicate and adjust will ease the burden and enable more time in a healthy target glucose range and provide more data for clinicians to help people with type 1 to make appropriate adjustments to their management. Devices can make logical decisions in a fraction of the time and with much greater precision than a human brain and will be unaffected by perceptions and fears.

Enabling wide uptake of commercial hybrid closed loop systems will also reduce the number of people who choose to create a diy (and therefore unregulated) version of this technology.

Are there any other issues that you would like the Appraisal Committee to consider?

This appraisal must be device agnostic in order to widen availability to hybrid-closed loop systems and keep the guidance relevant and up-to-date in the future as new manufacturers and devices are made available. There should be provision for people with type 1 diabetes to move between standard therapy and hybrid closed loop therapy easily according to their needs and changing circumstances.

8. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Hybrid-closed loop systems would have a substantial improvement on the short and long term clinical outcomes and quality of life of people living with type 1 diabetes.
- This improvement could manifest after initial adaptation in more clinical time being available for those with more complex needs. More data can be exchanged between people with type 1 diabetes and clinic remotely and more tailored advice can be given.
- All people with type 1 diabetes could benefit from hybrid-closed loop technology, and it is important that all patients are offered a full and informative discussion with their clinicians to make sure it is a viable option for them, ensuring that people who have not accessed technology in the past are not left behind.
- A number of people are making DIY versions of hybrid closed loop technology - which is unregulated and therefore not as rigorous as official assessment. This tells us that this technology can be very well accepted and beneficial to a wide group of people.
- This appraisal must be device agnostic in order to widen availability to hybrid-closed loop systems and keep the guidance relevant and up-to-date in the future as new manufacturers and devices are made available.

……

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☐x **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Julie Brake
2. Name of organisation	Liverpool University Hospitals NHS Foundation Trust
3. Job title or position	Nurse Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with type 1 diabetes ? ☒ A specialist in the clinical evidence base for type 1 diabetes or hybrid closed loop systems ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
8. What is the main aim of treatment for type 1 diabetes ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Reduce acute complications and long term complications whilst having the person with type 1 diabetes wants, needs, quality of life and psychological distress as factors when agreeing treatment plans with them. However a cure would be the ultimate outcome.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in the burden of managing diabetes for the person with type 1 diabetes and positive impact on quality of life. Improvement in TIR, TBR and TAR in line with agreed plan.
10. In your view, is there an unmet need for patients and healthcare professionals in type 1 diabetes ?	Yes
11. How is type 1 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	In type 1 diabetes care there is still some degree of postcode lottery. Depending on skill mix of the local T1D specialist team. In my region not all Type 1 diabetes services provide a quality pump service in adult diabetes, pump choice is limited in others and CGM provision even more sporadic. Some services are very HbA1c centric and often technology provision comes with strings attached including the attendance at formalised teachings or sessions before providing libre or similar technology. Improved access to technology would add to self management and potentially reduce the reliance on HCP input in the long term.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Technology is mainly tightly controlled due to the costs. The control lies with those not clinically involved with the PWT1D, and although this does give a degree of “fairness” it is a barrier that supports the current inequalities in healthcare provision. The funding process is also too long, generally 56 working days which is nearly 3 months. The location at which technology is provided is not the issue, the main consideration is the staff providing the technology. Experienced, trained and

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	supported type 1 MDT HCP's in community, secondary or specialist care can deliver technology and in different areas a different system may be more appropriate than another but staff knowledge, time, experience and having a T1D MDT is important. More people are using technology, more people want technology but with this comes additional education, training and support needs. The use of technology can have a psychological burden, increase as well as reduce health anxiety, dietary education support is needed when moving to the use of technology and DSN and Diabetes Consultant time implications especially in the transition period onto advanced technologies in managing type 1 diabetes. The HCL trial has made the team I am part of aware that this system does require a lot of HCP input at the start and at touch points to address urgent clinical need/sickness/pump failure That current platforms for pumps like Glooko are essential and CGM platforms so more timely virtual reviews can be completed to improve outcomes and reduce DKA risk, anxiety and A&E attendance.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Definitely and we have seen this in the HCL people already – those on the trial and others
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, lots of groups, but will be guided by individual need. However currently the criteria is too narrow. PWT1D who struggle daily to keep their HbA1c and TIR within good parameters, impacting on their quality of life and often causing distress due to the amount of time they have to invest hourly on keeping such good glucose management are penalised by not falling into criteria for a pump or cgm, being rewarded in some way by the fact that they can't have access to the technology that would help them holistically.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There will undoubtably be implications to HCP time and PWT1D access and availability, but this should not be a barrier to access. As teams providing services, we should be sharing good practice and have support for implementing new tech via HCP peer support and PWT1D peer support. The introduction of technology will require the provision of support for PWT1D when needed by the whole MDT. Rather than compartmentalising professional roles all members of the team should be able to deliver a level of advice, support and training.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Guidelines should be available to support decision making for both HCP's and the PWT1D. Outcome measures should be agreed and monitored. These could be wide and varied and in my experience the outcome measures agreed on commencement of technology or new treatments are not always the outcomes that PWT1D find most beneficial or that have the most impact.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Possibly
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	This technology is a big step change in managing type 1 diabetes In our experience reduction in hba1c and improved TIR appears consistent across most groups, HbA1c ranges and duration of diabetes. Considerable improvements in symptoms for those with complications of diabetes, especially gastroparesis and neuropathy.

• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Some effects can cause issues like site reactions to adhesives and cannula type but generally these are no different to those not using HCL tech who are using CSII therapy and Flash or other glucose sensors
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of the NICE guideline [NG17]?	No
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Questions on the external assessment report for clinical experts

Table 2 Key issues and questions for experts arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	More than 65% of the studies included looked at children and young adults, not a great deal of information on pre trial management or control or diagnosis duration
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	However this probably reflects more real world use of the system in centres that are used to delivering pump services. To me this data is valuable as it reflects the broad age range and duration of diabetes and characteristics of a “normal” clinic
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	I neither agree or disagree as there are equal arguments for and against each option. The meta analysis is arguably more robust, however in our experience with standard care the hba1c reduction was much less and more than the HCL mean reduction. If I had to chose I would say use the NHSE pilot study data and a reduction of 1.5%
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	Management by multiple people Safety Target levels

Clinical expert statement

	Unpredictability of daily activity Hormones and growth
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	Target levels Trimester differences Frequency of review HCP Teams can change when pwd becomes pregnant
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	As the majority of the data used was in under 25's it seems appropriate for this group mainly, however a 24 year scenario would also be beneficial Does anyone stay on the same treatment regime for 50 years? Technology and treatment options change so maybe 50 years is too far a horizon
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Yes
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment report).	SA06

Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate?	The carer effect may vary from children through young adults to adults and for the duration of time the carer has supported the person with diabetes and the level of diabetes wellness that the PWD has. Carer effect is influenced by more than hypoglycaemia, the effect of hypo glycaemia, or other diabetes impacts, on carers can be long reaching. Whether doubling is sufficient to show actual effect is difficult to say.
Are there any important issues that have been missed in EAG report?	

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Living with this condition or caring for a patient with type 1 diabetes

Table 1 About you, type 1 diabetes, current treatments and equality

1. Your name	Jo Richardson
2. Are you (please tick all that apply)	☐ A patient with type 1 diabetes ? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with type 1 diabetes ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Leeds Children's Diabetes / National Children and Young People's Diabetes Network
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with type 1 diabetes ? **If you are a carer (for someone with type 1 diabetes) please share your experience of caring for them**	I am a parent of a child with type 1 diabetes. Jake was diagnosed January 2013 aged 2 which was a huge life changing event for us. This resulted in rethinking family life – blood glucose checks multiple times a night; constant awareness of the effects of hypoglycaemia and hyperglycaemia; days out had to be meticulously planned to ensure we had the correct kit in our bag; cannula and sensor changes; prescription ordering had to occur timely to ensure no items ran out; consideration of family holidays and allowing extra time to pack and check in at airports; knowing Jake was completely unaware of how he felt when not in range. We've had the privilege of being a part of several trials of systems and currently use a hybrid closed loop system which has been a complete game changer for us all.
7a. What do you think of the current treatments and care available for type 1 diabetes on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a - I think that children in the NHS are fortunate to have choices of treatment available to them from insulin pens to pumps and to closed loop systems, along with blood glucose monitors, flash glucose and continuous glucose monitors. The choices can be reflective of their lifestyle and ability to cope with technology 7b - There still appears to be a discrepancy on availability countrywide – the postcode lottery does still exist unfortunately. This is unfair and there should be uniformity and equity for all irrespective of the clinic to whom you are registered with
8. If there are disadvantages for patients of current NHS treatments for type 1 diabetes (for example, how the treatment is given or taken, side effects of treatment, and any others) please describe these	For some children, the thought of wearing technology continually does not appeal as it can make their condition obvious. This can be more of an issue for teenagers and those who don't wish to draw attention to feeling different. There can be periods of their lives where they decline to administer insulin for various reasons which can

	lead to DKA. Having to calculate doses with insulin pen administration could lead to over or under dosing and potential hospital admissions. The availability of this system to those who do not fit the current criteria for use – those under a certain age and those who do not require a certain total daily insulin amount – these groups are currently exempt from hybrid closed loop systems but would potentially benefit more as these are generally the younger age group who can be unaware that their glucose levels are not in range.
9a. If there are advantages of hybrid closed loop systems over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	9a -The hybrid closed loop has many advantages for a child and family – it improves quality of life for patient and carers in that the auto adjusting insulin levels have allowed me to sleep full nights the majority of the time; it attempts to avert hypoglycaemia/hyperglycaemia by use of an algorithm so allows for more freedom for Jake as he's growing up into teenage years as it takes away some of the stress of constantly watching glucose levels; as a carer, it gives you the ability to see his glucose levels remotely which gives peace of mind when we are not together; it has allowed me to continue working and progress in my career by taking away some of the stress and workload required to keep Jake's glucose levels within range >70% of the time; I feel able to relax when he's not in my presence as I know the system will be doing its utmost to keep him within the accepted range as much as possible; it allows for him to continue playing cricket and football matches by giving him the freedom to set a temporary target which assists by trying to keep his glucose level at a slightly higher set target; at school, he has the ability to take part in all daily activities and extra curricular activities through the use of the system and my ability to watch his levels; it is discreet enough to stow away on his being with many people not realising he is even wearing it; the alarms can be set to audible or vibrate which gives choice to the patient as to how the alerts are received; it feels like an early warning system to changes outside of the accepted limits and provides me with a sense of relief that it's protecting him from becoming seriously unwell; the constant long term measures of HbA1c being within range and the knowledge that this will help to improve his long term health outcomes for his future.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Do hybrid closed loop systems help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9b – for me, it's the sense of it being an early warning system to changes in the accepted glucose levels and the rapid response it delivers. 9c -The hybrid closed loop system will assist with insulin administration- if in use as it will continually assess the glucose levels and auto adjust the amount administered to attempt to avert hyperglycaemia/hypoglycaemia and potentially lead to less hospital in patient stays and improved quality of long term health outcomes
10. If there are disadvantages of hybrid closed loop systems over current treatments on the NHS please describe these. For example, are there any risks with hybrid closed loop systems ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The main disadvantages of the hybrid closed loop can be the availability of consumable items required to use the pump and sensor; if the system runs out of battery power then the wearer can become very sick with DKA very quickly as it will be unable to alert the patient to the sudden changes in glucose levels; the availability to those who do not fit the required criteria for use.
11. Are there any groups of patients who might benefit more from hybrid closed loop systems or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I consider any patient group can have a huge benefit from a hybrid closed loop system – however, my thoughts are that the younger patients who cannot describe that they feel out of range; toddlers who graze on food as it gives the ability to administer small amounts of bolus insulin often; those with cognitive impairment as it will take away a huge amount of calculation required with MDI dosing; those with, for example, autism or trisomy 21 as it can allow for routines to continue and give those patients stability within their life; those who live alone as it has the ability to provide some reassurance that glucose levels will be kept in range as much as possible; teenagers who are becoming independent as it allows for them to "go it alone" but provides them with the safety net of auto adjustments and a carer share option to view glucose levels; the decision making the pump allows when asleep or unwell; university students leaving home for the first time are afforded the reassurance of the auto adjustments and carer share options.
12. Are there any potential equality issues that should be taken into account when considering type 1	The only equity issues I am aware of are the "postcode lottery" that unfortunately exists within the UK. There are clinics who struggle to implement the use of these

diabetes and hybrid closed loop systems ? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	systems due to workload, staffing or individual funding requests being required to obtain funding per patient.
13. Are there any other issues that you would like the committee to consider?	Nothing at present.

Part 2: Questions on the external assessment report for patient experts

Table 2 Key issues and questions for patients arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	Broadly mirror each other in model but in adults the uncertainties are around overall survival gains; severe visual loss and its effects upon survival, quality of life, and costs; ESRD and its effects upon survival, quality of life and costs.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	If HCL reduces HbA1c in pregnant women to the same extent as in the adult population the short-term additional costs of HCL will have some immediate cost offsets from reduced birth defects, with the potential for additional benefits to the child at no additional cost – there are increased risks for pregnancy and birth such as premature birth; miscarriage related to fetal

Patient expert statement

	abnormality; Increased proportion of babies delivered by caesarean section; Macrosomia;Respiratory distress syndrome in the new-born due to lack of surfactant production in the neonate; increased neonatal unit admissions for blood glucose monitoring and respiratory support It also seems likely that the baseline age of pregnant women is below the national diabetes audit mean age which is likely to further improve cost effectiveness. If after giving birth women remain on HCL into the long term the cost effectiveness estimate of HCL may trend towards that of the adult female T1DM population of the same age, but will remain superior to it.
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been	

Patient expert statement

systematically captured or reported. A scenario analysis doubles the quality-of-life effect (disutility) of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate? Does it adequately capture the effect on carers?	
Are there any important issues that have been missed in EAG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Improved quality of life for the whole family
- Allows freedom to the patient
- Early warning system to changes in glucose levels out of the accepted range
- Long term health outcomes improved
- Improved quality and length of sleep for carers and patients

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Nicola Birchmore
2. Name of organisation	FPH – Frimley Park Hospital
3. Job title or position	Paediatric Diabetes Nurse Specialist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with type 1 diabetes ? ☐ A specialist in the clinical evidence base for type 1 diabetes or hybrid closed loop systems ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

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7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for type 1 diabetes ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To manage type 1 diabetes effectively and efficiently to prevent long term complications and maintain normal life expectancy and normal life achievements.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Easier management of Type 1 Diabetes. Reduction in overall burden of Type 1 Diabetes for both patient and families. Reduction in HbA1c – which in turn improves longer term outcomes/complications.
10. In your view, is there an unmet need for patients and healthcare professionals in type 1 diabetes ?	Yes – not always consistent delivery or options for treatment across all hospitals/centres offering care. E.g. different locations/areas offer different treatment options.
11. How is type 1 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Yes

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – more access to this technology will enable all patients to have access to the technology which can help management of Type 1 diabetes and therefore better long term outcomes/ less complications.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	General population.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Additional training/learning will be required.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not aware
22. Are you aware of any new evidence for the comparator treatments since the publication of the NICE guideline [NG17]?	Not aware
23. How do data on real-world experience compare with the trial data?	Not aware
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this	

condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Questions on the external assessment report for clinical experts

Table 2 Key issues and questions for experts arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	Some of the RCT's showed some concern in bias overall in the randomisation of the studies, However as all studies had low concern for the measurement and outcomes of the data this reassures that the data could be used to support the use of HCP systems.
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	The before/after design and lack of control group leaves little protection against confounding variables and limits the ability of the research to draw conclusions from their data. Therefore, the data provided could be misconstrued and unreliable. Overall the outcome of the evidence from the NHSE pilot study did show same benefits to HCL systems as other studies.
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	Yes – as these were more reliable study resources than the HNSE pilot which used the before-after study design and no control group.
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	The key differences between diabetes in children and adults is the need for continuous insulin changes in the child population. As children are consistently going through hormonal changes and growth, therefore adding into the mix other hormones this

Clinical expert statement

	can make management of diabetes more tricky. The need for minimal insulin doses also plays a part in the management of Type 1 diabetes in children, as children may require smaller doses of insulin to maintain glucose management. Diabetes in children needs closer and more regular review in order to adjust insulin requirements to match growth.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	Diabetes in pregnancy requires much tighter diabetes management to prevent complications within pregnancy, and harm to the unborn child. Some HCL may not enable the patient to do this. However other HCL will allow this, which in turn could enable the management of Type 1 Diabetes to be tighter during pregnancy which will in turn have better outcomes for both the person living with Type 1 Diabetes and the baby.
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	Yes a time horizon of 50 years is appropriate as the life time expectancy of people living with Type 1 Diabetes has increased, thus it is more appropriate to look at the longer time horizon.
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Yes, it is appropriate to assume that the effect on HbA1c lasts for the lifetime of the model. As it would be assumed that the same outcome of HbA1c will continue with the use of HCL systems rather than noting a deterioration.
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario	A04: Durations of HbA1c effect of 5, 10 and 20 years.

analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate?	Although the scenario is doubling the quality-of-life effect of hypoglycaemia events to reflect possible carer effects, this does not also take into account other carer impacts in relation to helping/managing Type 1 Diabetes. Such as intervention due to hyperglycaemia, which would be less on a HCL but is still required in the event of pump failure, illness, growth etc. Therefore it would give an indicator but may still be less than reported.
Are there any important issues that have been missed in EAG report?	None noted.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Hybrid closed loop systems have proven to improve time in range compared to other methods of management of Type 1 Diabetes, thus meaning the overall management of Type 1 Diabetes is better, thus predicting there will be benefits in long term health also. Type 1 Diabetes is more challenging at times to manage in the Paediatric population. This in turn can be made easier with the use of HCL systems.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Living with this condition or caring for a patient with type 1 diabetes

Table 1 About you, type 1 diabetes, current treatments and equality

1. Your name	Alison Finney
2. Are you (please tick all that apply)	☒ A patient with type 1 diabetes ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with type 1 diabetes ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

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	☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I am an active member of support groups for people living with Type 1 diabetes, especially those using pump and CGM technology. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with type 1 diabetes ? **If you are a carer (for someone with type 1 diabetes) please share your experience of caring for them**	I have had Type 1 diabetes for 39 years, diagnosed aged 4. I have used multiple daily injections, and for the last 16 years insulin pump and CGM technology to manage it successfully. I have maintained an excellent quality of life and have no complications. I used insulin pump and CGM to manage diabetes during pregnancy, resulting in a healthy baby with no complications. The mental load of living with diabetes is significant. My clinically excellent results don't show the relentless effort required to maintain them. On a typical day I will: Do a blood test on waking, input to the pump and administer any recommended correction dose. Calculate carbohydrate values for breakfast and input into pump for recommendation on insulin dose. Before approving the insulin dose I'll consider my plans eg if I'm doing the school run I reduce due to the anticipated exercise which will cause a hypo; if I have an important meeting I can't risk going low in I may be more cautious with insulin; if I have a stressful day planned I may increase insulin slightly to offset the impact of adrenaline; if my period is due I'll increase basal levels and bolus ratio to counteract insulin resistance; if I'll be at my desk all day I'll increase insulin slightly to counteract the lack of activity. I do this for every meal. I always check my pump to see my BG every time I go to the toilet (no medical reason, its just convenient); when I put the kettle on and before I eat and make any adjustments needed. I'll check it at other times if I don't feel right eg if I'm struggling to concentrate

	on a piece of work I'd normally find easy it can be a sign of starting to go low; if I have a headache or feel groggy it can be a sign of going high. I'll also respond to any alarms alerting me to high or low BG. This cycle repeats constantly, all day, every day. Its thousands of micro decisions that are just always there, sometimes in the background, sometimes right at the foreground when something goes wrong eg I didn't put a temporary basal rate on early enough before the school run as I was in a meeting that overran. So then I end up low after the school run which makes us late for swimming lessons because I can't drive until I've eaten and my BG has recovered. I'll change my infusion set every 3 days and my sensor every 7 days. It takes about 5mins but needs to be done at the right time – I like to do my infusion set in the morning to ensure if it fails, I'm awake to spot the rise in BG that flags it to me, rather than having to deal with it overnight. Sensor changes mean I'll be without a working sensor for a few hours, so I avoid days when I have plans that are challenging for diabetes eg lots of physical activity or when I'll be too busy to pay attention to it. I'll also check my basal rates every couple of months by fasting to check whether my background insulin rates need adjusting.
7a. What do you think of the current treatments and care available for type 1 diabetes on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**a)** Treatment and care vary hugely from area to area. I used the charity INPUT to understand which hospitals were more supportive around pumps and asked my GP to refer me to a local one. Getting a pump took over a year of providing blood glucose data; writing statements as to why I met the criteria (which basically involves trying to prove that you've failed with MDI despite trying your best and therefore should be given access to better treatment). It was a frustrating, demoralising process which undermines the positive approach I've always tried to take to diabetes. For me MDI didn't provide the level of responsiveness I needed. I had an active life which changed most days eg I could be travelling for work across timezones; I may be in a meeting all day and barely moving; or I could be hiking in the countryside. Without the ability to adjust insulin precisely for the constant changes I was struggling with highs and lows. And the fluctuations in insulin requirements caused by my menstrual cycle also meant I needed to adjust insulin quickly, rather than

	waiting the couple of days that basal insulin changes could take to have an effect with MDI. Choice is very important. All treatments currently available have pros for some people, that's why its so important to have choice. There is a built in need to fail in the NHS system – you qualify for more sophisticated treatment methods generally only when you've failed to achieve results with simpler ones. This has a huge impact on confidence and self esteem, on top of the physical impact of having poor control while you find the right treatment. **b)** Awareness of treatment options varies greatly and I meet many people online and at Diabetes UK meetings who are not aware of what is available or the criteria they need to meet to get it. I meet many people in online support groups trying to get CSII&CGM or HCL and struggling. Some people are happy on MDI or CSII. They don't like the idea of a pump or a sensor.
8. If there are disadvantages for patients of current NHS treatments for type 1 diabetes (for example, how the treatment is given or taken, side effects of treatment, and any others) please describe these	In my experience MDI is too large hammer to crack the nut. You can't make the small adjustments in insulin dose necessary to get tighter control. I found hypos a much greater issue on MDI. CSII & CGM allow me a greater understanding of what's happening. For me CGM is like having a speedo on a car, you can see the speed at any time but also whether its increasing or decreasing. Blood tests just tell you the speed out of context at a couple of points during the day, you have no idea if you need to accelerate or brake. However, that extra data requires constant action – if I'm high I have to bolus and keep doing so until back in range. That mental load is heavy and is always there.
9a. If there are advantages of hybrid closed loop systems over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	a) I use CSII&CGM. My pump alarms if my glucose is high and I need to take action. If I'm in an important meeting I may have to mute alarms, meaning I can do nothing until I get out. If this is during the night it wakes me every two hours until my levels are back in range leading to disturbed sleep. HCL would proactively adjust insulin to prevent the high, and continue to take action until it was resolved. Without me having to be involved. This reduces the length of time

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Do hybrid closed loop systems help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	spent hyperglycaemic, and in my experience means the severity of the hyperglycaemia is also lessened. Which means I'd suffer less with symptoms like excessive thirst, tiredness, nausea, trouble concentrating and irritability. And fewer sleepless nights. It is very easy to overtreat hyperglycaemia, out of frustration and desire to fix it fast. This then leads to hypos, which when treated can swing back into hypers. Its an unpleasant cycle which leaves me feeling unwell and exhausted. HCL takes away the emotional element – it makes decisions based purely on data and adjusts by small amounts as it goes along. This takes away the clumsy, human, emotional response. c)It reduces the mental load by taking action automatically and at an earlier stage.
10. If there are disadvantages of hybrid closed loop systems over current treatments on the NHS please describe these. For example, are there any risks with hybrid closed loop systems ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Having an infusion set and sensor attached to my body 24/7 can take some getting used to. I haven't found it an issue but for some it raises issues around body image and never being able to physically escape diabetes, not even when you're in the shower. Reliability of sensors is a concern. I've found them to be very accurate and reliable, but on the occasion that they fail, full control is thrust back to you and you have to be aware that that could happen at any time. A back up plan is essential. Supply chain has been an issue during Brexit and Covid. Supplies of sensors and infusion sets (from Medtronic in my case) were disrupted and there was no certainty that deliveries would arrive in time.
11. Are there any groups of patients who might benefit more from hybrid closed loop systems or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Menstruation and menopause cause significant blood glucose management challenges for women, requiring large adjustments to insulin requirements in the short and long term (eg for a week before my period I increase my insulin to 200% due to insulin resistance, this then plummets to 75% when my period starts, before reverting to 100% for 2 weeks of the month). Such large changes in requirements need careful monitoring, it is easy to get the timing wrong. This is where smaller, proactive changes can make a big difference. I have suffered from anxiety and depression and diabetes is a lot to manage on top of them. My control suffered as I didn't have the energy to put into it that I usually would.

	HCL takes away some of the hour-to-hour decision making that I struggled with, which would be a real help. For those with cognitive impairment I would suggest a case by case decision is required – there is a need to balance the benefits of improved control with far less manual intervention against the ability to insert sensors, prepare the device and execute a back up plan in case of device failure. The devices are small and insertion requires a reasonable level of dexterity. Those with dexterity or visual impairments would need to consider it on a case by case basis.
12. Are there any potential equality issues that should be taken into account when considering type 1 diabetes and hybrid closed loop systems ? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Insulin pump usage is significantly lower in the black community. If no action is taken to understand why and respond to it there is a risk this trend would continue through to HCL usage.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Questions on the external assessment report for patient experts

Table 2 Key issues and questions for patients arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	**We consider patient perspectives may particularly help to address this issue**. I grew up with diabetes from the age of 4. Specific challenges I encountered as a child compared to an adult include: Growth hormones/puberty have a significant impact on insulin sensitivity making control more erratic. The smaller, proactive tweaks from HCL would

	have meant BG movement would have been spotted earlier and been automatically responded to. As a child I had a more active lifestyle than as an adult – sport, playing out, parties – this requires adjustments in insulin. HCL would reduce the need for manual adjustment, resulting in better control and less mental load on parents/child. No child wants to be bothered by their diabetes. Especially in teenage years there can be a desire to forget all about it. HCL would mean that even if a child/teen forgets to bolus for a mean, the system will increase insulin in response to rising BG. Not an ideal situation but far superior to the option on MDI or CSII which is the child takes no insulin and BG rises until they become ill or someone realises.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	**We consider patient perspectives may particularly help to address this issue**. Mental load on pregnant women with diabetes is huge. The pressure of knowing that your BG can impact the health of your child for the whole pregnancy is significant. And the constantly changing insulin requirements that come with pregnancy, along with any eating disruption from nausea make managing diabetes a greater challenge. Insulin resistance, especially in the 3rd trimester, was a challenge to manage. I managed having steroids prior to birth by checking my CGM and “micro-bolusing” every hour for 48 hours. I basically carried out the role of HCL manually. It was outstanding in terms of BG levels but costly in terms of lack of sleep. HCL would have made a big difference. Breastfeeding impacts insulin requirements and is hard to proactively adjust insulin for as you don’t know exactly when the baby will feed or for how long. This is also at a time when your mental space to manage diabetes is at its lowest. Automated decision making provided by HCL would really help.

A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Personally the improvements in my results have been sustained and improved over the 16 years I've been using CSII&CGM. I would anticipate a similar result for HCL because the improvements are driven by it being easier to get a better result because you have the most appropriate tool for the job. I've seen changes in control due to depression, pregnancy, burnout etc but they've still always been better than before CSII&CGM. Because doing a bad job with the right tools is still easier and better than doing a great job with less appropriate tools (in my case MDI).
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect (disutility) of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate? Does it adequately capture the effect on carers?	We consider patient perspectives may particularly help to address this issue. I suspect it still probably underestimates the impact on carer quality of life. Without this technology parents are waking multiple times a night to monitor their child's blood sugar and administer glucose/insulin as appropriate. Partners are being woken by CGM alarms. If I'm away for work in a hotel room alone my partner calls me every morning to make sure I'm not unconscious – I haven't had an episode of

	unconsciousness due to diabetes for 16 years, but he remembers when I did and carries the trauma from that. As a child with diabetes, the constant “caring” from parents about what BG levels are and what action needs to be taken can be infuriating. Having technology like HCL that takes more control of the day to day functions means parents can save their interventions for when they’re really needed. Lightening the load for parents and reducing the conflict around diabetes in their relationship with their child.
Are there any important issues that have been missed in EAG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Living with diabetes is relentless.
- In my experience this technology helps lighten the mental load on the patient and their carers.
- And it facilitates better blood sugar control. The reduction in long term complications that may result from this is important, but for me the increases in quality of life are more significant.
- Having the ability to manage your diabetes well, no matter what life throws at you is vital – technology like this means that everyday things like sports, last minute changes of plan and overrunning meetings are far more manageable.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Living with this condition or caring for a patient with type 1 diabetes

Table 1 About you, type 1 diabetes, current treatments and equality

1. Your name	Jeff Foot
2. Are you (please tick all that apply)	☒ A patient with type 1 diabetes ? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with type 1 diabetes ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	N/A -I applied as an individual to be a lay specialist member of the committee.
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	X I am drawing from personal experience X I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference X I have not completed part 2 of the statement
6. What is your experience of living with type 1 diabetes ? **If you are a carer (for someone with type 1 diabetes) please share your experience of caring for them**	I have lived with type 1 diabetes for 46 years - diagnosed in 1976. For the last 10 years I have used an insulin pump, and since 2019 I have been using a DIY hybrid closed loop system called Loop which combines information form a Dexcom continuous glucose monitor and an Ominpod pump with an app on an iPhone. I have had laser treatment on both eyes for retinopathy and have neuropathy in both feet. My diabetes management has never been as good as it has over the last 3 years and I have good quality of life.

7a. What do you think of the current treatments and care available for type 1 diabetes on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) The technology normally available (insulin pump, insulin pens, flash monitoring or finger prick monitoring and in some cases continuous glucose monitoring) is adequate to enable patients to achieve reasonable levels of diabetes management and a reasonably good quality of life most of the time. However, it places a huge burden on the patient (or their carer) and their family in having to take a lot of decisions every day, many of which involve multiple factors, and significant maths. This in its own right is extremely wearing and can frequently lead to "burn out" where patients find it too hard to keep making the endless decisions. When the unpredictability of diabetes is factored in, as well as the impact of external influences like illness, stress, hormone changes, the impact of exercise, the strain on mental health, and thus physical health, is enormous. There is some help available to support patients in dealing with this, but psychologists are in short supply, and the capacity of the NHS generally is insufficient to cope. Not only that, but the range of skills clinicians need to deal with this is too broad - clinical knowledge of complex physiological interactions in patients, combined with an ability to teach and educate patients with varying levels of education, psychological training to cope with distress, guilt, fear, burnout, depression, pharmacological knowledge regarding different insulins' activity profiles and nutritional knowledge to explain the impact of different foods on each other, the body and the insulin. As such, the current treatments and care is the best the NHS have the ability to provide, but is often completely inadequate. b) My views have been formed both from my own first-hand experience but also from many conversations with other people with diabetes, both face to face, and online, and including adults, and parents of children with type 1 diabetes. I believe my comments reflect similar views held by the majority of the people with tyep 1 diabetes that I have spoken to.

8. If there are disadvantages for patients of current NHS treatments for type 1 diabetes (for example, how the treatment is given or taken, side effects of treatment, and any others) please describe these	Disadvantages arise in several ways:- inability to access technology, inability to access advice and help to explain something, and inability to access care. The technology described is not always available to patients because CCGs in the patient's locale deem the treatment too expensive for their budgets. In addition, sometimes there is no clinician able to understand how to use the technology to best advantage meaning the patient doesn't get the full benefit. Sometimes technology is found to be uncomfortable, ineffective or difficult to use because of the way it is made or the patient's physique - a common example is the adhesive used for CGMs often produces a rash on the patient. Another could be the difficulty getting insulin absorbed well because of the patient being overweight - I have a similar problem where tissue damage from years of injecting in the same area on my thighs has rendered this site unusable for insulin pen injecting. The follow up from being given access to an insulin pump is sometimes patchy or fairly basic, with clinicians not having enough technical expertise to understand the full range of techniques for getting the best use out of the pump (using square wave boluses, pre-bolusing for meals, reducing basal rates by varying amounts depending on the type of exercise for example). Even if this knowledge is accessible, the clinician needs to be a good teacher to help patients with varying levels of education and maths ability understand how to take advantage of the knowledge being passed on. Many patients turn to peer to peer support for tips and hints on how to deal with these issues. Sometimes, the patients find appointments with clinicians are difficult to get, or they aren't comfortable with a phone or video consultation because of personal circumstances, or they may live a long way from a diabetes centre and find travel difficult. In these cases, it's hard to access the care they need, even if it's provided.

9a. If there are advantages of hybrid closed loop systems over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Do hybrid closed loop systems help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	a) The main advantage of hybrid closed loop systems is the ability of the system to manage blood glucose levels within a range "in the background" without so many patient interventions or decisions being required. This leads to a reduction in the burden on the patient from a mental health perspective, almost always results in better sleep (not just for the patient but also for their partner and family), and can often lead to improvements in the management of the diabetes overall. The key result is better quality of life for the patient, and for their partner and family. If there is also an improvement in diabetes management (from blood sugars remaining in range longer, with fewer hypos or hypers), then it is likely the risk of complications may reduce too. My experience is that I achieve a much "flatter line" in terms of blood glucose levels and can manage activity better, which in turn means I can get more jobs done, have better concentration levels and am not prevented from carrying out some tasks because of low or high blood sugars. The impact is I have almost no time off from work sick - last time was in 2019. b) I think the key benefit is the improved sleep - having an undisturbed night's sleep offers so many knock-on benefits it's not true. Before I started started using the loop, working in the background to prevent hypos before the even start to occur, I would be woken by my CGM alarm going off 2-3 times a week on average. While I managed to avoid hypos each time, I still had a broken night's sleep. The difference in mood, concentration ability, energy levels physical well-being from having undisturbed sleep each night in comparison is indescribable. Even with the best technology and help to optimise its use from the NHS I could not achieve this without Loop. c) In my opinion, hybrid closed loop systems in themselves simply offer a better technology solution usually leading to better diabetes management, improved quality of life. They still require clinicians to have multiple skillsets to help patients make the most of them, they still have the potential to be accessible for some but not others on cost grounds, and they still have the potential to not suit some patients because they essentially use the same components (CGM and pump) with their technological and dermatological features. Nevertheless, the improved quality of life, the reduction (in the longer term) of demands on the NHS care because of bad hypos, complications arising etc is enormous and significantly mitigates some of the access to care problems outlined in my answer to Q8.

Patient expert statement

10. If there are disadvantages of hybrid closed loop systems over current treatments on the NHS please describe these. For example, are there any risks with hybrid closed loop systems ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The key disadvantage from these systems is the reliance on technology, both because of the need for patients to be able to access and be comfortable using insulin pumps and CGMs, but also because of the algorithms controlling the insulin delivery by the pump. Some patients may well not feel comfortable wearing insulin pumps or CGMs and therefore the loop systems will not be suitable for them. Another key issue is the probable misconception that these systems offer a “plug and play and forget” solution to diabetes management. This is absolutely not the case. There is as much involvement most of the time in using a loop system as traditional treatment, in terms of carb counting and bolusing for food, or taking decisions (before the loop system) ahead of exercise to reduce basal delivery. However, for the most part, these are brief interventions, usually a quick check that sugar levels are flat or levelling off as expected. Rarely do you have the worry that you’ve got something wrong or diabetes has thrown a “curve ball” because the loop algorithm has smoothed out all the upward or downward trends before they become entrenched. The point is though, to get the benefit from loop systems, patients still need to actively manage their diabetes - they can’t just absolved themselves from this and dump their diabetes management onto loop. It can also require both a confidence with technology, apps and systems as well as an ability to understand complex interactions that some patients may not possess. I have a friend who is confident with technology but has discalcula and cannot cope with her perception of the level of maths and numeracy involved in using a loop system, so has chosen to continue using a CGM and insulin pump without a loop system.

11. Are there any groups of patients who might benefit more from hybrid closed loop systems or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	As mentioned above, a key concern I have is around patients who want a loop system to be a "silver bullet" and do everything for them in managing their diabetes. Identifying these patients will not always be straightforward, but I'd suggest the system will not be cost effective use of resources if prescribed for this type of person. Additionally, some patients will have issues with technology, either in terms of physically not liking CGMs or pumps attached to them, or lacking confidence with smartphone style apps, or have learning difficulties that make optimising the application of the system easy. For these people, loop systems may well increase the burden of diabetes management rather than reduce it. Perhaps it is fairly obvious, but patients with sight impairments or who find it difficult to use touchscreens because of loss of feeling in fingertips or manual dexterity are also likely to find it hard to benefit from this kind of technology but if they have carers who can help, they might still find it helps improve their quality of life. Similarly, ethnicity and familiarity with english language and numbers may have an impact too. Conversely, patients who already manage their diabetes very actively, are confident in taking decisions on varying their insulin delivery, and want more freedom to lead active lives, may well find a loop system improves their ability to manage blood sugars while active and therefore obtain a significant improvement in quality of life, if only because they achieve the reduction in hypos and hypers they're already striving for. Perhaps an unusual feature worth mentioning as a beneficial side effect of loop systems from personal experience is the reduction in neuropathy pain I have seen - Since using Loop my time in range has improved significantly and I have had far fewer high "excursions". Previously, having high blood sugars for several hours often produced severe neuropathy pain about 8 hours later. Avoiding these high blood sugar episodes happening as often has consequently led to less episodes of neuropathy pain, which is hugely welcome as you can imagine. While this is simply anecdotal evidence of a benefit, for me it's still very welcome.
13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Part 2: Questions on the external assessment report for patient experts

Table 2 Key issues and questions for patients arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	We consider patient perspectives may particularly help to address this issue.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	We consider patient perspectives may particularly help to address this issue.
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	

Patient expert statement

Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect (disutility) of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate? Does it adequately capture the effect on carers?	We consider patient perspectives may particularly help to address this issue.
Are there any important issues that have been missed in EAG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Peter Hindmarsh
2. Name of organisation	University College London Hospitals NHS Foundation Trust
3. Job title or position	Professor of Paediatric Endocrinology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with type 1 diabetes ? ☐ A specialist in the clinical evidence base for type 1 diabetes or hybrid closed loop systems ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for type 1 diabetes ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To maximise the health and well being of patients and their families and/or carers by replacing insulin in as physiological manner as possible thereby normalising blood glucose concentrations
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in glycosylated haemoglobin by 0.5% and/or the attainment of the NICE target of 6.5%. This to be achieved with less than 1% of time spent with a blood glucose concentration less than 1% and 70% of the time spent in the normal range of blood glucose
10. In your view, is there an unmet need for patients and healthcare professionals in type 1 diabetes ?	Simple systems (from the patient point of view) that deliver insulin to mimic normal physiology that are fully/semi automated
11. How is type 1 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	We use NICE NG 18 along with TA151 The pathway of care in paediatrics is well defined as part of the NHSE Best Practice Tariff The technology would not alter the pathway of care but would rationalise care delivery as fully/semi automated systems require less HCP input with time
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes as the cost of hybrid closed loop is the same as pump and CGM combined and there is a clear Procurement pathway through the NHS Supply Chain All paediatric diabetes care is in secondary care which is where this technology will be used

	Teams should already be trained in the use of pumps and CGM so the additional training for closed loop is minimal and probably no more than 2 hours per HCP
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The technology is clearly more effective than pump plus CGM, pump alone and injection therapy. The ability to normalise blood glucose will reduce long term complications and increase life expectancy We know already from clinic comments and the NHS Pilot that family quality of life is improved
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The Pilot data indicate that all patients with type 1 diabetes could benefit from this therapy
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	If the team is using pump and CGM already then the difference between that approach and closed loop is minimal so no effect overall
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules would be the same as for TA151
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more	Ease of use of the technology is not captured nor is fear of hypoglycaemia. Ability to drive more easily also is missing

easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Ys this is what we have always worked towards ie. the artificial pancreas. This is the only therapy that replaces insulin in a physiological manner with reduced risks of either over or under treatment The technology would allow ,more patients to safely attain the NICE goal for glycosylated haemoglobin
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects profile is exactly the same as any insulin therapy it is just safer and more effective
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials and particularly the NHS Pilot do reflect UK clinical practice. The outcomes are HbA1c along with time in range and time spent hypoglycaemic. These are all reported. Longer term studies will be needed to address complication rates.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of the NICE guideline [NG17]?	NHS Pilot data

23. How do data on real-world experience compare with the trial data?	Greater efficacy
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	From the National Paediatric Diabetes Audit we know that access to technology is affected by deprivation and ethnicity. We need a better understanding in these group of how they perceive technology and how technology fits in with their health and societal beliefs as well as health literacy and numeracy

Part 2: Questions on the external assessment report for clinical experts

Table 2 Key issues and questions for experts arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	The populations in the RCTs area s expected for this type of study. The NHS Pilot data is more real world experience particularly the paediatric population which showed overall a better improvement in HbA1c than the RCTs with a reduction in time spent hypoglycaemic an important consideration in this population as hypoglycaemia interferes with learning in school. The risk of bias is low and the NHS Pilot studies show that the RCT findings are applicable to broader population groups.
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	This is a fair observation. The studies were not designed as RCTs with control groups. The strength of the pilot was that it included a much broader range of patients than usually recruited to RCTs. Assessment of the impact of the hybrid closed loop system showed that the effect in paediatrics was across the range of HbA1c from good to poor control. In the good control group time spent hypoglycaemia was reduced by 60% and in the poor control group significant decreases in HbA1c of 20 mmol/mol were observed suggesting that hybrid closed loop therapy would be valuable in all with type 1 diabetes for different reasons
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	In essence yes. The point is not so much the overall effect size on HbA1c but the effect across the HbA1c range at the start of the study. It is also important that HbA1c is not the only measure. HbA1c may for example have remained unchanged in the study in certain individuals for example those with already good control but the time spent hypoglycaemic was reduced so that good control was attained with less hypoglycaemia risk
The EAG has reservations about the reliability the iQVIA core diabetes model	Hypoglycaemia has more impact on learning for children. It is always hard to know how improvements in HbA1c in children will translate into reduction in long term problems in

for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	children will actually translate into adulthood. Complication rates are low in children anyway. The modelling tends to focus on only life expectancy, quality adjusted life expectancy, cumulative incidence and time to onset of long-term complications as the outcomes of interest. Such data are usually unavailable for paediatric assessment and what might be available in 2022 would reflect practice 20 years ago at least.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	Not within my scope of expertise
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	Yes it is especially for paediatrics. Even for young adults this only gets us to 70 or 75 years of age
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Yes it is. Data from paediatrics using pump therapy alone indicates that once a HbA1c channel is achieved it is maintained. There are perturbations in puberty but these are transient with return to the original channel thereafter
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around	Hypoglycaemia is important at all ages although for different reasons such as driving, machinery use and schooling. Ideally it should be included

annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate?	Yes we collected such data in the paediatric pilot and the improvement in quality of life and sleep for families was at least to this order
Are there any important issues that have been missed in EAG report?	It is not just HbA1c although I understand why the focus is on this but on glycaemic status which has various components. It would have been useful to consider impact of hybrid closed loop on those with poorer control

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Hybrid closed loop delivers insulin in a way that best mimics the normal production of insulin which is a tenant of endocrine replacement therapies

There is an important reduction in HbA1c particularly in groups with poorer diabetes control

In patients with good control HbA!c is maintained without an increased rate of hypoglycaemia

In paediatric practice parents report improved quality of life and sleep

Click or tap here to enter text.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Sufyan Hussain
2. Name of organisation	Guys and St Thomas' NHS Trust
3. Job title or position	Consultant and Honorary Senior Lecturer
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with type 1 diabetes ? ☒ A specialist in the clinical evidence base for type 1 diabetes or hybrid closed loop systems ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N.A
8. What is the main aim of treatment for type 1 diabetes ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve quality of life and make living with the condition easier on a day to day basis with reduced burden of day to day management or medical issues – if this is accomplished the numeric aspects (HbA1c, time in range, hypos, time below range) will by default improve
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	HbA1c reduction of 0.6% or greater Time in range improvement of 10% or greater Time below range reduction to <5 % or lower Diabetes distress reduction to 2 or less (on 2 question scale)
10. In your view, is there an unmet need for patients and healthcare professionals in type 1 diabetes ?	Yes: For patients: Reduction in mental burden of day to day management – although excellent levels can be achieved by some eg with CSII and rtCGM, this requires a lot of work and is not achievable by most or will come at the expense of QoL. For HCPs: Time required to help on above is limited in clinics and HCPs cannot see their patients often enough meaning that better solutions for patients to self-manage are needed
11. How is type 1 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NICE clinical guidelines ABCD type 1 diabetes collaborative statements Diabetes technology network best practice guides International consensus statements for type 1 diabetes care – eg hybrid-closed loop The pathway of care in NHSE England is well-defined

• What impact would the technology have on the current pathway of care?	Prior to recent NICE guidance update in T1DM, this was based on the NHSE Type 1 technology pathway that mirrored NICE and NHSE funding arrangements With the recent update the pathway has modified: All patients with type 1 diabetes will have access to some form of CGM All patients on a pump that has an HCL system within it can get access to rtCGM The pump pathway (HbA1c>8.5% or recurrent disabling hypos) remain the same as from 2003's initial NICE tech appraisal. There is regional variation reflected in NDA results. This varies according to clinical proficiency with technology, clinician bias, CCG funding or difficulties in getting reimbursement for trusts At present with the recent updates, technology has already demonstrated significant improvement in real-world data from is-CGM, CGM, pumps and hybrid closed loops Benefits are improved glycaemia, reduced diabetes burden and in my experience improved quality of life
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	It is already being used in centres with experience With hybrid-closed loops there is initial investment of HCP time for training and education which is followed by reduced / less need for future interactions given automation

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It is used in specialist secondary or tertiary care centres with experience of pumps and sensors Investment needed includes: HCP training in technologies- time to enable this Different clinic pathways – front-loading of education for technologies to ensure optimal use esp . in those from ethnic minorities , mental health conditions and lower socio economic status Tele-medicine / video facilities to allow remote group interactions with ease
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – it has already done so in my experience/ practice - Yes to all On a day to day short term basis has a positive impact on ability to do things in life (eg exercise, work , shift work ,carer roles), less risk of dependency Long term it has ability to reduce complications
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective - Higher hba1c – groups unable to improve this - Psychological conditions - Hypoglycaemia issues Less effective - Those unable to use technology due to issues with consistent use (unable to wear devices eg mental health reasons or reactions) - hence there still is a need for curative solutions such as islet or cell therapy
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	Much easier to use given less requirement for HCP interaction after initial training and better results

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Practical implications are above in investment, training needed
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Rules are essentially based on improvement in glycaemia or hypos or reduction of mental burden Goals are set for the technology pre-treatment If these are not being met than it may need to be stopped Less testing needs with this technology
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes - The reduction in mental burden, especially from newer versions of HCL systems that are testing free and lower alarm burden, with improved algorithms have not been fully demonstrated in the evidence. Hence the QALY calculation underscores this - Depression, anxiety and other mental health issues in diabetes remains a big challenge and worsens ability to self-manage. These systems provide reduction in burden and help these situations immensely - Some of the evidence is based on older systems and in patient groups where the comparators were doing well anyway – so the drop in HbA1c/ TIR is under represented - Improvement in hypos is also noted especially for those with higher baseline levels
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Yes, to all. It improves current need by: Reducing mental burden of day-to-day management of their condition Improved night time control (and sleep) Improved ability to focus on work tasks Less high glucose levels and less hypos with less efforts.

• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Alarms- can add to mental burden , however newer versions have less alarm burden Skin / adhesive reactions – make some aspects of the technology esp. cgm unwearable
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No – they are done in groups of individuals who are already doing well in their diabetes management and more motivated For UK , this still means improvements will be noted but are underestimated Reduction in HbA1c, improvement in time in range, improvement in time below range, reduction in distress or burden or other psychosocial impact Psychosocial impact was less reliably measured Surrogate outcomes: Time in range has good data to reflect it can be used to gauge development of complications Adverse effects: Skin reactions Training needed and different philosophy of managing the condition : if this is missed it can lead to hyperglycaemic and hypoglycaemic problems which in their worst case can be severe - i.e. HCP competency and patient education is key
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No However ADAPT study missing in evaluation https://www.sciencedirect.com/science/article/abs/pii/S2213858722002121

22. Are you aware of any new evidence for the comparator treatments since the publication of the NICE guideline [NG17]?	https://www.sciencedirect.com/science/article/abs/pii/S2213858722002121
23. How do data on real-world experience compare with the trial data?	Real-world experience mirrors trial data There is more inclusion of people with high hba1c – hence improvements in glycaemia are more apparent
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	Yes: Current guidance on access to pumps has meant those from lower socio-economic groups or ethnic disparities have less access to pumps If they have less access to pumps, their ability to use HCL systems will not be possible More training is needed in such groups to overcome the challenges in tech literacy .Once achieved this is likely to achieve improved outcomes that would not be possible without technology/HCL

Find more general information about the Equality Act and equalities issues here.	

Part 2: Questions on the external assessment report for clinical experts

Table 2 Key issues and questions for experts arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	I have concern in the recruitment of patients Most from these studies (most in the US) will be from groups with medical coverage, motivated and white Caucasian populations Hence their baseline type 1 diabetes management is likely to be good The percentage improvements are likely to be less Education needs are lower in these groups and therefore safety in using the technology is better Sub-analysis of studies using data from those with less well-managed diabetes at baseline is required A study (ADAPT study) which addresses this in part was not included
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	It actually mirrors real-world NHS practice better and does eliminate some of the biases in RCT studies funded by industry in individuals for the reasons above Of course, there are inherent limitations but overall, the end result can be better reflected in such real-world evaluations. The value it provides is reflecting that groups with higher hba1c, in a real-world practice situation (where you don't have extra expenses for staffing or visits) can achieve improvements in glycaemia and hypoglycaemia, as well as reduction in diabetes burden.
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop	No I do not Firstly, this is a mixture of 1st and further generation HCL systems underscoring there potential

Clinical expert statement

systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	Secondly, in technology , higher starting hba1c gives a bigger drop – the RCTs baseline was much better and % reduction was not as strong. I would like to again draw reference to the ADAPT study https://www.sciencedirect.com/science/article/abs/pii/S2213858722002121
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	As an adult diabetes physician who looks after young adults differences include: Children: tend to have less predictable behaviour and activity ; but may have some/more endogenous insulin compared to adults with longer duration of diabetes; children may also be more insulin sensitive and there may be issues around having injections at school; hence pump accessibility is better. Less proficiency in self management Adults are quite varied (eg young adults to elderly) with variable needs at different stages of their life and can be more complex given multiple influences. Difficulties in self-management in those in carer, shift-work, busy routines, or due to cognitive impact can be apparent in this group at different stages . More complexity in medical situation , insulin absorption , less endogenous insulin, hypo unawareness also becomes apparent with longer duration of the condition
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	Different licensing requirements and lower targets are needed in pregnancy
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	Yes, although in older adults this may not be realistic

Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Yes- there may be some change, but largely our clinical experience is improvements persist
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	SA07b gives a better estimation of the cost from SHE / NSHE SA09 is also important – mental health effects of SHE and NSHE are important including depression and anxiety which is higher in this group
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate?	Yes
Are there any important issues that have been missed in EAG report?	As mentioned previously, I feel the comparator group does not mirror the clinical pathway hence the benefits of HCL are underrepresented Is-CGM and rt-cgm are not the same cost wise or clinically Cost of HCL for those on rtCGM/CSII already are over-estimated - most CSII's currently have an algorithm at no extra cost

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Comparator group does not mirror clinical pathway following recent updates in NICE CG – this is a key aspect which will mean that the impact of guidance on improving patient care in type 1 diabetes will become limited.
Patient groups in RCTs usually have higher levels of motivation and better ability to self-manage than NHS populations
RWE from NHS audit and ADAPT study are the better examples at present, or sub-analysis of high HbA1c/time in range individuals to gauge what threshold of starting HbA1c/time in range leads to a more significant improvement and better cost/QALY
Terms
Is-CGM and rt-cgm are different modalities on cost and efficacy but grouped in the same baseline

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Fiona Regan
2. Name of organisation	Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust (previously Frimley Health Foundation Trust)
3. Job title or position	Paediatric Consultant in Diabetes and Endocrinology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with type 1 diabetes ? ☐ A specialist in the clinical evidence base for type 1 diabetes or hybrid closed loop systems ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes

Clinical expert statement

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for type 1 diabetes ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To optimise glycaemic control, whilst still living a full and active life without restrictions, thereby minimising risk of both short and long term diabetes complications.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	An improvement in Time in Range of 10% or more and/or and improvement in HbA1c of 5mmol/mol or more and/or improved Quality of Life
10. In your view, is there an unmet need for patients and healthcare professionals in type 1 diabetes ?	Yes
11. How is type 1 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	In paediatrics we treat type 1 diabetes with multiple daily injections of insulin or use insulin pump therapy. We have been using hybrid closed loop pumps for the last 5 years and have found them to be very effective. Available guidelines include: NICE guideline NG18 sets out the management for children and young people with diabetes. NICE Technology appraisal TA151 sets out use of insulin pumps for children 12 years and over NICE Diagnostics guidance DG21 looked at sensor augmented pump therapy in 2016 and reviewed MiniMed Paradigm Veo and Vibe pumps – neither are available any longer. NICE Medtech innovation briefing MIB110 sets out use of Freestyle Libre for glucose monitoring NICE Medtech innovation briefing MIB233 sets out how to the use Dexcom G6 real time continuous glucose monitoring The pathway of care for new and emerging technology has not been well defined, particularly with regard to access to funding. This has resulted in a

	postcode lottery for patients with diabetes. The difficulties with funding has prevented some professionals in engaging fully with these technologies. Even when a pathway for funding the technologies has been published often this has not included the additional staffing required for training patients and/or professionals to use the technology. Hybrid closed loop pumps could markedly alter the pathway of care, particularly if it was considered to best standard of care from diagnosis.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will continue to be used as it is currently but I would anticipate the use of these pumps will markedly increase, particularly as the technology improves with time. As mentioned above I would anticipate that it may become used frequently from diagnosis. The cost of these pumps is not a lot more than standard pump therapy. These pumps will need to be instigated by specialist clinics. Investment will be needed to fund additional staff training and patient and family training, particularly if this is to be instigated from diagnosis.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect that this technology will improve 'Time in Range' for glucose levels and also improve HbA1c thereby reducing both short and long term diabetes complications. The improved glycaemic control and some of the automated features of the hybrid closed loop pumps will improve quality of life for those using the technology successfully.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology is very helpful in very young patients (pre-school children) in whom glycaemic control can be difficult due to varied activity levels and varied food intake. I also feel this technology is helpful in young people undergoing their puberty in whom both insulin resistance and compliance can impede attaining good diabetes control. The partial automation of the pump can help alleviate some of the problems.

	Some patients will not want to use insulin pump therapy as they do not want to have something connected to them 24/7.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology will be easier for patients to use. Healthcare professionals will need to be trained how to use the pumps and how to make adjustments to improve glycaemic control. Each system works slightly differently and so professionals will need training on each system separately. Patients will need to be using continuous glucose monitors for the pumps to work. They will also need to be able to download their pumps to facilitate optimal self management.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Prior to starting this technology patients should sign a contract stipulating their commitment and the diabetes team's commitment to using the technology to enable clinical benefit. This should include conditions in which the technology will be withdrawn.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Impact on quality of life may not be captured for paediatric patients and their parents, particularly relating to absence at school/work days lost for parents/sleep quality and quantity and quality for both children and their parents.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	The integration of continuous glucose monitoring and insulin pump therapy will improve glycaemic control and reduce risk of diabetes related complications. It has been shown that in the same patient overnight insulin requirements can vary by up to 30%, the integrated system can help adjust the basal insulin without the patient or their parent getting up to correct high or low glucose levels. Daytime insulin requirements can also vary hugely not only with varied food intake but also with changes in emotions,

• Does the use of the technology address any particular unmet need of the patient population?	pubertal hormones, stress levels and exercise. The integrated system can help overcome some of these variations. This does result in a 'step-change' in the management of diabetes.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I would not anticipate any adverse side effects other than those that exist from using pump therapy and continuous glucose monitors. However we are aware that the alarms in those using pumps and continuous glucose monitoring can result in alarm/disease fatigue. The increased amount of data available can cause also anxiety and 'micro management' in some patients and families. Micro management can impact on the systems being able to learn from results and feedback and limit their effectiveness.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials are now being published showing that these systems can improve both 'Time in Range' and HbA1c. Initial trials were industry led but now real world data is becoming available which have confirmed the initial data regarding improvements.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Many clinics have reviewed data on their own patients and found similar results to that demonstrated in larger scale trials. Some of these have been displayed in poster presentations rather than publications due to the small numbers involved. It is encouraging to see that good results can be achieved outside of clinical trials.
22. Are you aware of any new evidence for the comparator treatments since the publication of the NICE guideline [NG17]?	There have been some papers published since 08/2022 including Roberts et al Diabetes Med 2022 Sep;39(9) Messer et al Diabetes Technol Ther 2022 Oct 4

23. How do data on real-world experience compare with the trial data?	Real world data shows similar improvements in time in range and HbA1c as the trial data.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	It has been clear from UK National Paediatric Diabetes Audit data that there are inequalities between patients who are using insulin pump therapy and/or continuous glucose monitoring. Those in more deprived areas and non white populations are less likely to be using pumps and/or continuous glucose monitoring and are therefore less likely to be on hybrid closed loop insulin pumps. These groups have also been shown to have worse glycaemic control. A variety of initiatives are underway to try and address these inequalities. The issues of inequality for this technology are likely be the same as we are already encountering for insulin pumps and continuous glucose monitoring. Access to technology to be able to use these newer pumps including smart phones and ability to download pumps may be part of the problem in these groups, both areas that are being considered in current initiatives.

Part 2: Questions on the external assessment report for clinical experts

Table 2 Key issues and questions for experts arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	It is a little concerning that the information on randomisation is not clear for 6/12 of the studies. We need to know that these devices can work for all patient groups and that is was trialled equitably in all patients and not selectively trialled.
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	The NHSE pilot studies were certainly limited by lack of a control group. However I think they demonstrate that in centres using this technology already good effect can be demonstrated in all patient groups. Most of the RCTs have been carried out on populations with diabetes control already in the acceptable range prior to use of the technology. We are keen to reduce inequalities in care in the UK so I think it is useful to know in those patients groups with suboptimal glycaemic control that this technology may confer clinical benefit.
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	I think using the RCT meta-analysis as the base case of the model was a sensible decision but as mentioned above I think the NHSE pilot data is useful supplementary information for potential results in patients with suboptimal glycaemic control.
The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	Children are more insulin sensitive than adults and thereby small changes in insulin dosing can have significant effects. They also tend to have a more varied lifestyle than adults in terms of activity levels and food intake. As

	children grown and develop their hormonal milieu changes, impacting on insulin sensitivity. Very young children will not be able to recognise or anticipate their glycaemic variations and are not in a position to adjust their insulin dosing accordingly. Children are exposed to being cared for in multiple different environments during daily life including nursery, school, college, after school clubs, sports clubs, relatives homes, friends homes etc. To have personnel trained to administer and adjust insulin in all these settings is very difficult and a level of insulin automation is very helpful.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	In the current climate in which we would anticipate people with diabetes living for 50+years I think using a long time line horizon is useful.
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Yes I think particularly given that the systems do have some integrated artificial intelligence to continually improve insulin adjustment it is reasonable to assume the effects do last for the lifetime of the model.
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of	

these events are explored in model scenario analyses (see list page 205 in the assessment report). Which of these scenario analyses is most appropriate?	
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate?	From my clinical practise the vast majority of parents of children with diabetes who have started HCL insulin pumps have found them invaluable and have noted a positive impact on their quality of life. Notwithstanding this some patients I have looked after have started HCL and then reverted to standard insulin pump therapy, although these are in the minority. This data is difficult to capture in a numerical way so I think the method suggested is reasonable.
Are there any important issues that have been missed in EAG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

HCL insulin pump therapy can improve HbA1c significantly.

HCL insulin pump therapy can improve Time in Range significantly.

HCL insulin pump therapy can improve Quality of Life for patients and their carers.

Given the above I think HCL insulin pump therapy is cost effective and beneficial for patients and their families both in the short and long term.

The widespread role out of HCL insulin pump therapy will require significant additional staffing time for training and education, particularly if it is envisaged to become the standard therapy from diagnosis.

Clinical expert statement

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form
Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Part 1: Treating type 1 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Philip Weston
2. Name of organisation	Liverpool University Hospitals Foundation Trust
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with type 1 diabetes ? ☐ A specialist in the clinical evidence base for type 1 diabetes or hybrid closed loop systems ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Part 2: Questions on the external assessment report for clinical experts

Table 2 Key issues and questions for experts arising from the external assessment report

The populations from the RCTs included in the network meta-analysis are listed in table 1 on page 68 of the assessment report. The risk of bias summary is on page 109. Do you have any concerns about the generalisability/bias of any of the RCTs?	The available studies looking at HCL technology consist of small numbers of study subject, are of short duration and often have affiliated links to device companies. The majority of the studies available look at children and younger adults whereas most pump users in our adult clinics are not in either of these groups. As always with RCTs we extrapolate from these data to our clinic populations.
The NHSE pilot studies were non-randomised with no control group and a before-after study design. The external assessment group note that the design limits the scientific value of the evidence. What is your opinion on the value of the evidence from the NHSE pilot studies?	Whilst I agree the NHSE studies were scientifically limited in that they were a 'before and after' study rather than an RCT, the advantage of these studies is they were based on 'real world' scenarios with a broad selection of people living with diabetes. These are the patients that we see daily in clinic that struggle to achieve glycaemic targets and who experience the physical and psychological impacts of type 1 diabetes.
The network meta-analysis of data from 12 RCTs showed that hybrid closed loop systems were associated with a decrease in HbA1c of 0.28%. The NHSE pilot data showed that hybrid closed loop systems were associated with a decrease in HbA1c levels of 1.50%. The EAG used the network meta-analysis result in the base case of the model. Do you agree with this decision?	The selection criteria for the NHSE studies was solely based on HbA1c. We know from any diabetes intervention study that those with the highest HbA1c at entry to the study have the greatest fall in HbA1c during the study. It is therefore no surprise that the NHSE study patients had such a significant HbA1c fall. If we look at time below glucose range there was no benefit in TBR in the NHSE studies as this was not a problem for the majority of the patients recruited to the studies. In the RCTs TBR was significantly reduced in those studies reporting that measure. As patients with diabetes with lower HbA1c are recruited in the RCTs the HbA1c falls were lower compared to the NHSE studies.

The EAG has reservations about the reliability the iQVIA core diabetes model for modelling a paediatric population. What are the key clinical differences between diabetes in children and adults?	Adults generally are self managed. Paediatric populations usually have parents managing or helping to manage their diabetes. Children grow and this has an impact on diabetes control/insulin requirements etc.
The EAG has not considered the cost effectiveness of hybrid closed loop systems for pregnant women. What are the key clinical differences between diabetes in pregnant and non-pregnant people?	I presume this relates to type 1 diabetes in pregnancy rather than gestational diabetes? HbA1c is a less effective clinical measure (or study outcome) of diabetes control in pregnant women. The evidence for improvements in time in range is increasing but limited at present.
A key driver of model results is the time horizon of the model. The model base case uses a time horizon of 50 years. Time horizons of 8, 12 and 24 years were explored in scenario analyses. Is a 50-year time horizon appropriate?	
Another key driver of the model results is the duration of the effect of hybrid closed loop systems on HbA1c. The model assumes the effect endures for the lifetime of the model. Durations of HbA1c effect of 5,10 and 20 years were explored in scenario analyses. Is it appropriate to assume that the effect of hybrid closed loop systems on HbA1c lasts for the lifetime of the model?	Most clinical interventions are associated with an initial fall in HbA1c the, over time, HbA1c and other measures of glycaemic control drift up. The NHSE pilot studies showed a more sustained fall in HbA1c (but still only over 12 months) which is unusual for a diabetes intervention.
The base case model does not include severe hypoglycaemic events (SHE) and non-severe hypoglycaemic events (NSHE) because of the high uncertainty around annual event rates. Inclusion of these events are explored in model scenario analyses (see list page 205 in the assessment	It is very important to include SHE and NSHE in the case model as the data shows significant clinical impacts of HCL technology on these issues. There are also significant health and personal costs from patients who experience severe hypoglycaemia.

report). Which of these scenario analyses is most appropriate?	SA09 captures these issues.
The base case model does not include an impact on the quality of life of carers because outcomes have not been systematically captured or reported. A scenario analysis doubles the quality-of-life effect of hypoglycaemia events to reflect possible carer effects. Is this analysis appropriate?	I feel it is essential to look at the impact of these technologies on quality of life of people living with diabetes and their carers. As a long-term health condition type 1 diabetes is associated with significant psychological issues and 'diabetes distress' has an enormous impact on quality of life as well as diabetes outcomes in such patients.
Are there any important issues that have been missed in EAG report?	

Title: **Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes**

Produced by: Warwick Evidence

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Contributions of authors

Asra Asgharzadeh: senior clinical effectiveness (screening for clinical evidence, assessment of study inclusion, data abstraction, write-up of clinical results) , Mubarak Patel: statistical analysis (network meta-analysis, write-up of results), Martin Connok: statistical analysis (clinical study analysis, write-up of results), Sara Dmery: clinical effectiveness (screening for clinical evidence, assessment of study inclusion, data abstraction, risk of bias write-up), Iman Ghosh: clinical effectiveness (quality appraisal), Mary Jordan: systematic review of cost-effectiveness, Kevin Momanyi: screening for clinical evidence, assessment of study inclusion, quality assessment, Karoline Freeman: clinical effectiveness (screening for clinical evidence, assessment of study inclusion, data abstraction, Rachel Court: senior information specialist (review and update searches, locate records, reference), Anna Brown: information specialist (design searches, locate records), Sharin Baldwin: clinical effectiveness (screening for clinical evidence, assessment of study inclusion), Fatai Ogunlayi: clinical effectiveness (screening for clinical evidence, assessment of study inclusion), Chris Stinton: clinical effectiveness (screening for clinical evidence, assessment of study inclusion), Ewen Cummins: senior cost-effectiveness (cost-effectiveness lead and production), Lena Al-Khudairy: clinical effectiveness lead.

Please note that: *Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.* Depersonalised Data (DPD) is highlighted in pink.

ABSTRACT

Background: Hybrid closed loop systems are a new class of technology to manage type 1 diabetes. The system includes a combination of real-time glucose monitoring from a continuous glucose monitoring device and a control algorithm to direct insulin delivery through an insulin pump. Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families.

Aim: The aim of this appraisal was to assess the clinical and cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring.

Methods: a systematic review of clinical and cost-effective evidence following a pre-defined inclusion criteria informed by the aim of this review. An independent economic assessment using iQVIA CDM to model cost effectiveness.

Results: The clinical evidence identified 12 randomised controlled trials (RCTs) that compared HCL to CSII+CGM or SAP therapy. HCL arm of RCTs achieved improvement in HbA1c % (HCL decreased HbA1c % by 0.28 (-0.34 to -0.21), increased % TIR (between 3.9 – 10.0 mmol/L) with a mean difference of 8.6 (7.03 to 10.22), significantly decreased TIR (% above 10.0 mmol/L), with a mean difference of -7.2 (-8.89 to -5.51) but did not significantly affect % time within range (<3.9 mmol/L). Comparator arms also showed improvements but this was less than that observed in the HCL arm. Outcomes were superior in the HCL arm vs. comparator arm. The cost effectiveness search identified six studies which were included in the review systematic review. Studies reported subjective cost-effectiveness that was influenced by the willingness to pay thresholds. Economic evaluation showed that the published model validation papers suggest that an earlier version of the iQVIA CDM tended to overestimate the incidences of the complications of diabetes, this being particularly important for severe visual loss and ESRD. Medium term modelling of overall survival appeared good, but there was uncertainty about its longer term modelling.

Current prices suggest that HCL is around an annual average £1,500 more expensive than CSII+CGM, though this may increase by around a further £500 for some systems.

The EAG base case applies the EAG RCT NMA estimate of -0.29% HbA1c for HCL relative to CSII+CGM. There was no direct evidence of an effect upon symptomatic or severe hypoglycaemia events, therefore the EAG does not include these in its base case.

The change in HbA1c results in a gain in undiscounted life expectancy of 0.458 years and a gain of 0.160 QALYs. Net lifetime treatment costs are £31,185, with reduced complications leading to a net total cost of £28,628. The cost effectiveness estimate is £179k per QALY. The EAG has some concerns about using the iQVIA T1DM to model a paediatric population. The EAG does not formally consider the cost effectiveness of HCL compared to CSII+CGM for pregnant women. It only notes the relationship between HbA1c and birth defects.

Conclusions: RCTs of HCL interventions in comparison CSII+CGM or sensor augmented pump therapy achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10 mmol/L, and in hyperglycaemic levels.

Word count: 526

SCIENTIFIC SUMMARY

Background

Type 1 diabetes was formerly known as insulin-dependent diabetes. It is the result of an autoimmune process leading to destruction of the insulin-producing beta cells in the pancreas. The cause of this auto-immune disease is not known. Diabetes is managed by lifestyle and education, glucose monitoring, and insulin delivery. Treatment with insulin is aimed at replicating the function of the pancreas. The aim of treatment is to control hyperglycaemia and avoid hypoglycaemia. The NICE target for type 1 diabetes is 48 mmol/mol (formerly 6.5%) but few people with T1DM achieve that. Interventions to manage diabetes include: education, continuous glucose monitoring (include a sensor, transmitter and display device), insulin therapy (multiple daily injections or continuous subcutaneous insulin infusion). Continuous subcutaneous insulin infusion (CSII) is an alternative therapy to multiple daily injections. CSII is an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. Sensor-augmented pump (SAP) therapy systems combine CGM with CSII. The systems are designed to measure interstitial glucose levels (every few minutes) and allow immediate real-time adjustment of insulin therapy. The systems may produce alerts if the glucose levels become too high or too low. SAP can operate in standard (manual) and advanced (automatic) modes. In the manual open loop mode, the continuous glucose monitor and glucose pump do not communicate with each other, and insulin doses are programmed by the user, who makes manual adjustments. Hybrid closed loop systems are a new class of technology that use a combination of real-time glucose monitoring from a continuous glucose monitoring device and a control algorithm to direct insulin delivery through an insulin pump. Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families.

Objectives

The intervention of interest is a class of automated insulin delivery systems which consists of three components – a CGM, a microprocessor with control algorithms, and a pump. The

overall objectives of this project are to examine the clinical and cost-effectiveness of hybrid closed loop systems for managing glucose levels in people who have T1DM.

1. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?
2. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Methods

Systematic review methods followed the principles outlined in the Cochrane Handbook of Diagnostic Test Accuracy and the NICE Diagnostic Assessment Programme manual.

A comprehensive search was developed iteratively and undertaken in a range of relevant bibliographic databases and other sources, following the recommendations in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions. Date limits have been used, in order to identify records added to databases since the searches for DG21 (run in 2014). Two reviewers screened titles and abstracts and assessed eligibility of studies. Studies that satisfy the following criteria were included:

Populations: People who have T1DM who are having difficulty managing their condition

despite prior use of at least one of the following technologies: continuous subcutaneous insulin

infusion, real time continuous glucose monitoring, flash glucose monitoring

If evidence permits the following T1DM subpopulations will be included:

- Pregnant women and those planning pregnancies (excluding gestational diabetes).[b]
- Children (5 years and under, 6 – 11 years, 12 - 19 years).

- People with extreme fear of hypoglycaemia.

People with diabetes related complications that are at risk of deterioration.

Target: Type 1 diabetes mellitus

Intervention: Hybrid closed loop systems

Comparator: Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated).
Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.

Outcomes: Intermediate measures

- Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l)
- Time below and above target range
- Change in HbA1c
- Rate of glycaemic variability
- Fear of hypoglycaemia
- Rate of severe hypoglycaemic events
- Rate of severe hyperglycaemic events
- Episodes of diabetic ketoacidosis
- Rate of ambulance call outs
- Rate of hospital out-patient visits
- Rate of weight gain

Clinical outcomes

- Retinopathy
- Neuropathy

Intermediate measures

- Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l)
- Time below and above target range

- Change in HbA1c
- Rate of glycaemic variability
- Fear of hypoglycaemia
- Rate of severe hypoglycaemic events
- Rate of severe hyperglycaemic events
- Episodes of diabetic ketoacidosis
- Rate of ambulance call outs
- Rate of hospital out-patient visits
- Rate of weight gain

Clinical outcomes

- Retinopathy
- Neuropathy
- Cognitive impairment
- End-stage renal disease
- Cardiovascular disease
- Mortality

Additional clinical outcomes in women who are pregnant/have recently given birth:

- Premature birth
- Miscarriage related to fetal abnormality
- Increased proportion of babies delivered by caesarean section
- Macrosomia (excessive birth weight)
- Respiratory distress syndrome in the new-born

Device related outcomes

- Adverse events related to the use of devices

Patient-reported outcomes

- Heath-related quality of life
- Psychological well being
- Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)
- Anxiety about experiencing hypoglycaemia
- Acceptability of testing and method of insulin administration

Carer reported outcomes

- Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)

Study design: Hybrid closed loop systems studies included any design. All comparator studies: comparative effectiveness studies.

Healthcare setting: Self-use supervised by primary or secondary care

Publication type: Peer reviewed papers

Language: English

Prioritization for full text assessment: We applied a two-step approach for identifying and assessing relevant evidence. The elements used to prioritise evidence (study design, study length, sample size). The most rigorous and relevant studies (mainly RCTs) were prioritised for data extraction and quality assessment. Observational studies were recorded and reported narratively. Two reviewers extracted data independently, using a piloted data extraction form. Disagreements was resolved through consensus, with the inclusion of a third reviewer when required. The risk of bias of randomised trials was assessed using the revised Cochrane risk-of-bias tool for randomized trials. We synthesised the evidence statistically. The network meta-analysis was conducted under a frequentist approach using a random-effects model.

Results

Clinical

Systematic review

The clinical evidence identified 12 randomised controlled trials that compared HCL to CSII+CGM or SAP therapy. Studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining mean difference between intervention and comparators. Studies did not consistently describe comparators. Cross-over studies did not provide data at different cross-over time points. Overall, the HCL arm of RCTs achieved improvement in HbA1c % (HCL decreased HbA1c % by 0.28 (-0.34 to -0.21), increased % TIR (between 3.9 – 10.0 mmol/L) with a mean difference of 8.6 (7.03 to 10.22), significantly decreased TIR (% above 10.0 mmol/L), with a mean difference of -7.2 (-8.89 to -5.51) but did not significantly affect % time within range (<3.9 mmol/L). Comparator arms also showed improvements but this was less than that observed in the HCL arm. Outcomes were superior in the HCL arm vs. comparator arm. Available evidence from the RCTs suggests that these gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration.

External submissions

NHSE submitted two observational audit studies, the first audit was conducted in adults and the second in children and young people (CYP). The audit included adult participants that had poorer glycaemic control in terms of HbA1c and hyperglycaemia at baseline than published observational studies. The pilot studies were non-randomised studies with no control group with a before-after study design. The before-and-after design limits the scientific value of the evidence since there is a greater risk of bias due to lack of randomisation, lack of a true control, and selection bias.

The improvement in HbA1c % and % time in range (between 3.9 and 10 mmol/L) levels were much greater in the NHS adult study in comparison to published evidence. The baseline level of the audit was considerably above than in all other observational studies

assessed in this report, therefore there was a greater scope for improvement. In the NHS audit of CYP baseline HbA1c was lower (~7.8%) and benefit was more modest (-0.7%) than in adults. For % time in range < 3.9 mmol/L the NHS audit adult study reported a change of -0.5% and an associated P value of <0.001. The CYP Pilot also reported a statistically significant improvement.

Economics

Systematic literature review of cost effectiveness

The literature search identified six studies which were included in the review systematic review. Five of these studies were economic evaluations of hybrid closed loop systems, whereas one was a budget impact analysis that aimed at estimating the financial impact of reimbursing HCL systems for individuals with type 1 diabetes. These studies were assessed using the CHEERS and Phillips checklists where applicable. According to the assessment, four studies were identified as cost effectiveness analyses in their titles The structure of the models used in the cost effectiveness studies was judged to be of good quality. The studies clearly stated their decision problem/research question, the viewpoint of their analyses and their modelling objectives, which were coherent with the decision problem. Both the IQVIA CORE Diabetes Model and the Sheffield type 1 diabetes model are validated models for evaluating diabetes technologies. The studies that used the IQVIA CORE diabetes Model described the model as one with a complex semi-Markov model structure with interdependent sub-models, so more thorough, easier access to its reported features would be of benefit to the intended audience. None of the studies clearly showed the illustrative model structure, which depicted the clinical pathway for T1DM. All the cost effectiveness studies noted that hybrid closed loop systems were cost effective over the lifetime compared with their comparator interventions. This inference was, however, subjective as the studies chose arbitrary willingness to pay thresholds. A major limitation of most of the cost effectiveness studies is that their findings might not be generalisable. This is because the studies did not use baseline characteristics and treatment effects data for their target populations.

Company submission

The EAG received economic submissions from Medtronic, Dexcom and Camdiab. The Tandem submission referenced the economics of the Dexcom submission.

The Medtronic treatment costs applied the anticipated April 2023 CiC prices rather than current list prices. Using the iQVIA CDM it estimated that compared to the 640G system with rtCGM the 780G HCL system improved HbA1c by 0.8% which resulted in a saving of £5,816, patient gains of 0.21 QALYs and dominance for HCL. For the comparison with CSII+isCGM the same HbA1c improvement was applied alongside an annual reduction of 0.9 severe hypoglycaemia events. This resulted in a net cost of £13,057, a patient gain of 0.70 QALYs and a cost effectiveness of £18,672 per QALY.

Dexcom used the [redacted]

The Camdiab submission presented [redacted]

Independent economic assessment

Due to the complexity of modelling T1DM the EAG does not build a de novo model. There are two main T1DM economic models available, the Sheffield T1DM model and the iQVIA CDM. In common with NG17 and DG21 and most of the company submissions, the EAG uses the iQVIA CDM to model cost effectiveness. The published model validation papers suggest that an earlier version of the iQVIA CDM tended to overestimate the incidences of the complications of diabetes, this being particularly important for severe visual loss and ESRD. Medium term modelling of overall survival appeared good, but there was uncertainty about its longer term modelling. It is not known whether these issues persist in the current iQVIA CDM.

The EAG assesses the cost effectiveness of HCL, PLGS and CSII+CGM. PLGS is extendedly dominated throughout and for this summary the EAG does not consider it further.

Direct treatment costs are supplied by the NHS supply chain using current list prices. The EAG provides a cPAS appendix that applies the confidential possible future prices. Current prices suggest that HCL is around an annual average £1,500 more expensive than CSII+CGM, though this may increase by around a further £500 for some systems. CSII+CGM is cheaper than HCL in large part due to 90% or more of adult patients using isCGM sensors rather than rtCMG sensors.

Patient baseline characteristics for the EAG base case are drawn from the National Diabetes Audit subgroup of T1DM patients on pumps.

The EAG base case applies the EAG RCT NMA estimate of -0.29% HbA1c for HCL relative to CSII+CGM. Due to there being no direct evidence of an effect upon symptomatic or severe hypoglycaemia events the EAG does not include these in its base case.

The change in HbA1c results in a gain in undiscounted life expectancy of 0.458 years and a gain of 0.160 QALYs. Net lifetime treatment costs are £31,185, with reduced complications leading to a net total cost of £28,628. The cost effectiveness estimate is £179k per QALY.

The EAG provides scenario analyses that estimate symptomatic and severe hypoglycaemia events based upon the differences in the time below 3.0mmol/l for HCL and CSII+CGM. These improve the cost effectiveness of HCL to £163k per QALY if valued using the EAG preferred source, to £121k if valued using the same source as NG17 and to £109k if valued using other credible sources.

These results show are sensitive to time horizons of less than the patient lifetime, durations of HbA1c effect of less than the patient lifetime and higher HCL treatment costs which tend to worsen the cost effectiveness of HCL. If mortality for those without complications is higher than that of the base case or there is an annual worsening of HbA1c this tends to improve the cost effectiveness of HCL. All the resulting cost effectiveness estimates are above £100k per QALY.

If the NHSE adult pilot change between baseline and six months of -1.5% HbA1c is assumed to be the net effect of HCL compared to CSII+CGM the undiscounted gain in life expectancy more than doubles to 1.004 years, and the patient gain to 3.103 QALYs. Net lifetime treatment costs increase to £35,912 due to the greater life expectancy, but considerable cost savings from reduced eye complications of £16,442 and reduced renal complications of £6,731 lead to a net total cost of £12,447 and a cost effectiveness of £12,398 per QALY. Reducing the modelled complication costs by their possible overestimation worsens the cost effectiveness to £21,583 per QALY. This does not take into account any quality of life effects and survival effects from possible overestimation of complication rates.

The key model inputs are:

- The net effect upon HbA1c.
- The duration of the net effect upon HbA1c.
- The model time horizon.
- Treatment costs.

Other important model inputs are:

- Hypoglycaemia event rates.
- What source is used to value the disutilities of hypoglycaemia event rates.

- What non-specific mortality is applied.
- Whether HbA1c worsens annually among T1DM patients and if so by how much.

The key modelling uncertainties are around:

- Overall survival gains.
- Severe visual loss and its effects upon survival, quality of life and costs.
- ESRD and its effects upon survival, quality of life and costs.

The EAG has some concerns about using the iQVIA T1DM to model a paediatric population. Exploratory modelling of a paediatric population broadly mirrors that of the adult population, though the NHSE paediatric pilot reported a smaller -0.70 HbA1c change between baseline and six months with a corresponding worsening in the cost effectiveness estimate for this scenario.

The EAG does not formally consider the cost effectiveness of HCL compared to CSII+CGM for pregnant women. It only notes the relationship between HbA1c and birth defects. If HCL reduces HbA1c in pregnant women to the same extent as in the adult population the short-term additional costs of HCL will have some immediate cost offsets from reduced birth defects, with the potential for additional benefits to the child at no additional cost. It also seems likely that the baseline age of pregnant women is below the national diabetes audit mean age which is likely to further improve cost effectiveness. If after giving birth women remain on HCL into the long term the cost effectiveness estimate of HCL may trend towards that of the adult female T1DM population of the same age, but will remain superior to it.

Conclusions

RCTs of HCL interventions in comparison CSII+CGM or sensor augmented pump therapy achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10

mmol/L, and in hyperglycaemic levels. The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range (3.9 to 10 mmol/L), and % time above range >10 mmol/L all improved on transfer to HCL. There is a research need of well designed studies because identified studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining mean difference between intervention and comparators. Future research should clearly describe comparators because this is not clear in the current literature.

Word count: 3182

PLAIN ENGLISH SUMMARY

Type 1 Diabetes (T1DM) is a life-long condition where the individual's pancreas significantly reduces \ stops producing the hormone insulin that manages blood glucose levels. As a result, the individual must self-administer insulin, monitor their blood glucose levels, and take into consideration many multiple variables to achieve a tight blood glucose control range.

With the challenge of self-management, blood glucose levels may swing high (hyperglycemia) and low (hypoglycemia) multiple times a day. This can result in the individual experiencing confusion, fatigue, nausea and possible unconsciousness as part of their daily management. The long-term risks of high blood glucose levels include damage to blood vessels, impacting sight, sense of touch and other vital organs. During self management, the individual uses the information they have to administer the amount of insulin the body requires while limiting high and low blood sugar. The day-to-day management of diabetes can be difficult and, and at times people with diabetes may struggle to maintain control of their blood glucose level. This can put a significant burden on the patient and carers which can result in impact on quality of life and a feeling that the condition limits \ controls their abilities.

Management of Type 1 Diabetes

Type 1 Diabetes is managed via lifestyle adjustments and review of multiple sources of data to help calculate the amount of insulin that a person needs. This commonly covers the following:

- *Lifestyle*
    - A balanced diet including complex carbohydrates, fats and proteins and avoiding processed food slows the impact of food on the blood glucose level reducing the possibility of sudden highs or lows.
    - Exercise improves the body's sensitivity to insulin, therefore, reducing the amount to be injected. This can reduce the possibility of unexpected sudden

blood glucose changes that a larger dose of insulin may bring, as well as general well-being in reducing stress that can cause insulin resistance.

- *Data*
    - Patients' understanding and monitoring of their body's reaction to insulin and foods to calculate their sensitivity to insulin and carbohydrates.
    - Monitoring of blood glucose levels via "finger pricks" where the individual draws a small amount of blood to get a point in time reading or continuous glucose monitors that provide a real-time reading of blood glucose.
- *Insulin Delivery*
    - Via daily injections or insulin pump that is connected to the body 24/7. Injections can be of rapid acting insulins that take effect within a short time frame (bolus) and long-acting insulins that release over a 12-to-24 hour period providing an amount of background insulin in the body (basal). Insulin pumps provide rapid acting insulin with the ability to deliver a bolus quickly and easily along with continuous background basal delivery that can be precisely adjusted for example every 5 minutes to form a unique 24-hour profile for the individual.

Processing of this information and deciding the best action is an ongoing challenge for the individual. Examples of such challenges include:

- Diet: Poor diet education, cost of access to fresh food and the challenge of avoiding easily accessible but cheap highly processed foods.
- Exercise: Lifestyle habits and motivation to exercise, along with the management of changes to insulin sensitivity, during and after exercise.
- Insulin Delivery: The inconvenience of injections and their limited control of insulin delivery, pumps with an overwhelming number of options for consideration.
- Blood Glucose Monitoring: This can be uncomfortable and provide a person with limited visibility of trend data. Compared to the data provided by manual blood

glucose tests, continuous glucose monitors provide an overwhelming amount of real-time data for the individual to process.

- Alarm fatigue: insulin pumps can cause frustration, due to automatic alarms set to inform the individual of high or low blood glucose or lack of proactive information to prevent such events.
- Overtreatment: Miscalculation, frustration or unexpected sensitivity/resistance to insulin that can result in multiple blood sugar highs and lows within a short timeframe.
- Changes in sensitivity to insulin, and to food along with many other factors that can changes an individuals response to insulin over time and day to day.

Hybrid closed loop systems

Hybrid closed loop systems provide a control algorithm that reviews data, along with reviewing the impact of its past actions. It can action frequent minor adjustments of insulin delivery to allow blood glucose levels to be managed. The system is proactive versus reactive using the real-time feed of data provided by the continuous glucose monitor to make calculations and take actions and to take actions using a high level of controlled delivery offered by an insulin pump at a frequency that is unattainable by a human being. As a result, such systems can significantly reduce the burden on the patient by taking responsibility for handling the volume of data and technology required for management of their condition and providing intervention when needed.

The aim of the current project is to review the clinical and cost-effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM and are having difficulty managing their condition.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Term	Definition
AHCL	Advanced Hybrid Closed Loop
A&E	Accident and emergency
AID	Automated insulin delivery
BL	Baseline
CADTH	Canadian Agency for Drugs and Technology in Health
CDM	CORE Diabetes Model
CEAC	Cost effectiveness acceptability curve
CGM	Continuous glucose monitoring plus RT CGM
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CL	Closed loop
CSII	Continuous subcutaneous insulin infusion (insulin pump)
CV	Coefficient of Variation
CVD	Cardiovascular disease
DDS	Diabetes Distress Scale
DIY	Do It Yourself closed loop systems
DAFNE	Dose Adjustment for Normal Eating
DAFNE-HART	DAFNE-Hypoglycaemia Awareness Restoration Training
DBLHU	Diabeloop for Highly Unstable Diabetes
DKA	Diabetic ketoacidosis

DTSQ	Diabetes Treatment Satisfaction Questionnaire
EPOC	Effective Practice and Organisation of Care
EQ-5d	The most widely used multi attribute utility instrument for measuring health-related quality of life in cost-effectiveness analysis
FGM	Flash Glucose monitoring
FLAIR	Fuzzy Logic Automated Insulin Regulation
FoH	fear of hypoglycaemia
GMI	Glucose Management Indicator
HbA1c	Haemoglobin A1c or glycated haemoglobin
HCL	Hybrid Closed Loop
HFS	Hypoglycaemia Fear Survey
HTA	Health technology assessment
ICD10	International Classification of Disease
ICER	Incremental cost effectiveness ratio
IQR	Interquartile Range
isCGM	intermittently scanned continuous glucose monitoring
LGS	Low glucose suspend
MC	Multicentre
MD	Mean difference
MDI	Multiple daily injections
NHS	National Health Service
NHSE	National Health System England
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis

OL	Open Loop
PedsQL	Pedatric Quality of Life Inventory
PLGS	Predictive low glucose suspend
PLGM	Predictive Low-Glucose Management
PWT1D	people with type 1 diabetes
RoB	risk-of-bias tool for randomized trials
rtCGM	real-time continuous glucose monitoring (
T1DM	Type 1 diabetes mellitus
TIR	Time in Range
QALY	Quality adjusted life year
QoL	Quality of Life
RCTs	Randomised Clinical Trials
SADE	Serious adverse device effects
SAP-PLGS	Sensor-augmented pumps and it was followed by the predictive low glucose suspend feature
SBP	Systolic blood pressure
SHE	Severe hypoglycaemic rates
SHTG	Scottish Health Technologies Group
SEK	Swedish krona
SHEs	severe hypoglycaemic rates
SF-6D	A generic preference-based single index measure of health that can be used to generate QALYs and hence which can be used in cost-utility analysis
SMBG	Standard self-monitoring of blood glucose
SUCRA	Surface under the cumulative ranking curve

AHCL	Advanced Hybrid Closed Loop
UADE	Unanticipated adverse device effects
WTP	Willingness to pay

2 BACKGROUND

2.1 Description of health problem

Type 1 diabetes was formerly known as insulin-dependent diabetes. It is the result of an autoimmune process leading to destruction of the insulin-producing beta cells in the pancreas. The cause of this auto-immune disease is not known.

2.1.1 Aetiology, pathology and prognosis

Insulin is essential for survival. Diabetes is characterised by high blood glucose levels – hyperglycaemia. Injected insulin lowers blood glucose. It can cause abnormally low glucose – hypoglycaemia. The aim of insulin treatment is to keep plasma glucose as close to normal as possible and so prevent the development of the long-term complications of diabetes due to hyperglycaemia, including

- retinopathy, which can lead to visual impairment and blindness
- nephropathy which can lead to renal failure and dialysis
- neuropathy, which can cause various symptoms and increase the risk of amputation

Treatment also aims to reduce the increased risk of cardiovascular disease seen in diabetes. Deficiency of insulin can lead to diabetic ketoacidosis which can be fatal.

2.1.2 Epidemiology

Type 1 diabetes usually comes in late childhood or early adolescence but can develop at any age. Type 1 diabetes accounts for 5-10% of diabetes cases. The prevalence of type 1 diabetes is higher in adults than in children, the highest prevalence is observed in adults aged 30 years and above.[1, 2] There are about 250,000 people with T1DM in the UK.

2.1.3 Impact of health problem

Hypoglycaemia

Hypoglycaemia can be mild, moderate or severe.

People with diabetes are rightly scared of hypoglycaemia, and this fear may lead to them allowing blood glucose to run higher than is desirable which can increase the risk of long-term complications. The episodes of hypoglycaemia are usually called “hypos”.

The American Diabetes Association [3] defines hypoglycaemia as follows;

1) Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma.
2) Documented symptomatic hypoglycemia: an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of 3.9 mmol/l).
3) Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration of 70 mg/dl (3.9 mmol/l).

Non-severe hypoglycaemia can be mild or moderate. Mild hypoglycaemia may present with symptoms such as sweating, shaking, hunger, and nervousness. Some symptoms are due to the release of adrenaline. Mild is easily self-managed by taking rapidly-absorbed carbohydrate.

Moderate hypoglycaemia can cause difficulty concentrating or speaking, confusion, weakness, vision changes and mood swings.

Mild and moderate hypos can usually be managed by the diabetic person themselves, but moderate hypos often lead to interruption of activities.

In the guidance on the Medtronic Veo suspend pump (DG21), NICE defined disabling hypoglycaemia as follows:

"People with type 1 diabetes may experience 'disabling hypoglycaemia', which is when hypoglycaemic episodes occur frequently or without warning so that the person is constantly anxious about having more episodes. This can have a negative effect on quality of life."

Severe hypoglycaemia can lead to cognitive impairment, unconsciousness and convulsions, and can be fatal. People having severe hypos need assistance and may need to attend an accident and emergency (A&E) department, seek support from paramedics. They may require admission to hospital. A population-based study in (2003) by Leese and colleagues [4] in Tayside found that on average, about 1 person in 14 had a hypo event each year which was severe enough to require NHS assistance, from the ambulance service, A&E, or admission.

In young children, repeated severe hypos can cause some cognitive impairment.

Hypoglycaemia can trigger an adrenergic response that acts as a warning that glucose should be consumed. Unfortunately, in some people, after repeated hypos, this warning may be lost.

This is known as hypoglycaemic unawareness, and such people are at increased risk of severe hypoglycaemia and its effects. These individuals are covered by the recommendation in DG21 [5] and in TA151,[6] in guidance on insulin pumps.

Nocturnal hypoglycaemia occurs during sleep and may not be detected. However it may disturb sleep and wake people up. It can have two adverse effects. One is rebound hyperglycaemia, the result of the body's reaction to hypoglycaemia such as release of other hormones that increase blood glucose, so that nocturnal hypoglycaemia may result in unusually high blood glucose levels around breakfast. The other consequence is that nocturnal hypoglycaemia may itself contribute to hypoglycaemic unawareness.

Past appraisals

In a technology appraisal (TA53) of long-acting insulin analogues (at that time only glargine),[7] the NICE Appraisal Committee accepted that both hypoglycaemic episodes, and the fear of such episodes recurring, caused significant disutility. A utility decrement of 0.0052 per non-severe hypoglycaemic event (NSHE) was accepted. As regards fear of hypos, the NICE Glargine guidance (TA53) [7] states:

"*The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. This is partly the result of an individual's objective fear of symptomatic hypoglycaemic attacks as indicated in the economic models reviewed in the Assessment Report. In addition, as reported by the experts who attended the appraisal meeting, individuals' quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemia and the benefits of longer-term glycaemic control. The Committee understood that improvement in this area of concern regarding the balance between hypoglycaemia and hyperglycaemia could have a significant effect on an individual's quality of life."*

However, the guidance did not specify the amount of utility lost because of fear of hypos, and nor did the Technology Assessment Report [8] because it was based on the industry submission from Aventis, which was classed as confidential. But clearly the utility gain from reducing the fear of hypoglycaemia was enough to change a substantial cost per QALY to an affordable one. There is the probability that a reduction in the rate of severe hypoglycaemia events may reduce the fear of severe hypoglycaemia events, though the impact of this seems likely to be variable across patients. The quality-of-life impact arising from this would be

over and above the direct quality of life impact of the severe hypoglycaemia events in themselves.

Fear of severe hypos was estimated to reduce QoL by 0.020 in the development of type 2 guidelines in 2008. The assessment group (Waugh et al, Aberdeen [9]) considered the reasonableness of this

"This fear effect may only apply to a sub-group of patients, but as an illustration of the possible impact of this, the social tariffs derived by Dolan and colleagues [10] suggest that a move from level 2 within the anxiety subscale of EQ-5D to level 1 would be associated with a 0.07 QoL gain. In a similar vein, the coefficients derived by Brazier and colleagues [11] for the SF-6D questionnaire for the consistent model using standard gamble valuations suggest that a movement within the social dimension from health problems interfering moderately to not interfering would be associated with a 0.022 QoL improvement. Similarly, an improvement in the mental health subscale from feeling downhearted some of the time to little or none of the time would be associated with a 0.021 QoL improvement."

Studies of the disutility of hypoglycaemia

Brod et al [12] carried out a survey to estimate the effect of non-severe hypos on work – productivity, costs and a self-management. They used telephone interviews and focus groups, supplemented by a literature review. Respondents were required to have had a non-severe hypoglycaemic event (NSHE) in the previous month. NSHE was defined as a hypo event not requiring assistance from anyone else, with or without blood glucose measurement, and with or without symptoms. They were asked about duration, effect on work, and likely cause, and whether it occurred at work, at other times of day, or during sleep. 713 had type 1 diabetes, and half of this group had NSHEs at least once a week, with 27% having at least one a month. 22% had hypos only a few times a year.

About 95% of people identified hypos by symptoms, and about 60% of episodes were confirmed by a blood glucose test. The average duration of a NSHE was 33 minutes, but the effect on self-management lasted a week, with an extra six blood glucose tests, a reduction in insulin dose by an average of 6.5 units per day for 4 days in 25% of people, and an unplanned contact with a health care professional by 25%.

The effects on work included;

- Leaving early or missing a full day in 18%. The average work time lost was 10 hours.

- Missing meetings or being unable to finish a task – 24%

Work time was lost not only because of NSHEs occurring at work but also outwith work including nocturnal hypos. No breakdown by insulin regimen was reported such as CSII versus MDI.

Leckie et al [13] recruited 243 people with diabetes (216 people with T1DM and some with T2DM on insulin) who were in employment. Their insulin regimens included mostly MDI but 51 were on twice-daily mixtures of soluble and NPH. Over a 12-month follow-up, they recorded their hypo events, severity and effect on work, every month. A total of 1,955 NSHEs were reported, plus 238 severe hypos (some involving unconsciousness and seizures, and a few resulted in soft tissue injuries). However, 66% of patients had no severe hypos. Most (62%) of the severe episodes occurred at home, 52% during sleep, but 15% occurred at work. 55% of the NSHEs occurred at home and 30% at work. It should be noted that the mean HbA1c was over 9% in most patients, with the exception of patients having more than two severe hypos over the year, in whom it was 8.4% - still far above target.

Frier et al [14] carried out a survey amongst 466 people with T1DM of the frequency of non-severe hypoglycaemia and found that people with T1DM had an average of 2.4 episodes a week (median = 2), with around a quarter being nocturnal. The after-effects include fatigue and reduced alertness, and persisted longer after nocturnal NSHEs (10 hours) than after daytime episodes (5 hours). Amongst those in employment, 20% of NSHE led to loss of work time. Most did not contact their health care professionals. Self-testing of blood glucose increased in the week after the episode, with an average 4 extra tests. The survey showed that NSHEs are troublesome for patients and have effects lasting at least into the following day. The commonest after-effects were tiredness, reduced alertness and feeling emotionally down.

Choudhary et al [15] reported that use of pumps with a low glucose suspend facility meant that 66% of NSHEs lasted less than 10 minutes, and only 12% lasted for up to 2 hours. Nocturnal hypos were greatly reduced.

About 30% of people with type 1 diabetes have impaired awareness of hypos [16] and they are 3-6 times more likely to have severe hypos. The Gold scale rates awareness on a scale of 1 to 7 where 7 means complete absence of symptoms of hypoglycaemia. Structured education such as DAFNE restores awareness in about half of people with impaired awareness. Better control with avoidance of hypoglycaemia can also restore awareness. A trial by Little et al [17] (the HypoCOMPass trial) showed that better control for 24 weeks improved the Gold score

by one point and reduced the fear of hypo level from 58 to 45 (higher scores indicate greater fear, with the maximum being 132), without adversely affecting HbA1c.

Evans et al [18] used the time trade-off method to estimate the disutility of hypos on the HRQoL scale (0 to 1 where I is perfect health and 0 is death). They interviewed 551 people with type 1 diabetes and 8286 people with no diabetes. They note that hypos can affect HRQoL in two ways, firstly the direct effects of the episodes, and secondly through fear of future hypos which can lead to precautions such as insufficient insulin dose (increasing the risk of complications), restricting physical activity, over-eating. In addition, repeated hypos can lead to hypoglycaemic unawareness which increases the risk of future hypos. They estimated that daytime NSHEs reduce HRQoL in a range of 0.032 for one event a month to 0.071 for three episodes a week. Nocturnal NSHEs reduce it by slightly more. Severe events, even only once or twice a year, reduce HRQoL by about 0.08.

The general public valuation of disutility per event per year ranged from 0.004 for non-severe daytime hypos to 0.06 per severe event. People with type 1 diabetes had slightly lower estimates of the disutility of severe events, at 0.047.

Using data from this study, Lauridson et al [19] reported that the disutility of NSHEs may diminish if there are repeated events.

The study by Harris et al [20] reports the Canadian results from this study.

Levy and colleagues [21] elicited utility values for non-severe hypoglycaemia from 51 Canadians (but only half had T1DM) and non-diabetic controls. The disutility from a single NSHE was 0.0033. Levy et al argue that a minimum significant utility loss is 0.03, which would be reached by people having 10 NSHEs a year.

Adler et al [22] found that severe, frequent and nocturnal hypoglycaemia reduced quality of life, ranging from 0.84 in people with diabetes who had the least severe state) non-severe, daytime only, only once a year, not causing any worry) to 0.40 (severe frequent hypoglycaemia day and night, causing anxiety).

Currie and colleagues [23] surveyed 1,305 UK patients with type 1 and type 2 diabetes using both the Hypoglycaemia Fear Survey and the EQ-5D. Each severe hypoglycaemic event avoided was associated with a change of 5.9 on the Hypoglycaemia Fear Survey (HFS). Given a further estimate that each unit change on the HFS was associated with an EQ-5D quality of life change of 0.008 this led to an estimated benefit from reduced fear of severe hypoglycaemic events of 0.047 per annual event avoided. This was coupled with a direct

utility loss associated with a severe hypoglycaemic event in T1DM of 0.00118 to yield an overall patient benefit of 0.05 per unit reduction in annual severe hypoglycaemic events. Currie et al also reported direct disutilities in type 1 diabetes of 0.0036 per NSH event.

Conclusions on hypoglycaemia

Hypoglycaemia remains a major problem in type 1 diabetes and has not improved over recent decades. This may be because the increased emphasis on improving glycaemic control, through more intensive insulin treatment, has offset other advances in treatment; tightly managed diabetes can make it more likely that hypoglycaemia might occur. The frequency and severity of hypos can be reduced by structured education and by the use of CSII (insulin pumps) but they remain a problem leading to economic disutilities. For individual events, disutilities and costs are much greater for severe hypos but the much larger number of NSHEs lead to significant impacts on quality of life.

2.2 Current service provision

2.2.1 Management of disease

In people without type 1 diabetes, the pancreas produces a little insulin throughout the day but peaks of insulin release after meals. The release after meals is very fast and enables the body to handle and store nutrients. The pancreas releases insulin into the portal vein that goes into the liver, its main site of action.

Treatment with insulin is aimed at replicating the function of the pancreas. Insulin is injected under the skin – subcutaneously. Modern insulin regimens have two components – short-acting insulin to cover mealtimes, and long-acting insulin to cover the rest of the day, usually given twice a day. The long-acting form is called basal, and the combination is often referred to as "basal-bolus" insulin, or as MDI – multiple daily injections – with three injections of short-acting insulins and two of long-acting (glargine or detemir). However, subcutaneous insulin injections cannot achieve as rapid an effect as pancreatic insulin, and because of the slower onset of action and more prolonged effects, hyperglycaemia is common shortly after meals, often followed by later hypoglycaemia.

Good control of plasma glucose by intensified insulin therapy requires more than just insulin injections. It also requires regular monitoring of blood glucose by finger-pricking and measurement using a portable meter, or by using a continuous blood glucose measurement

(CGM) device, and then adjustment of insulin dose to take account of calorie intake from food and energy expenditure in exercise. People with diabetes almost always manage their own diabetes, supported by structured education packages such as DAFNE (Dose Adjustment for Normal Eating).

The aim of treatment is to control hyperglycaemia and avoid hypoglycaemia. Glycaemic control is assessed using glycated haemoglobin, HbA1c, which gives an average measure over 2-3 months. The NICE target for type 1 diabetes is 48 mmol/mol (formerly 6.5%) but few people with T1DM achieve that. With the spread of continuous glucose measurement (CGM) devices, “time in range” is increasingly used as another measure of glycaemic control.

The alternative to MDI is continuous subcutaneous insulin infusion (CSII) using an insulin pump. CSII was approved by NICE with restrictions (see Box 1).[6]

Box 1. NICE guidance: Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus [TA151]

Continuous subcutaneous insulin infusion (CSII or 'insulin pump') therapy is recommended as a treatment option for adults and children 12 years and older with type 1 diabetes mellitus provided that:

- attempts to achieve target haemoglobin A1c (HbA1c) levels with multiple daily injections (MDIs) result in the person experiencing disabling hypoglycaemia. For the purpose of this guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life

  or

- HbA1c levels have remained high (that is, at 8.5% [69 mmol/mol] or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

CSII therapy is recommended as a treatment option for children younger than 12 years with type 1 diabetes mellitus provided that:

- MDI therapy is considered to be impractical or inappropriate, and
- children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years.

The guidance on the use of the Veo pump also had restrictions (see Box 2).[5]

Box 2: NICE guidance: Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) [DG21]

1. The MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if: • they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion,

2. The MiniMed Paradigm Veo system should be used under the supervision of a trained multidisciplinary team who are experienced in continuous subcutaneous insulin infusion and continuous glucose monitoring for managing type 1 diabetes only if the person or their carer: • agrees to use the sensors for at least 70% of the time • understands how to use it and is physically able to use the system and • agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.

3. People who start to use the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set.

The guidance did not comment on reduction of severity of hypos.

In non-diabetic people, hypoglycaemia is rare, because if the blood glucose drops, a counter-regulatory mechanism kicks in, including release of glucagon (which raises blood glucose) and adrenaline, and cessation of insulin release. In people on MDI, there are pools of long-acting and short-acting insulin under the skin (subcutaneous) which unlike pancreatic insulin, cannot be switched off. In people on CSII, there is only a little short-acting insulin, so stopping the pump gives a quick response. (There can be a hazard here, in that should a pump fail, the patient soon has no insulin and is at risk of hyperglycaemia and diabetic ketoacedocis (DKA).

Interventions to reduce hypoglycaemia

One intervention to reduce the risk of hypoglycaemia is structured education such as the DAFNE Programme. Structured education is recommended in NG17 (Recommendations | Type 1 diabetes in adults: diagnosis and management | Guidance | NICE). The assessment report for the original appraisal of patient education in diabetes has been published in the HTA Monograph series (Loveman et al 2003)

Iqbal and Heller [24] provide a recent review of the role of structured education and hypoglycaemia. They note that until recently, the frequency of severe hypoglycaemia had not fallen over the last 20 years despite advances in treatment. They conclude that structured education can reduce the incidence of severe hypoglycaemia by about 50%, and that there is some evidence, albeit from an observational study with no control group, that the DAFNE-Hypoglycaemia Awareness Restoration Training (DAFNE-HART) programme can reduce hypoglycaemia even in patients with hypoglycaemia unawareness.

Continuous glucose monitoring

There are various forms of CGM. The term "continuous" is slightly misleading – glucose levels are measured every few minutes. The device measures the level of glucose under the skin ("interstitial glucose") which reflects the level in the blood, but with a slight delay.

There are three elements in CGM

- A sensor that sits just underneath the skin and measures glucose levels.
- A transmitter attached to the sensor and sends the results to a display device.
- A display device that shows the glucose level.

The diabetic person checks the CGM data and adjusts insulin dose, calorie intake or activity levels to maintain blood glucose levels.

So, the traditional "loop" involves CGM, the patient using the data, and insulin dosage.

Autosuspend pumps

The mechanism here is that the CGM – patient – pump loop is augmented by direct communication between CGM device and the pump. If blood glucose is falling too low, the CGM device communicates with the pump and switches off the insulin infusions, for say 2 hours. This is particularly useful in nocturnal hypoglycaemia when the patient is asleep.

Closed loop systems

This term refers to systems with three components – CGM, a microprocessor with algorithms, and a pump. In effect, the microprocessor replaces the person. The microprocessor (in effect a small computer) receives data from the CGM and adjusts the infusion rate from the pump.

Devices such as the Veo only control the pump when hypoglycaemia is occurring. They may switch off the insulin infusion when blood glucose falls to low, or if it is heading in that direction.

Closed loop systems can also control insulin infusion if blood glucose is too high. The most advanced system is the iLet from BetaBionics which is a dual pump which infuses insulin if blood glucose is too high, and glucagon if it is too low.

2.2.2 Variation in services and/or uncertainty about best practice

At diagnosis, the diabetes professional team should work with adults with type 1 diabetes to develop a plan for early care. Individual care plans include diabetes education, including dietary advice, insulin therapy, (including dosage adjustment, self-monitoring, avoiding hypoglycaemia and maintaining hypoglycaemia awareness), family planning, cardiovascular risk factor monitoring and management, complications monitoring and management, and communicating with the diabetes professional team. There are different factors that should be taken into account to offer an appropriate glucose monitoring device for any person. Based on individual preferences, needs, characteristics, and the functionality of the devices available, adults with type 1 diabetes may be offered a choice of glucose monitoring. Modes include real-time continuous glucose monitoring (rtCGM) or intermittently scanned

continuous glucose monitoring (isCGM, commonly referred to as 'flash'), these measurement systems are coupled with multiple daily injection basal–bolus insulin regimens, or insulin pumps (Continuous subcutaneous insulin infusion (CSII) therapy), using Rapid-acting insulin, and/or Mixed insulin.[2]

People with type 1 diabetes may experience significant improvements in their lives as a result of the rapidly evolving technologies such as closed loop systems and artificial pancreas.[25] Demand for these technologies is increasing, with many people with type 1 diabetes anticipated to benefit from an artificial pancreas or closed loop system in the future.[25]

There is evidence using key outcomes, such as HbA1c, time in range and severe or nocturnal hypoglycaemia, to demonstrate whether devices provide clinical benefits over standard self-monitoring of blood glucose. However, quality or sample size of the studies is frequently not good enough to clearly show the clinical benefits of one technology over another.

2.2.3 Relevant national guidelines, including National Service Frameworks

NICE guideline [NG17] covers care and treatment for adults (aged 18 and over) with type 1 diabetes, including advice on diagnosis, education and support, blood glucose management, cardiovascular risk, and identifying and managing long-term complications.[2] Evidence reviews by NICE evaluated the most effective method of glucose monitoring to improve glycaemic control in adults with type 1 diabetes. Overall, 17 studies were included in clinical effectiveness analysis to examine rtCGM vs isCGM , rtCGM vs standard self-monitoring of blood glucose (SMBG), and isCGM vs SMBG. Two UK studies among 14 primary studies that contained cost utility analyses were included in this evidence review. Results show time in range (TIR) to be a better measure than HbA1c as it captures variation and can be more directly linked to risk of complications. There was a clinically meaningful positive effect on time in range for rtCGM vs both isCGM and SMBG, as well as is CGM vs SMBG, on the pre-set minimally important difference (MID) of a 5% change.[26] The authors clarified that the service user should consult with a member of the diabetes care team with expertise in the use of CGM. This guideline reported both published UK cost-effectiveness studies (one on rtCGM and one on isCGM) found these technologies to be cost-effective compared to intermittent capillary blood glucose monitoring. Based on the results of economic modelling (using clinical data from the RCTs included in the clinical review), isCGM glucose monitoring was clearly cost-effective for the overall population of people with type 1 diabetes, and this finding was robust to all the sensitivity analyses undertaken.[26]

The Scottish Health Technology Group (SHTG) review examined the cost-effectiveness of using closed loop systems and the artificial pancreas for the management of type 1 diabetes compared with current diabetes management options, and considered clinical effectiveness, safety and patient aspects.[25]

The evidence reviewed on the clinical effectiveness consisted of small cross-over RCTs that tested the use of closed loop systems over relatively short periods of time, in people with well controlled diabetes who had had the condition for several years and who often had experience with using insulin pumps. The results of an NMA and three pairwise meta-analyses show significant improvements in mean percentage time in range for people with type 1 diabetes using a closed loop system compared with other insulin-based therapies. The pairwise meta-analyses also reported statistically significant reductions in mean percentage time spent in hyperglycaemia and hypoglycaemia. High heterogeneity was present in all meta-analyses, for all outcomes. This is potentially a result of small study size, multiple different closed loops systems in the intervention group, and use of a variety of methods of insulin therapy in the control groups. It should be noted that some of the secondary evidence reviewed may be based on technologies that have since been superseded by newer models because of the rapidly changing nature of these systems.

Also, adverse events were rarely reported in either the closed loop system or control groups.

The SHTG economic model, showed that closed loop systems were associated with the highest costs and QALYs in a Scottish adult population with type 1 diabetes, except in the comparison with CGM plus CSII. Base case results showed that the technology is cost-effective compared with CGM plus CSII, but not cost-effective in comparison with flash or continuous glucose monitoring combined with multiple daily injections in people with well controlled type 1 diabetes. There are some uncertainties because of a lack of published studies underpinning assumptions in the model.

2.3 Description of technology under assessment

2.3.1 Summary of Intervention

The intervention of interest is a class of automated insulin delivery systems called hybrid closed loop systems which consist of three components – a CGM, a microprocessor with control algorithms, and a pump. The microprocessor receives data from the CGM and adjusts the infusion rate from the pump, to help keep glucose levels in a healthy range. These systems are

aimed at reducing user or caregiver input in insulin dosing and some only require users to deliver meal boluses by entering the estimated amount of carbohydrates for meals at the time they are eaten.

There are several hybrid closed loop systems available in the UK. Some of these systems have received regulatory approval for a fixed combination of CGM, control algorithm, and insulin pump. However, some systems involve combining interoperable devices. The following systems are representative of the intervention of interest and have been identified by NICE as currently available in the UK.

Advanced HCL

HCL systems use control algorithms to automate basal insulin delivery based on glucose sensor values, in order to increase the time that a patient spends in the target range and thus reduce the frequency and duration of hypoglycaemia. The user of the HCL system is required to enter their carbohydrate intake before each meal, so that the appropriate meal-time insulin bolus can be delivered by the system.

Advanced HCL (AHCL) systems have additional features that include automated correction of bolus insulin delivered up to every 5 minutes when glucose levels are elevated. These systems may also enable greater personalisation of insulin delivery and monitoring and can include meal detection modules that allow the system to deliver more aggressive auto correction boluses.[27]

2.3.1.1 MiniMed 670G

MiniMed 670G (Medtronic) is a CE marked hybrid closed loop system that uses a control algorithm called SmartGuard. SmartGuard technology has a manual mode and an auto mode. In manual mode, the 670G works just like other sensor-augmented pump systems. In auto-mode function, blood glucose data measured by the CGM (Guardian sensor) is sent wirelessly to the insulin pump (670G), to enable adjustment of basal insulin every five minutes to maintain sensor glucose levels near a target glucose of 120 mg/dL (6.7 mmol/L). The system requires some user interaction to administer mealtime bolus doses. The 670G is not licensed for use in children under 7 years old. The device is also not to be used in people who require less than a

total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

2.3.1.2 MiniMed 780G

MiniMed 780G (Medtronic) is a CE marked hybrid closed loop system launched in 2020. It has an advancement on the algorithm used in the 670G system and has Bluetooth connectivity. The system includes different glucose targets, according to the users' needs. In addition to the target glucose of 120 mg/dL (6.7 mmol/L), users can also select to achieve a tighter glucose target of 5.5 - 6.1 millimoles per litre. In contrast to its predecessor system, the 780G has an 'autocorrection feature' that delivers correction boluses automatically when sustained hyperglycemia is detected. This requires minimal user or carer interaction. The CGM (Guardian sensor) is connected to the MiniMed mobile app via Bluetooth, which optionally automatically uploads data to the CareLink connect system to notify carers or for clinician review. The 780G is not licensed for use in children under 7 years or for people who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

2.3.1.3 Control IQ

The Control-IQ (Tandem Diabetes Care) is a CE marked system that combines t:slimX2 insulin pump and Control-IQ technology. This system can be interlinked with a compatible CGM to form a hybrid closed loop system which suspends insulin delivery in response to predicted hypoglycaemia, or gives a correction bolus in response to predicted hyperglycaemia. Control-IQ has 6 settings, including optional settings for sleep and exercise, to adjust basal insulin delivery depending on user need. Mealtime bolus doses are administered manually. Data from Control-IQ can be uploaded on the Diasend or Tidepool data clouds for clinician review. Control-IQ is not licensed for use in children under 6 years or for people who require less than a total daily insulin dose of 10 units per day or who weigh less than 55 pounds, as those are the required minimum values needed to operate safely.

2.3.1.4 CamAPS FX

CamAPS FX (Camdiab) is a CE marked android app developed at the University of Cambridge. The app can be interlinked with a compatible CGM (Dexcom G6) and insulin pump (Dana RS or Dana-I) to form a hybrid closed loop system. CamAPS FX can operate on an auto mode 'off' whereby basal insulin delivery is pre-programmed by the user or an auto mode 'on' where

insulin delivery is directed by the app. In auto mode on, a bolus dose calculator embedded in the app allows the user to initiate the delivery of mealtime insulin dose. If the auto mode 'on' feature is prevented from coming on, an auto mode 'attempting' feature is initiated in which insulin delivery is reverted to pre-programmed basal rates. Data from CamAPS FX can be uploaded to the Diasend data cloud, for clinician review. CamAPS FX is licensed for use in people aged 1 year and older and in pregnancy, however, other age restrictions may apply depending on the chosen CGM and insulin pump.

2.3.2 Identification of important sub-groups

The NICE scope (March 2022) states the following subgroups if evidence permits:

- Women with type 1 diabetes who are pregnant and those planning pregnancy (not including gestational diabetes). *Note that in this assessment this subpopulation is not required to fulfil the criteria of prior use of at least 1 technology.*
- Children with type 1 diabetes.
- If possible, evidence should be analysed based on the following age groups:
- 5 years and under,
- 6 - 11 years
- 12 -19 years
- People with extreme fear of hypoglycaemia
- People with diabetes related complications that are at risk of deterioration

2.3.3 Current usage in the NHS

The management of T1DM involves lifestyle adjustments, monitoring of blood glucose levels, and insulin replacement therapy, with the aim of recreating normal fluctuations in circulating insulin concentrations. Blood glucose levels are monitored to determine the type and amount of insulin needed to regulate blood glucose levels and reduce the risk of complications.

NICE guidelines recommend that adult and pregnant women with T1DM should be empowered to self-monitor their blood glucose, supported by structured education packages (e.g., Dose Adjustment for Normal Eating) on how to measure glucose levels and interpret the results.[2] NICE also recommends that children and young people with T1DM and their families or carers should be offered a continuing programme of education from diagnosis. Several systems of monitoring glucose levels and delivering insulin are available in clinical practice. The system

recommended for individuals is based on the individual's age, whether they are pregnant, their glycaemic control, and personal preferences (Figure 1).

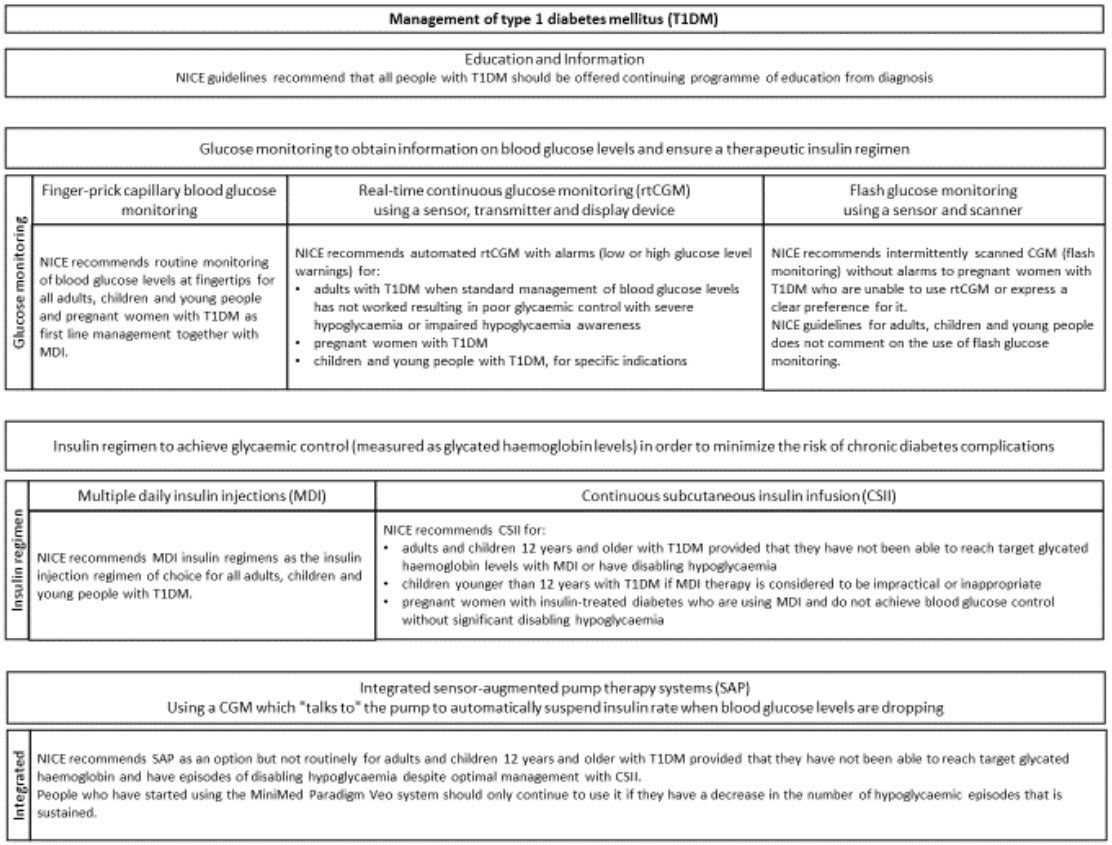


Figure 1. Management of type 1 diabetes mellitus (www.nice.org.uk/guidance/ng17)

2.3.3.1 Blood glucose monitoring

Capillary blood glucose monitoring

Blood glucose concentrations in diabetes can vary considerable from day-to-day and over the course of a 24-hour period. Routine blood glucose testing is typically done using capillary blood glucose monitoring. Capillary blood glucose monitoring involves pricking a part of the body (usually the finger) with a lancet device to obtain a small blood sample at certain times of the day. The drop of blood is then applied to a test strip which is inserted into a blood glucose meter for automated determination of the glucose concentration in the blood sample at the time of the test. Blood glucose measurements are taken after several hours of fasting, usually in the morning before breakfast, and before and after each meal to measure the change in glucose concentration.

NICE recommends routine self-monitoring of blood glucose levels at fingertips for all adults with T1DM at least 4 times a day, including before each meal and before bed.[2] For pregnant women with T1DM, the NICE recommendation is to test fasting, pre-meal, 1-hour post-meal, and bedtime blood glucose levels daily. The NICE recommendation for children and young people with T1DM is capillary blood glucose testing 5 times per day.[28]

Real time continuous blood glucose measurement (rtCGM)

rtCGM is an alternative to routine finger-prick blood glucose monitoring for people (including pregnant women) aged 2 and over, who have diabetes, have multiple daily injections of insulin or use insulin pumps, and are self-managing their diabetes. This involves measuring interstitial fluid glucose levels throughout the day and night.

A rtCGM system comprises three parts:

- A sensor that sits just underneath the skin and measures glucose levels
- A transmitter that is attached to the sensor and sends glucose levels to a display device
- A display device that shows the glucose level (separate handheld device (known as "standalone" CGM) or a pump (known as an "integrated system")

For most rtCGM systems, calibration by checking the finger-prick blood glucose level is needed once or twice a day. rtCGM systems monitors glucose levels regularly (approximately every 5 minutes), and alerts can be set for high, low or rate of change.

NICE does not recommend offering rtCGM routinely to adults with T1DM. Instead, rtCGM with an alarm should be considered for adults with T1DM for whom standard management of blood glucose levels has not worked or been difficult, i.e., those with recurrent severe hypoglycaemia or impaired awareness of hypoglycaemia. The users must also be willing to commit to using the technology at least 70% of the time and to calibrate it as needed. For children and young people with T1DM, NICE recommends that ongoing rtCGM with alarms should be offered to those who continue to have severe hypoglycaemia or impaired hypoglycaemia awareness, or those who are not able to recognise or communicate symptoms of hypoglycaemia. The NICE recommendation is to offer rtCGM to all pregnant women with T1DM to help them meet their pregnancy blood glucose targets and improve neonatal outcomes.

Flash/intermittently scanned glucose monitoring

Flash glucose monitoring systems comprise a reader and a sensor applied to the skin to measure interstitial fluid glucose levels. It only provides a reading or trends when the sensor is scanned. The NICE guidelines for adults and children with T1DM do not comment on the use of flash systems for intermittent interstitial fluid glucose monitoring.

For pregnant women with T1DM, the NICE recommendation is to offer intermittently scanned flash monitoring to those who are unable to use rtCGM or express a clear preference for it. In standard practice and in accordance with the NHS long-term plan, most centres offer flash and/or CGM to pregnant women with T1DM.

HbA1c

Longer-term control is measured by glycated haemoglobin levels (HbA1c), which reflect the average blood glucose levels over 2 to 3 months. HbA1c is correlated to CGM results over the preceding 8-to-12 weeks.[29] NICE guidelines on diabetes (type 1 and type 2) in children and young people, adults, and diabetes in pregnancy recommend that people with T1DM should

aim for a target HbA1c level of 6.5% (48 mmol/mol) or lower to minimise the risk of long term complications from diabetes. Poor glycaemic control may trigger a discussion about different options for insulin administration.

2.3.3.2 Insulin regimens

Multiple daily injections (MDI)

Insulin is injected subcutaneously. Modern insulin regimens have two components – short-acting insulin to cover mealtimes, and long-acting insulin to cover the rest of the day, which is usually given twice a day. The long-acting form is called basal, and the combination is often referred to as "basal-bolus" insulin, or as multiple daily injections (MDI), with three injections of short-acting insulins and one or two of long-acting insulin. However, subcutaneous insulin injections cannot achieve as rapid an effect as pancreatic insulin, and because of the slower onset of action and more prolonged effect, hyperglycaemia is common shortly after meals, often followed by hypoglycaemia later.

The NICE recommendation is to offer MDI basal–bolus insulin regimens for all adults, children and young people with T1DM. For pregnant women with diabetes, NICE recommends that rapid-acting insulin analogues should be considered.

Continuous subcutaneous insulin infusion (CSII)

The alternative to MDI is continuous subcutaneous insulin infusion (CSII) using an insulin pump. It makes use of an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. CSII was approved by NICE as a treatment option for adults and children 12 years and older with T1DM provided that:

- attempts to achieve target HbA1c levels with MDIs result in the person experiencing disabling hypoglycaemia. For the purpose of this guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life, or
- HbA1c levels have remained high (that is, at 8.5% (69 mmol/mol) or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

CSII therapy is recommended as a treatment option for children younger than 12 years with T1DM provided that:

- MDI therapy is considered to be impractical or inappropriate, and
- children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years.

For pregnant women with T1DM, NICE recommends that CSII should be offered to women who are using MDI and do not achieve blood glucose control without significant disabling hypoglycaemia.

Integrated sensor-augmented pump therapy systems (SAP)

Integrated sensor-augmented pump therapy systems combine rtCGM with CSII. The systems are designed to measure interstitial glucose levels (every few minutes) and allow immediate real-time adjustment of insulin therapy. The systems may produce alerts if the glucose levels become too high or too low. NICE's diagnostic guidance (DG21) on integrated sensor-augmented pump therapy systems for managing blood glucose levels in T1DM recommends the MiniMed Paradigm Veo system as an option for managing blood glucose levels in people with T1DM only if they have episodes of disabling hypoglycaemia despite optimal management with CSII.[5] As with other pumps the user can program one or more basal rate settings for different times of the day/night. A built-in bolus calculator works out how much insulin is needed for a meal following the input of carbohydrates consumed. The advanced feature of sensor-augmented pump is that the rtCGM – patient – pump loop is augmented by direct communication between the rtCGM device and the pump. If blood glucose is falling too low, the rtCGM device communicates with the pump and automatically switches off (suspends) the insulin infusions. Depending on the device, the user either must restart insulin delivery or the pump resumes insulin delivery after 2 hours.

LGS/PLGS

SAP systems can operate in standard (manual) and advanced (automatic) modes. In the manual open loop mode, the continuous glucose monitor and glucose pump do not communicate with each other, and insulin doses are programmed by the user, who makes manual adjustments.

In advanced, automatic mode, the CGM device and pump can communicate with each other automatically based on real-time glucose data, in order to adjust the insulin basal rate and suspend the insulin infusion without the input of the wearer in order to prevent potential hypoglycaemia. Glucose suspension can be a simple 'low glucose suspend' (LGS) function, in which insulin infusion is suspended when glucose monitoring systems detect that glucose levels have fallen below a specific hypoglycaemia threshold. In this case, insulin is suspended for a period of time and may resume when the system determines that glucose levels have returned to within target range or when the glucose suspension is overridden by the patient.

Predictive low glucose suspend (PLGS) is a more advanced use of technology in which prediction algorithms are used which essentially forecast future hypoglycaemia (e.g. within the next half hour), and pre-emptively suspend insulin delivery before hypoglycaemia develops. PLGS systems will then automatically resume insulin infusions if the user overrides the suspension, or if glucose levels begin to rise or rise above a specific threshold.[30, 31]

3 DEFINITION OF THE DECISION PROBLEM

3.1 Decision problem

3.1.1 Interventions

The interventions of interest are hybrid closed loop systems - a class of automated insulin delivery systems which consists of three components – a CGM, a microprocessor with control algorithms, and a pump.

There are several hybrid closed loop systems available in the UK such as MiniMed 670G and MiniMed 780G. The systems are representative of the intervention of interest and have been identified by NICE as currently available in the UK.

3.1.2 Population including sub-groups

Population and sub-groups are per NICE scope (published March 2022).

Populations	People who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring[ab] If evidence permits the following T1DM subpopulations will be included: • Pregnant women and those planning pregnancies (excluding gestational diabetes).[b] • Children (5 years and under, 6 – 11 years, 12 - 19 years). • People with extreme fear of hypoglycaemia. • People with diabetes related complications that are at risk of deterioration. [a] For the purpose of this review, difficulty refers to (1) not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below (for pregnant women/those planning pregnancies: not maintaining fasting plasma glucose levels of 5.2 mmol/l or below, or not maintaining non-fasting plasma glucose of 7.7 mmol/L (one hour after eating)/ 6.3 mmol/L (two hours after eating)), (2) not maintaining at least 70% time in range of 3.9 -10 mmol/l, or (3) repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life. [b] Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.

3.1.3 Relevant comparators

Comparator	• Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.

	Where evidence permits, scenarios assessing the following comparators will be presented for women with type 1 diabetes who are pregnant/planning pregnancy: • Real time continuous glucose monitoring with multiple daily insulin injections. • Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections. • Self-blood glucose monitoring with continuous subcutaneous insulin infusion.

3.1.4 Outcomes

Intermediate measures • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below and above target range • Change in HbA1c • Rate of glycaemic variability • Fear of hypoglycaemia • Rate of severe hypoglycaemic events • Rate of severe hyperglycaemic events • Episodes of diabetic ketoacidosis • Rate of ambulance call outs • Rate of hospital out-patient visits • Rate of weight gain
Clinical outcomes • Retinopathy • Neuropathy • Cognitive impairment • End-stage renal disease • Cardiovascular disease • Mortality
Additional clinical outcomes in women who are pregnant/have recently given birth • Premature birth

- Miscarriage related to fetal abnormality
- Increased proportion of babies delivered by caesarean section
- Macrosomia (excessive birth weight)
- Respiratory distress syndrome in the new-born

Device related outcomes

- Adverse events related to the use of devices

Patient-reported outcomes

- Heath-related quality of life
- Psychological well being
- Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)
- Anxiety about experiencing hypoglycaemia
- Acceptability of testing and method of insulin administration

Carer reported outcomes

Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)

3.2 Overall aims and objectives of assessment

The overall objectives of this project are to examine the clinical and cost-effectiveness of hybrid closed loop systems for managing glucose levels in people who have T1DM. The key questions for this review are provided in the box below.

Key question 1

What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Sub questions

1. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in pregnant women who have T1DM?

2. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in children who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

3. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, an extreme fear of hypoglycaemia, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

4. What is the clinical effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, with diabetes related comorbidities that are at risk of deterioration, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Key question 2

What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Sub questions

1. What is the cost effectiveness of hybrid closed loop systems for managing glucose in pregnant women who have T1DM?

2. What is the cost effectiveness of hybrid closed loop systems for managing glucose in children who have T1DM and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

3. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, an extreme fear of hypoglycaemia, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

4. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, with diabetes related comorbidities that are at risk of deterioration, and are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

Systematic review methods followed the principles outlined in the Cochrane Handbook of Diagnostic Test Accuracy [32] and the NICE Diagnostic Assessment Programme manual.[33]

4.1 Methods for reviewing effectiveness

4.1.1 Identification of studies

4.1.2 Search strategy

The search strategy comprised the following main elements:

1) Searching of electronic bibliographic databases and other online sources,

2) Contacting experts in the field, and

3) Scrutiny of references of included studies, relevant systematic reviews, and the most recent NICE guidance on systems that combine CGM and CSII.[5]

A comprehensive search was developed iteratively and undertaken in a range of relevant bibliographic databases and other sources, following the recommendations in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions.[34] Search terms were related to T1DM (including a separate set of terms relating to pregnant women and women planning pregnancy) and technologies to manage blood glucose levels. Search strings applied in the previous technology assessment on integrated sensor-augmented pump therapy systems (DG21) [35] were used as the basis for developing selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections, and other systematic reviews informed the lines relating to pregnancy.[36-38] The main MEDLINE search strategies were independently peer reviewed by a second Information Specialist.

Date limits were used, in order to identify records added to databases since the searches for DG21 (run in 2014).[35] Searches were conducted in March and April 2021, and updated in April 2022, in the following resources: MEDLINE ALL (Ovid); Embase (Ovid); Science Citation Index and Conference Proceedings (Web of Science); Cochrane Database of Systematic Reviews (Wiley); CENTRAL (Wiley); Clinicaltrials.gov; HTA database (CRD); International HTA database (INAHTA); NIHR Journals Library; and the following websites:

- U.S. Food & Drug Administration (FDA)

- Medicines & Healthcare Products Regulatory Agency (MHRA)
- Agency for Healthcare Research and Quality (AHRQ)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Swedish Agency For Health Technology Assessment And Assessment Of Social Services (SBU)

The search was developed in MEDLINE (Ovid) and adapted as appropriate for other resources. Full search strategies are provided in Appendix 1: Record of searches – Clinical effectiveness (see section 9.1.1).

Records were exported to EndNote X9, where duplicates were systematically identified and removed. Where available, alerts were set up so that the team were aware of any new, relevant publications added to databases beyond the original search date.

4.1.3 Inclusion and exclusion criteria

Studies that satisfy the following criteria were included:

Populations	People who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring[ab] If evidence permits the following T1DM subpopulations will be included: • Pregnant women and those planning pregnancies (excluding gestational diabetes).[b] • Children (5 years and under, 6 – 11 years, 12 - 19 years). • People with extreme fear of hypoglycaemia. • People with diabetes related complications that are at risk of deterioration. [a] For the purpose of this review, difficulty refers to (1) not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below (for pregnant women/those planning pregnancies: not maintaining fasting plasma glucose levels of 5.2 mmol/l or below, or not maintaining non-fasting plasma glucose of 7.7 mmol/L (one hour after eating)/ 6.3 mmol/L (two hours after eating)), (2)

	not maintaining at least 70% time in range of 3.9 -10 mmol/l, or (3) repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life. [b] Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.
Target condition	Type 1 diabetes mellitus
Intervention	Hybrid closed loop systems
Comparator	• Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion. • Where evidence permits, scenarios assessing the following comparators will be presented for women with type 1 diabetes who are pregnant/planning pregnancy: • Real time continuous glucose monitoring with multiple daily insulin injections. • Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections. • Self-blood glucose monitoring with continuous subcutaneous insulin infusion.
Outcomes	<u>Intermediate measures</u> • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below and above target range • Change in HbA1c • Rate of glycaemic variability • Fear of hypoglycaemia

	• Rate of severe hypoglycaemic events • Rate of severe hyperglycaemic events • Episodes of diabetic ketoacidosis • Rate of ambulance call outs • Rate of hospital out-patient visits • Rate of weight gain <u>Clinical outcomes</u> • Retinopathy • Neuropathy • Cognitive impairment • End-stage renal disease • Cardiovascular disease • Mortality <u>Additional clinical outcomes in women who are pregnant/have recently given birth:</u> • Premature birth • Miscarriage related to fetal abnormality • Increased proportion of babies delivered by caesarean section • Macrosomia (excessive birth weight) • Respiratory distress syndrome in the new-born <u>Device related outcomes</u> • Adverse events related to the use of devices <u>Patient-reported outcomes</u> • Heath-related quality of life • Psychological well being • Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep) • Anxiety about experiencing hypoglycaemia • Acceptability of testing and method of insulin administration <u>Carer reported outcomes</u>

	• Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)
Study design	<u>Hybrid closed loop systems studies</u> • Any design <u>All comparator studies</u> • Comparative effectiveness study designs
Healthcare setting	Self-use supervised by primary or secondary care
Publication type	Peer reviewed papers Abstracts and manufacturer data will be included only if they provide numerical data and sufficient detail on methodology to enable assessment of study quality/risk of bias. Further, only data on outcomes that have not been reported in peer-reviewed full text papers will be extracted and reported.
Language	English

Research papers were included where it could not be established if all study participants had difficulty managing their condition (defined by HbA1c, fasting plasma glucose, non-fasting plasma glucose, or time in range as above), if the group mean met this criterion.

Papers that fulfilled the following criteria have been excluded:

Non-human studies, letters, editorials, and communications. Qualitative studies. Studies conducted outside of routine clinical care settings, e.g., inpatient research facilities, diabetic summer camps. Studies where more than 10% of the sample did not meet the inclusion criteria (for example over 10% were inpatients). Studies without extractable numerical data. Studies that provided insufficient information for assessment of methodological quality/risk of bias. Articles not available in the English language. Studies evaluating individual components and

not complete hybrid close loop systems. Studies of DIY closed loop systems, which are not approved by regulatory bodies.[39] Studies evaluating automated insulin delivery systems which only suspend insulin delivery when glucose levels are low/ are predicted to get low.

4.1.4 Review strategy

4.1.4.1 Prioritization strategy for full text assessment

We applied a two-step approach for identifying and assessing relevant evidence. We applied stricter criteria at the point of data extraction/risk of bias than title and abstract assessment to prioritise and select the best available evidence.[40-42] The elements used to prioritise evidence (study design, study length, sample size) were chosen in collaboration with NICE and diabetes clinicians as those that will provide the most applicable evidence.

Step one: The studies were scoped in Endnote before deciding which studies qualified for full text assessment (step two). Records were coded in terms of study design and study duration. Randomised controlled trials (RCTs) were prioritised over controlled trials. Non-randomised controlled trials/comparative effectiveness studies were prioritised over non-comparative studies. Longer term studies (6 months or more) were prioritised (see section 4.1.4.1) over shorter-term studies.

Step two: studies identified from step one went through the standard systematic reviewing approach of full text assessment. We followed the pre-defined PICO (see for study 4.1.3 eligibility criteria) to assess the eligibility of studies.

4.1.4.2 Prioritization strategy for data extraction and risk of bias

Given the limited time and resources available, deprioritised studies i.e. the large number of observational studies which otherwise met the inclusion criteria for this review were narratively reported and listed. RCTs were prioritised for data extraction and quality assessment.[42].

4.1.5 Data abstraction strategy

We extracted the following study characteristics:

Details on study design and methodology, participant characteristics, intervention characteristics, comparator characteristics, outcomes, outcome measures, and additional notes (such as funding).

Two reviewers extracted data independently, using a piloted data extraction form. Disagreements was resolved through consensus, with the inclusion of a third reviewer when required.

4.1.6 Critical appraisal strategy

The risk of bias of randomised trials was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[43] Two reviewers assessed risks of bias. Disagreements were resolved through consensus, with the inclusion of a third reviewer if required.

4.1.7 Methods of data analysis/synthesis

We synthesised the RCT evidence statistically. The network meta-analysis was conducted using a frequentist approach and a random-effects model.

Subgroup analyses were undertaken where possible for the different combinations of interventions study participants had previously used to manage their blood glucose (i.e., flash glucose monitor and multiple daily insulin injections, flash glucose monitor and CSII, rtCGM and multiple daily insulin injections, rtCGM and CSII, self-blood glucose monitoring and CSII).

4.1.7.1 Pairwise and network meta-analysis

The analysis compared hybrid close-loop systems and relevant comparators for managing blood glucose levels in T1DM. The primary effectiveness outcome was HbA1c. Other clinically relevant outcomes include the ‘time in target range’ which gives the percentage of time that a person spends with blood glucose level in target range of 70 to 180mg/dl, and adverse events (e.g., severe hypoglycaemia, diabetic ketoacidosis).

Decisions about information to include in the NMA were informed by relevance to the decision problem and sufficient similarity across studies (e.g., patient characteristics and study design) to reduce the risk of violating underlying assumptions of transitivity/coherence when pooling direct and indirect evidence across studies. We used an iterative process[46] to define the extent of the treatment network and to identify studies for inclusion. This involved first defining an

initial core set of interventions that met the criteria set out in the projects' scope and included trials of such interventions in T1DM populations.

Publication bias was assessed visually using a comparison-adjusted funnel plot, where publication bias is present if the funnel plot is asymmetrical. Egger's test was also used, where publication bias is considered to exist if $p<0.05$.

Transitivity was assessed by looking at the distributions of potential effect modifiers across all studies included in the systematic review.

To check for consistency of each network, net splitting can be performed which splits the estimates in the network into direct and indirect estimates. Statistically significant inconsistency is present between the direct and indirect estimates if the p-value of the difference between effect estimates is <0.05. However, due to the small number of studies and treatments in each network, net splitting was not feasible. Loop consistency was also not tested as there were no closed loops in the networks for any of the outcomes.

Treatments were ranked using P-score, which measures the certainty that one treatment is better than another treatment, averaged over all competing treatments.

Statistical analyses were performed using RStudio version 4.1.0.

4.1.8 Dealing with missing data

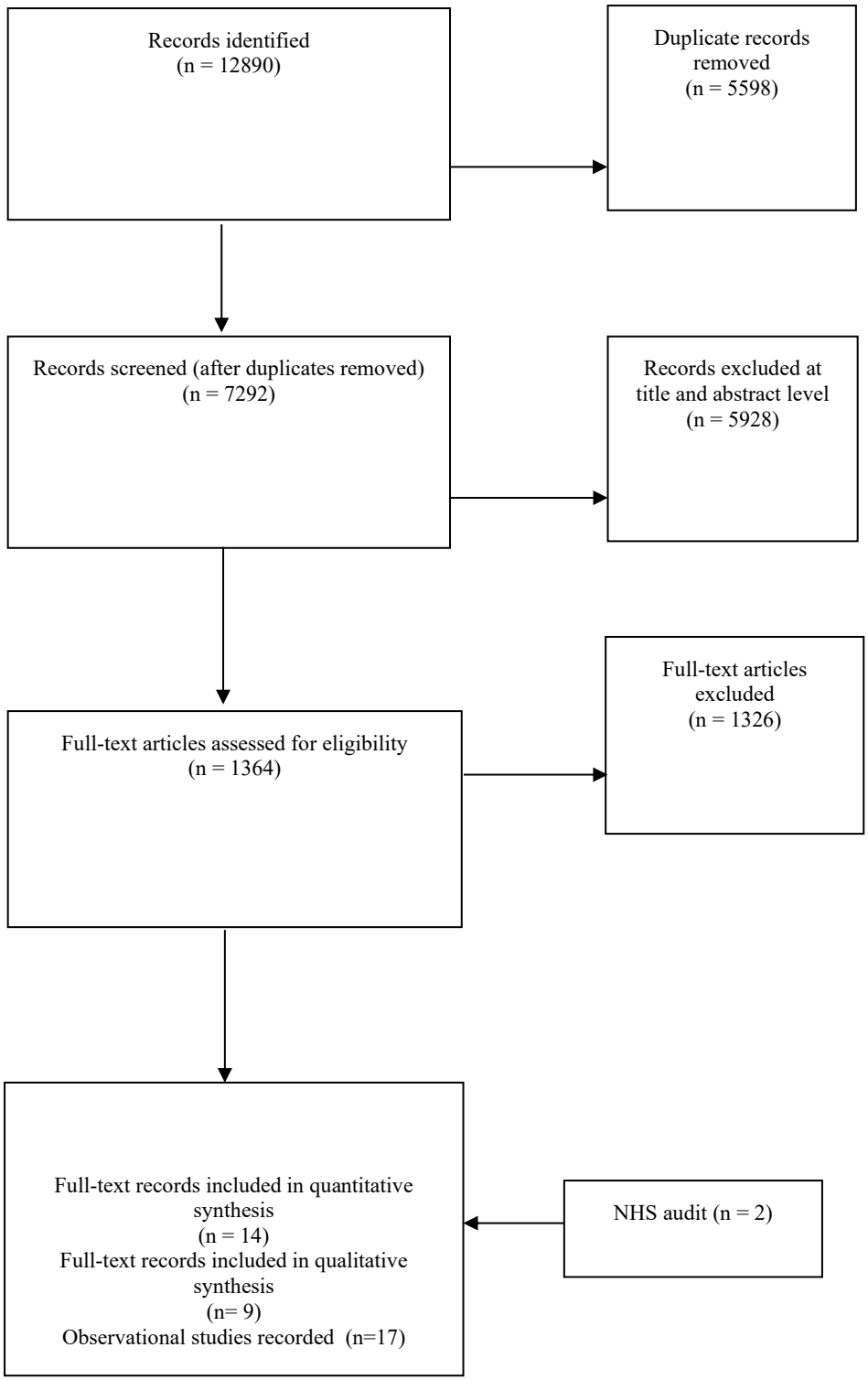
We conducted the review according to the registered protocol.

4.2 Results

4.2.1.1 Number of studies identified

The literature search provided 12890 records potentially related to the area of interest; 7292 records remained after removing duplicates. After the abstract screening, 1364 records were identified for full paper screening. A further 1326 articles were excluded at the full-text stage mainly due to incorrect intervention/comparators, study design, incorrect population, abstract/poster presentation only or further duplication identified. 14 records (12 RCTs) [27, 47-59] and 9 observational studies [27, 60-65] are presented for this systematic review of clinical effectiveness. Three papers drew on the same study participants. External submissions, including NHS England evidence and company submissions are also presented in this report.

The PRISMA flow diagram is shown in the figure below.



4.2.1.2 Number and type of studies included

Randomised controlled trials

Randomised studies

Eleven RCTs (one with two relevant intervention arms,54 13 records) 47-57, 59 were identified that yielded data of potential relevance to the decision problem assessing HCL against a comparator. RCTs in which HCL treatment was received for ≥ 4 weeks (range 4 to 26 weeks) were included if the comparator was relevant to the decision problem (comparators were classified as CSII + CGM and LGS/PLGS).

Most of these studies reported results for outcomes relevant to monitoring glycaemic control. These data were assembled using CGM technology that accumulates large amount of data and they assessed change in % time in range over a specified period of observation (baseline to final). Most studies reported change in HbA1c level (final minus baseline values). The RCTs thus provided quantitative data potentially amenable to network meta-analysis. Two Publications (Bergenstal 2021 27 and Weinzimer 2022 58) were derived from the FLAIR study and presented data comparing different types of AHCL; since HCL has been viewed here as a generic intervention the FLAIR study can be considered more similar to a single arm study (with two subgroups) than an RCT and is considered in the section describing single arm studies.

These RCTs were heterogeneous in multiple respects including trial design (parallel groups or cross over design with wash-out phase between different treatments), participants' age, number of participants, and other demographics including run-in times, duration of observation periods, and number and types of previous treatments. Studies screened relatively small numbers of patients. The number of participants randomised ranged from < 20 to 135.

Table 1 summarises the main characteristics of patients recruited in RCTs with treatment duration 4 to 26 months (additional RCT details are in 9.2. Most studies were conducted in children or young adults. For young children it would likely be difficult to clearly establish whether they were having difficulty in controlling glycaemia prior to recruitment. Only McAuley 2022 51 and Boughton 2019 48 looked at HCL use in elderly patients (age >60 years); in control arm for practical reasons and familiarity with method the participants continued with their previous method of glycaemic control which presumably was long established (i.e. they were not "re-trained" in a new non-HCL method). In treatment arm participants were trained and then transferred to HCL. Both these studies in the elderly enrolled relatively few patients.

Table 1. Main characteristics of populations recruited in RCTs

Study	Inclusion criteria	Age description	N
Ware 2022a [56]	Diag: ≥ 0.5yr previous; pump ≥3 months; HbA1c < 11% no previous HCL..	Very young children 1 to 7 yr	74
von dem Berge 2022 [55]	Pump ≥3 months; total insulin > 8 U/day; HbA1c 7.4% (±0.9); no severe hypo in last 3 months.	Pre-school and school children; 2 to14 yr	38
Thabit 2015 children/adolescents arm[54]	Diag: ≥ 0.5yr previous; age ≥ 6 y; pump ≥3 months; HbA1c < 10%;	Children /adolescents 6 to 18 yr.	25
Ware 2022b [57]	Diag: ≥ 1yr previous; pump ≥3 months; HbA1c 7.5% to 10%;	Children /adolescents 6 to 18 yr	135
Tauschmann 2018 [53]	Diag: ≥ 1yr previous; age ≥ 6 to 20 yr ; pump ≥3 months; HbA1c 7.5% to 10%; no CGM previous 3 months	Children and young adults 22yr (13 to 26)	86
Thabit 2015 adults arm [54]	Diag: ≥ 0.5yr previous; age ≥18 y; pump ≥ 0.5y; HbA1c 7.5% to 10%;	Adults, 40 yr (±9·4)	33
Benhamou 2019 [66]	Diag: ≥ 2yr previous; aged ≥18 years ; ≤ 50 U per day; HbA1c ≤ 10%	Adults, 48·2 yr (±13·4)	63
Boughton 2019 [48]	Diag: ≥ 1 yr ; Age ≥ 60 yr; pump ≥3 months; HbA1c ≤10·0%. No current use of a closed-loop system, no more than 1 severe in preceding 6 months.	Elderly, 68 yr (62 to 70)	37
McAuley 2022 [51]	Diag: ≥ 10 yr ; Age ≥ 60 yr; using i pump; HbA1c ≤10.5% ; no dementia.	Elderly , 67 yr (± 5)	30
Collyns 2021 [49] and Wheeler 2022 patient reported outcomes based on Collyns [59]	Diag: ≥ 1 yr; age 7 to 80 yr ; pump ≥6 months ; daily insulin min 8 units ; HbA1c < 10% ; no pregnancy.	Children 7-13,N 19, adolescents14-21 N 14, adults 22- 80yr N 26	59
Kariyawasam 2022 [50]	Diag: ≥ 1 yr ; Age 6 to 12 yrs; pump ≥3 months; HbA1c ≤9·0%; hospital 3days then 6 wks post-hospital phase	Young, 6-12 years	22
Stewart 2018 [52]	Women (singleton pregnancy); Diag: ≥ 1 yr prior to pregnancy; age 18-45 yr; HbA1c (8% (±1.1); Excluded if insulin dose ≥ 1.5 units/kg.	Pregnant, 32.8 (±5) yr;	16

The major outcomes reported in the RCTs related to monitoring glycaemic control. These included change in % HbA1c and % time within, above or below a defined blood glucose level (mmol/ litre) including: % time within range indicating satisfactory control (3.9 to 10 mmol/litre, % time in a hyperglycaemic range (> 10 mmol/litre), and % time in a hypoglycaemic range variously <3.9, <3.5, <3.3, <3.0 and < 2.8 mmol/litre depending on

study. Low rates of severe hypoglycaemia and of ketotic episodes were also reported; it may be that the small number of participants and relatively short treatment periods mean that accurate estimates of the rates of these events is difficult. The outcomes reported in RCTs are summarised in Table 2. Additional outcomes are reported in

Table 2. Glycaemic-control outcomes reported in RCTs of potential relevance

Study	Change in HbA1c %	% time >10 mM	% time 3.9 to 10 mM	% time <3.9 mM	% time <3.5 mM	% time <3.3 mM	% time <3.0 mM	% time <2.8 mM	Hypo events	Ketotic events
Ware 2022a[56]	√	√	√	√	√		√		√	√
von dem Berge 2022[55]	√	√	√				√	√	√	√
Thabit 2015[54]	√	√	√	√				√	√	√
Ware 2022b [57]	√	√	√	√					√	√
Tauschmann 2018 [53]	√	√	√	√	√			√	√	√
Benhamou 2019[66]	√	√	√	√		√		√	√	√
Boughton 2019 [48]	√	√	√	√	√		√		√	√
McAuley 2022[51]	√	√	√	√		√	√		√	√
Collyns 2021 [49] and Wheeler 2022 [59]	√	√	√	√			√		√	√
Kariyawasam 2022 [50]	√	√	√	√					√	√
Stewart 2018 [52]	√	√	§					√		
§ Stewart report TIR 3.5 to 7.8 mmol/L.										

Outcome results reported in the RCTs are summarised below in Table 2 and presented graphically in forest plots. Glycaemic control outcomes by study arm were reported in various ways, as mean (± sd) or median (IQR) values, often baseline values for each arm were not reported or were unclear so that change from baseline was sometimes and or unreported and only end of treatment values were provided. Trials reported mean difference and 95% CI between arms whether this was derived from median or mean estimates for the outcome. These reported values were available for NMA. Where necessary some outcome results have been calculated from numerical data in the relevant published reports; these

together with most other data reported, were often strongly rounded to only a few decimal places. Table 3 summarises the data extracted from the included RCTs. We present combined results of all RCTs together covering all subpopulations, before presenting results by individual subpopulations.

Table 3. Summary of main outcome measure reported in RCTs

	HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd* *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR*	*N hypo non-severe mean sd** **Median IQR*	*N hypo sev; mean sd**	*N DKA Event* *mean sd*
Tauschmann 2018 [53] HCL vs. CSII+CGM ;22 yr, 21 yr ; N =86 ; Tx 12 wks Lancet. 2021;392(10155):1321-9											
Inter Base	8.0 (0.6)	44 (11)	52 (10)	*3.5 (2.0,5.4)	*1.8 (0.8,3.2)	NR	NR	* 0.4 (0.1,1.0)			
Inter end	7.4 (0.6)	32 (8)	65(8)	* 2.6 (1.9,3.6)	* 1.4 (0.9,1.9)	NR	NR	* 0.3 (0.2,0.6)			
DIFF calc	-0.6 (0.125)	-12 (2.0)	13	* -0.9	* -0.4	NR	NR	* 0.1	NR	2	1
Comp base	7.8 (0.6) (	44 (11)	52 (9)	*3.3 (1.2, 5.5)	*1.9 (0.6,3.30	NR	NR	* 0.5 (0.1,1.0)			
Comp end	7.7 (0.5)	42 (10)	54 (9)	* 3.9 (1.7,5.3)	* 2.0 (0.9,3.0)	NR	NR	* 05.(0.2,0.9)	NR	*2*	0
DIFF calc	-0.1 (0.123)	-2 (2.35)	2	* 0.6	* 0.1	NR	NR	* 0.0			
Rep.Net effect 95%CI	*-0.36 (-0.53,-0.19)*	*-10 (-13.2,-7.5)*	*10.8 (8.2,13.5)*	*-0.83 (-1.4,-0.16)*	*-0.33 (-0.81,0.04)*	*NR*	*NR*	* 0.09 (-0.24,0.1)*		*0*	*+ 1*
Ware et al., 2022: [56] 5.6 yr ; HCL vs. CSII+CGM ; 5.6 yr (1.61) very young children ; N = 74 ; Tx 16 wks. N Engl J Med. 2022;386:209- 19											
Inter Base	7.3 (0.7)	*32.2 (24.0,42.7)	61.5 (9.5)	*4.5 (2.4,6.7)	NR	NR	*0.8 (0.2,1.8)	NR	NR		
Inter end	6.6 (0.6)	*22.9 (19.3,27.3)	71.6 (5.9)	*4.9 (3.3,6.7)	*2.6 (1.8,3.7)	NR	*1.0 (0.6,1.4)	NR	NR		
DIFF calc	-0.7 (0.16)	*-9.3	10.1	*0.3		NR	*0.2	NR	NR	1	0
Comp base	7.4 (0.6)	*36.7 (21.6,41.8)	60.8 (10.9)_	*3.9 (2.0,7.4)		NR	*0.6 (0.3,1.4)	NR	NR		
Comp end	7.0 (0.7)	*31.7 (23.4,40.1)	62.9 (9.0)	*4.5 (2.9,7.3)	*2.4 (1.4,4.2)	NR	*0.9 (0.4,1.6)	NR	NR		
DIFF calc	-0.4 (0.16)	*-5.0	2.1	*0.6		NR	*0.3	NR	NR	0	0
Net effect 95%CI	*-0.4 (-0.5,-0.3)*	*-8.5 (-9.9,-7.1)*	*8.7 (7.4,9.9)*	*0.1 (-0.4, 0.5) n.s*	*0.04 (-0.3,0.3) n.s*	NR	*0.02 (-0.1,0.1) n.s*	NR	NR	*1*	*0*

	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** **Median IQR	*N hypo sev; mean sd**	*N DKA Event* *mean sd
Ware et al., 2022b [57] HCL vs. CSII+CGM; children / adolescents: 13.1 yr (2.6) & 12.8 (2.9) yr; N = 135 ; Tx 6 months.											
Inter Base	*8.2 (0.7)*	46 (15)	47 (12)	*6.1(2.7,9.5)	NR	NR	NR	NR	NR	NR	NR
Inter end	7.6 (1.1)	38 (20)	54 (17)	*6.1 (3.0,12.1)	NR	NR	NR	NR	NR	NR	NR
DIFF calc	-0.6 (0.17)	-8 (3.1)	7	* 0	NR	NR	NR	NR	11	2	2
Comp base	8.3 (0.7)	47 (16)	46 (13)	*4.9(0.32,9.4),	NR	NR	NR	NR	NR	NR	NR
Comp end	8.1 (0.8)	46 (15)	47 (12)	*5.4 (2.0,12.0)	NR	NR	NR	NR	NR	NR	NR
DIFF calc	-0.2 (0.13)	-1 (2.6)	1	* 0.5	NR	NR	NR	NR	12	0	0
Net effect 95%CI	*-0.32 (-0.59,-0.04)*	*-7.0 (-12.5,-1.5)*	6.7 *(2.2,11.3)*	**-0.53 (-1.78,2.83)*	NR	NR	NR	NR	1	2	2
Benhamou et al., 2019: [66] HCL vs. CSII+CGM ; adult 48.2 (11.7) yr ; N=63; Tx 12 wks. X-over trial. Lancet Digit Health. 2019;1(1):e17-25											
HCL	-0.29 (0.6)	29.5 (10.2)	68.5 (9.4)	2 (2.40)	NR	0.8 (0.8)	NR	0.2 (0.8)	NR	5	0
Comparator	-0.14 (0.6)	36.3 (10.20	59.4 (10.20)	4.3 (2.40)	NR	2 (1.6)	NR	0.7 (0.8)	NR	3	0
Net effect 95%CI	*-0.15 (-0.33,0.03)*	*-6.8 (-9.7,-3.9)*	*9.2 (6.4,11.9)*	*-2.4 (-3.0,-1.7)*	NR	*-1.3 (-1.6,-0.9)*	NR	*-0.5 (-0.33,0.03)*	NR	*2*	*0*
Thabit 2015 children/adolescents: [54] HCL vs. CSII+CGM ; 12 (3.4) yr ; N = 25 ; Tx 12 wks. N Engl J Med. 2015 November 26; 373(22): 2129–2140											
Inter Base	7.8 (0.7)	NR	NR		NR	NR	NR		NR		2
Inter end	7.6 (1.1)	NR	NR		NR	NR	NR		NR		0
DIFF calc	-0.2	36.0 (12.5)	61.2 (11.9)	*2.9 (1.4,4.5)	NR	NR	NR	*0.2 (0.1,0.4)	NR	2; 1 pnt HCL off	2
Comp base	7.8 (0.6)	NR	NR		NR	NR	NR		NR		
Comp end	7..9 (10.6)	NR	NR		NR	NR	NR	*0.4 (0.2,0.7)	NR		
DIFF calc	0	44.5 (12.7)	51.6 (11.8)	*3.0 (1.8,6.1)	NR	NR	NR		NR		

	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** **Median IQR	*N hypo sev; mean sd**	*N DKA Event* *mean sd*
Net effect 95%CI	*-0.3 (-0.6,0.1)*	*-7.7 (-11.0,-4.4)*	*8.9 (5.9,11.8)*	¥ *0.83 (0.62,1.1) P 0.18*	NR	NR	NR	¥ *0.47 (0.22,1.1)* ***P 0.05***	NR		
Thabit 2015 adults: [54] HCL vs. CSII+CGM ; 40 (9.4) yr ; N = 33 ; Tx 12 wks. N Engl J Med. 2015 November 26; 373(22): 2129–2140											
Inter Base	7.6 (0.9)	NR	NR		NR	NR	NR		NR		
Inter end	7.3 (0.8)	NR	NR		NR	NR	NR		NR		
DIFF calc	-0.3 (0.21)	29.2 (11.4)	67.(10.60)	*2.9 (1.4,4.5)	NR	NR	NR	*0.3 (0.1,0.7)	NR	1	1
Comp base	7.6 (0.8)	NR	NR		NR	NR	NR		NR		
Comp end	7.6 (1.1)	NR	NR		NR	NR	NR	*0.4 (0.1,0.9)	NR	0	1
DIFF calc	0 (0.24)	38.9 (16.6)	56.8 (14.2)	*3.0 (1.8,6.1)	NR	NR	NR		NR		
Net effect 95%CI	*-0.3 (-0.5,-0.1)*	*-9.6 (-13.0,-6.3)*	*11.0 (8.1,13.8)*	¥ *0.81 (0.68,0.96) P 0.02*	NR	NR	NR	¥ *0.45 (0.31,0.56)* ***P <0.001***	NR	*1*	*0*
¥ Net effect reported as ratio and 95% CI											
McAuley et al., 2022 : [51] intervention: HCL vs. LGS/PLGS; elderly adult 67 yr (5); N = 30 ; X over ; Tx 4 months.											
Inter Base	7.5 (6)	NR	NR	NR	NR	NR	NR	NR	NR		
Inter end	*7.3 (7.1,7.5)	23.6 (6.6)	75.2 (6.3)	*1.21 (0.6,1.68)	NR	*0.37 (0.12,0.49)	*0.13 (0.03,0.24)	NR	NR	3	0
DIFF	NR	NR	NR	NR	NR	NR	-NR	NR	NR		
Comp base	7.5 (6)	NR	NR	NR	NR	NR	NR	NR	NR		
Comp end	*7.5 (7.1,7.9)	29.0 (9.8)	69.0 (9.1)	*1.69 (1.0,2.54)	NR	*0.41 (0.2,0.78)	*0.16 (0.10,0.38)	NR	NR	2	*1*
DIFF	NR	NR	NR	NR	NR	NR	NR	NR	NR		

	HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd* *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR*	*N hypo non-severe mean sd** ***Median IQR*	*N hypo sev; mean sd**	*N DKA Event* *mean sd*
Net effect 95%CI	*-0.2 (-0.3, 0.0)*	*-5.4 (-7.3,-3.5)*	*6.2 (4.4, 8.0)*	**-0.47 (-1.05,-0.25)*	NR	**-0.19 (-0.36,-0.06)*	**-0.11 (-0.16,-0.05)*	NR	NR	*+1*	*-1*
In 12 months pre-trial there were N=5 single severe hypo events and N= 4 patients with ≥ 2 severe hypo events. A minimum of 13 severe hypo events in 30 person years ~ 0.43/person year. HCL rate was 0.3/person year and SAP rate 0.2/person year											
Boughton et al., [48] HCL (*CamAPS FX, CamDiab, Cambridge, UK*) vs. CSII+CGM ; Age 68 (63,70) vs 67 (62,70) ; N = 20 vs. N =17 ; Tx 16 weeks . Sci Transl Med. 2019;11(484)											
Inter Base	7.5 (1.0)	*25.5 (15.1,41.9)	69.6 (14.1)	*1.8(0.8,3.2)	NR	NR	*0.1 (0.0,0.4)	NR	NR		NR
Inter end	6.7 (0.7)	*16.7 (11.4,23.9)	79.9 (7.9)	*1.7 (1.3,2.4)	*0.7 (0.5,1.1)	NR	*0.2 (0.1,0.3)	NR	NR		NR
DIFF	-0.8 (0.27)	*-8.8	10.3	*-0.1	NR	NR	NR	NR	NR	0	NR
Comp base	7.4 (0.9)	*25.5 (15.9,39.8)	70.3 (13.7)	*1.6 (0.4,2.7)	NR	NR	*0.1 (0.0,0.4)	NR	NR		NR
Comp end	6.9 (0.9)	*21.4 (16.9,36.50	71.4 (13.2)	*1.7 (0.9,2.7)	*0.7 (0.4,1.2)	NR	*0.2 (0.1,0.3)	NR	NR		NR
DIFF	-0.5 (0.31)	*-4.1	1.1	*0.1	NR	NR	NR	NR	NR	2	NR
Net effect 95%CI	*-0.2 (-0.4,-0.10*	**-8.5 (-10.9,-6.1)*	*8.6 (6.3,11.0)*	**-0.1 (-0.3,0.2)*	**0.0 (-0.2,0.1)*	*NR*	**0.0 (-0.1,0.1)*	*NR*	*NR*	*-2 (17.6 / 100PYR)*	*NR*
von dem Berge 2022 [55] HCL vs. LGS/PLGS; N =38 : (age 2-6 yrs N 18) and (14- 17 yrs N 20) ; Tx 8 weeks. X-over trial Diabetes Obes Metab. 2022;1–9											
Inter Base	7.4 (0.9)	36.3 (14.5)	60.4 (12.3)	NR	NR	NR	0.8 (0.9)			0	0
Inter end	6.9 (0.5)	25.8 (8.1)	70.8 (7.2)	NR	NR	NR	0.8 (0.7)			0	0
DIFF calc	-0.5 (0.17)	-10.5 (2.7)	10.4	NR	NR	NR	0		<3.9mM**16 (13.5,19.0) < 3mM**4 (3.4,5.9)		NR
Comp base	7.4 (0.9)	36.3 (14.5)	60.4 (12.3)	NR	NR	NR	0.8 (0.9)			0	0
Comp end	7.1 (0.6)	36.5 (15.2)	60.3 (13.9)	NR	NR	NR	0.6 (0.50			0	0

	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** **Median IQR	*N hypo sev; mean sd**	*N DKA Event *mean sd*
DIFF calc	-0.3 (0.18)	-0.2 (3.41)	-0.1	NR	NR	NR	-0.2		<3.9mM **18 (13.7,20.6) <<3mM **3 (2.6,4.6)		NR
Net effect 95%CI	*P 0.0002*	*P <0.0001*	*P <0.0001*	*NR*	*NR*	*NR*	*n.s.*		*n.s. n.s.*	0	*NR*
Kariyawasam 2022 [50] HCL vs. CSII+CGM; N =20 (N=17 for 6 wk home phase) ; age 2-6 yrs ; Tx 6 weeks. Lancet digit Health; X-over RCT											
Inter Base	7.6 (0.52)	NR	NR	NR	NR	NR	NR	NR		0	0
Inter end	NR	31.1 (7.7)	66.19 (6.5)	2.62 (2.39)	NR	NR	0.57 (0.77)	NR		0	0
DIFF calc	NR	NR	NR	NR	NR	NR	NR	NR	* 13 (11.6) /person yr		NR
Comp base	7.4 (0.95)	NR	NR	NR	NR	NR	NR	NR		0	0
Comp end	NR	36.11 (7.7)	58.68 (6.5)	5.24 (2.39)	NR	NR	1.01 (0.77))	NR		0	0
DIFF calc	NR	NR	7.51	NR	NR	NR	NR	NR	* 24.57 (12) /person yr		NR
Net effect 95%C (calc) reported P	*NR*	*-5 (-10.2,0.18) P 0.015*	*7.51 (3.14,11.8) P <0.001*	*-2.62 (-4.22,-1.01) P <0.0001*	*NR*	*NR*	*-0.44 (-0.96,-.08) P 0.003*	*NR*	*-11.57 (-19.5,-3.6) P <0.0001*	0	*0*
Collyns 2021 [49] HCL vs. LGS/PLGS; N = 60 ; age 23.5 (7 to 65) ; Tx 4 weeks with 2 to 4 wk run in. ; X-over RCT; all 3 age groups. ALL 59 (completed)											
Inter Base	7.6 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inter end	NR	27.5(8.1)	70.4 (8.1)	2.1 (1.4)	NR	NR	0.5 (0.5)	NR	0	0	0
DIFF calc	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Comp base	7.6 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Comp end	NR	39.6 (12.1)	57.9 (11.7)	2.5 (1.6)	NR	NR	0.5 (0.5)	NR	0	0	1

	*HbA1c% mean sd *median IQR*	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe mean sd* **Median IQR*	*N hypo sev; mean sd**	*N DKA Event *mean sd*
DIFF calc	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Net effect 95%C (rep) reported P	*-0.6 (-1.38,0.18)*	*-12.1 (9.0) P<0.001*	*12.5 (8.5) P <0.001*	*-0.4 (1.3) P 0.0318*	*NR*	*NR*	*-0.1(0.4) P 0.025*	*NR*	*0*	0	*-1*
Collyns 2021 [49] HCL vs. LGS/PLGS; N = 19 ; age 7 to 13yr ; Tx 4 weeks with 2 wk run in. ; X-over RCT; children											
Net effect 95%C (rep) reported P	*NR*	*-11.2 (8.0) P<0.001*	*11.8 (7.4) P <0.001*	*-0.7 (1.8) P 0.1216*	*NR*	*NR*	*-0.2(0.5) P 0.067*	NR	NR	NR	NR
Collyns 2021 HCL vs. LGS/PLGS; N = 14 ; age 14 to 21yr ; Tx 4 weeks with 2 wk run in. ; X-over RCT; adolescents											
Net effect 95%C (rep) reported P	*NR*	*-14.0 (8.5) P<0.001*	*14.4 (8.4) P <0.001*	*-0.74 (1.1) P 0.1804*	*NR*	*NR*	*-0.1(0.3) P 0.2441*	NR	NR	NR	NR
Collyns 2021 HCL vs. LGS/PLGS; N = 26 ; age 22 to 80yr ; Tx 4 weeks with 2 wk run in. ; X-over RCT; adults											
Net effect 95%CI (reported P)	*NR*	*-11.8 (10) P<0.001*	*11.9 (9.5) P <0.001*	*-0.1 (0.9) P 0.5184*	*NR*	*NR*	*-0.0(0.2) P 0.5462*	NR	NR	NR	NR

	HbA1c %	% TIR >10 mmol/L	%TIR >7.8 mmol/L	% TIR 3.5-7.8 mmol/L	% TIR <3.5mmol/L	% TIR <2.8 mmol/L	Hypo events median (range) Unclear if IQR	N severe hypo	DKA event
Stewart 2018 [52] HCL vs. CSII+CGM; N = 16 ; age 32.8 (sd 5); Tx 4 weeks; X-over RCT; adult pregnant women; study reported TIRs that were in most cases atypical of other studies.									

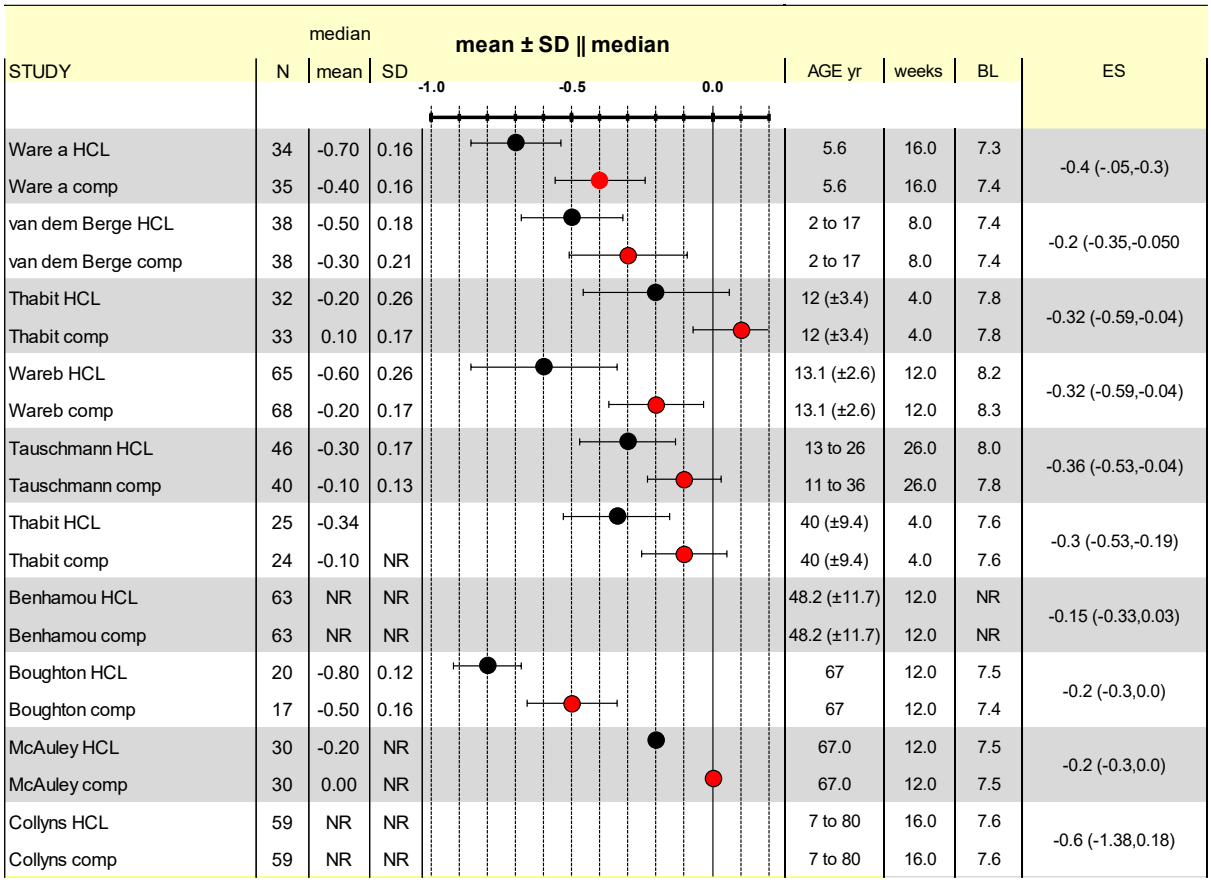
	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median IQR	*% TIR <2.8 mmol/L [50mg/dl] mean sd* *median IQR	*N hypo non-severe mean sd** ***Median IQR	*N hypo sev; mean sd**	*N DKA Event* *mean sd
end INT	6.6%	14.6	36.1	62.3	1.6	0.2	8 (1 to 17)	0	NR		
end Comp	6.4%	14.8	36.6	60.1	2.7	0.5	12.5 (1 to 53)	0	NR		
Net effect 95%CI (rep) P	*P 0.15*	*-0.1 (-4.2,4.0) P 0.94*	*-0.6 (-7.4,6.30 P 0.86*	*2.1 (-4.1,8.3) P 0.47*	*-1.1 (-0.2 ,-2.1) P 0.02*	*-0.2 (-0.0,-0.5) P 0.03*	*P 0.04*		NR		
No statistically significant improvement in glycaemic control over 4 weeks except for less time in hypoglycaemic range possible reflected in fewer hypo (non severe) events											

DIFF = difference; DKA = diabetic ketoacidosis; IQR = inter quartile range; N = number of participants; Net effect = comparison HCL vs. comparator; sd = standard deviation; TIR = time in range ; Tx = treatment duration; wk = weeks; X over = RCT cross over design; yr = years.

4.2.2 %HbA1c - Forest plots

Figure 1 shows the change from baseline in %HbA1c for each arm over the treatment period. A negative effect estimate (ES), comparing HCL vs. comparator, infers superior glycaemic with HCL.

Figure 1. Change (mean ± sd or median) in %HbA1c over treatment period in RCTs



STUDY	N	mean	SD	AGE yr	weeks	BL	ES
Ware a HCL	34	-0.70	0.16	5.6	16.0	7.3	-0.4 (-.05,-0.3)
Ware a comp	35	-0.40	0.16	5.6	16.0	7.4	
van dem Berge HCL	38	-0.50	0.18	2 to 17	8.0	7.4	-0.2 (-0.35,-0.050
van dem Berge comp	38	-0.30	0.21	2 to 17	8.0	7.4	
Thabit HCL	32	-0.20	0.26	12 (±3.4)	4.0	7.8	-0.32 (-0.59,-0.04)
Thabit comp	33	0.10	0.17	12 (±3.4)	4.0	7.8	
Wareb HCL	65	-0.60	0.26	13.1 (±2.6)	12.0	8.2	-0.32 (-0.59,-0.04)
Wareb comp	68	-0.20	0.17	13.1 (±2.6)	12.0	8.3	
Tauschmann HCL	46	-0.30	0.17	13 to 26	26.0	8.0	-0.36 (-0.53,-0.04)
Tauschmann comp	40	-0.10	0.13	11 to 36	26.0	7.8	
Thabit HCL	25	-0.34		40 (±9.4)	4.0	7.6	-0.3 (-0.53,-0.19)
Thabit comp	24	-0.10	NR	40 (±9.4)	4.0	7.6	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-0.15 (-0.33,0.03)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.80	0.12	67	12.0	7.5	-0.2 (-0.3,0.0)
Boughton comp	17	-0.50	0.16	67	12.0	7.4	
McAuley HCL	30	-0.20	NR	67.0	12.0	7.5	-0.2 (-0.3,0.0)
McAuley comp	30	0.00	NR	67.0	12.0	7.5	
Collyns HCL	59	NR	NR	7 to 80	16.0	7.6	-0.6 (-1.38,0.18)
Collyns comp	59	NR	NR	7 to 80	16.0	7.6	

Weeks = treatment period; BL = baseline value ; comp = comparator; HCL = hybrid closed loop; N = number of participants; yr = years; ES = net effect size mean difference 95% CI [HCL vs. comparator]; medians have no error bars.

Range of mean baseline (BL) %HbA1c in the RCTs was narrow: 7.3 to 8.3. In all studies reduction in %HbA1c is greater for HCL than comparator. Change in %HbA1c over treatment (TX) period in HCL is modest (range -0.2 to -0.8). Net effect sizes (ES 95% CI; HCL vs. comparator) are modest ranging from -0.15 to -0.6. Relative to the NHS real world pilot study BL is lower in these studies (NHS BL = 9.4 %HbA1c) and the net ES smaller (NHS ES = -1.5). In the NHS pilot study (described in section 4.3.1) treatment with HCL brings the mean % HbA1c to 7.9 approaching a level comparable with the upper range values

seen in RCTs after HCL use. Not included in the forest plot is the FLAIR study [27] comparing two types of HCL with each other with BL %HbA1c = 7.9. Change from baseline was similar to the RCTs above: -0.5 (± 0.10) with one HCL and -0.3 (± 0.09)

with the other.

4.2.3 %HbA1c – NMA

There were 12 estimates from 11 studies that were included in this NMA as estimates from Thabit study arms were split into adult and children estimates. The reference treatment class was CSII+CGM, where estimates >0 favoured CSII+CGM. The network map is presented in Figure 2 and the forest plot of the NMA is presented in Figure 3.

Compared to CSII+CGM, treatment with HCL decreased HbA1c % by 0.29 (-0.37 to -0.21). There was no statistically significant difference between CSII+GCM and LGS/PLGS.

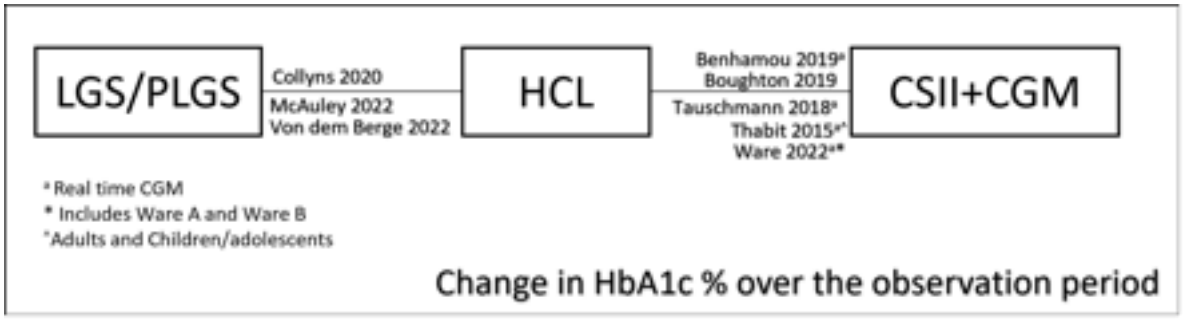


Figure 2. Network map of the outcome Change in HbA1c % over observation period

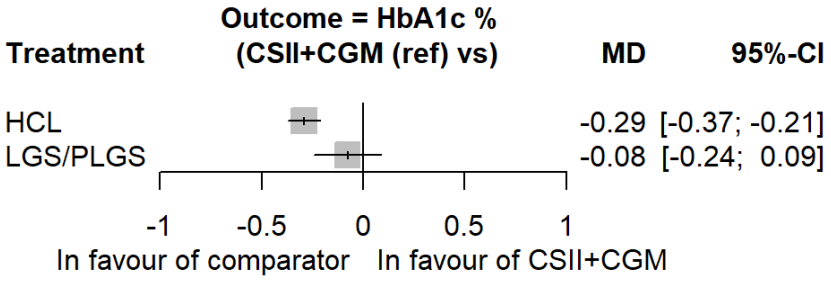


Figure 3. Results of the NMA of the outcome Change in HbA1c % over observation period

4.2.4 % time within range (between 3.9-10.0 mmol/L) - Forest plots

In all the RCTs the increase in % time in range was greater in the HCL arm than the comparator arm, in all cases reaching statistical significance (< P 0.05). The lowest mean BL % time in range was 46-47%, in all other studies it was > 50%. In the NHS Pilot study (described in section 6.1) BL was 34.2% allowing considerable scope for improvement with HCL treatment which was 28.5% (unadjusted; 95% CI: 25.6 to 13.5). The change from baseline in the HCL arm of RCTs with adults of similar age range as adult NHS Pilot (e.g. [53], [48]) ranged from 10% to 15%, approximately half that in Pilot. The size of improvement in % TIR appears to be greater the smaller the BL level.

Figure 4. change from baseline in % time in range (3.9 mmol/L to 10.0 mmol/L)

STUDY	N	mean	SD	mean ± SD -2 0 2 4 6 8 10 12 14 16 18 20	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR		2 to 6	6.0	NR	7.51 (3.14,11.8)
Kariyawasam comp	17	NR	NR		2 to 6	6.0	NR	
Ware a HCL	34	10.10	0.18		5.6	16.0	61.5	8.7 (7.4,9.9)
Ware a comp	35	2.10	0.21		5.6	16.0	60.8	
von dem Berge HCL	38	10.40	0.57		2 to 17	8.0	60.4	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04		2 to 17	8.0	60.4	
Collyns HCL	19	NR	NR		7 to 13	4.0	NR	11.8 (8.5,15.1)
Collyns comp	19	NR	NR		7 to 13	4.0	NR	
Thabit HCL	32	NR	NR		12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR		12 (±3.4)	12.0	NR	
Ware b HCL	65	7.00	2.70		13.1 (±2.6)	26.0	47.0	6.7 (2.2,11.3)
Ware b comp	68	1.00	0.90		13.1(±2.6)	26.0	46.0	
Collyns HCL	14	NR	NR		14 to 21	4.0	NR	14.4 (10.0,18.8)
Collyns comp	14	NR	NR		14 to 21	4.0	NR	
Tauschmann HCL	46	13.00	7.40		13 to 26	12.0	52.0	10.8 (8.2,13.5)
Tauschmann comp	40	2.00	7.90		11 to 36	12.0	52.0	
Stewart HCL	16	NR	NR		32 (±5)	4.0	NR	2.1 (-4.1,8.3)
Stewart comp	16	NR	NR		32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR		40 (±9.4)	12.0	NR	11.0 (8.1,13.8)
Thabit comp	24	NR	NR		40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR		48.2 (±11.7)	12.0	NR	9.2 (6.4,11.9)
Benhamou comp	63	NR	NR		48.2 (±11.7)	12.0	NR	
Boughton HCL	20	11.30	3.60		67	16.0	69.6	8.6 (6.3,11.0)
Boughton comp	17	1.10	4.60		67	16.0	70.3	
McAuley HCL	30	NR	NR		67.0	16.0	NR	6.2 (8.4,8.0)
McAuley comp	30	NR	NR		67.0	16.0	NR	
Collyns HCL	59	NR	NR		7 to 80	4.0	NR	12.5 (8.0,17.0)
Collyns comp	59	NR	NR		7 to 80	4.0	NR	

Weeks = treatment period; BL = baseline value ; comp = comparator; HCL = hybrid closed loop; N = number of participants; yr = years; ES = net effect size mean difference 95% CI [HCL vs. comparator]; medians have no error bars. NB. The population in Stewart et al., was pregnant women and the TIR refers to 3.5 to 7.8 mM rather than 3.9 to 10 mM.

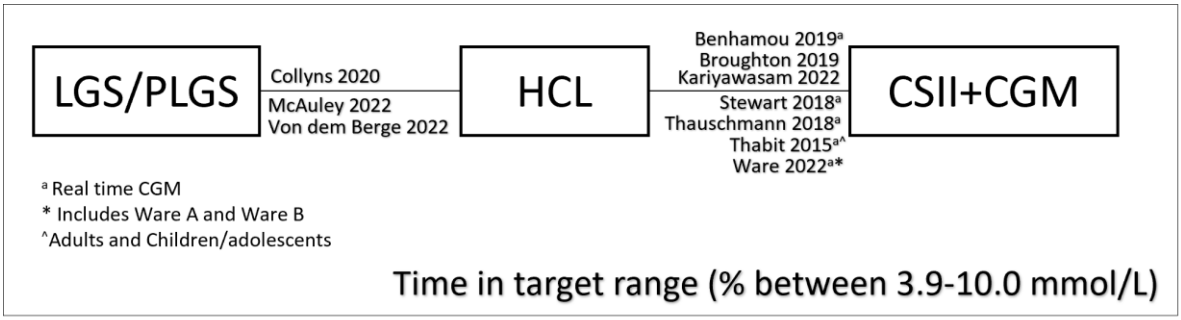
4.2.5 % time within range (between 3.9-10.0 mmol/L) – NMA

There were 13 estimates from 12 studies that were included in this NMA as estimates from Thabit were split into adult and children estimates. The reference treatment class was CSII+CGM, where estimates <0 favoured CSII+CGM. The network map is presented in Figure 5 and the forest plot of the NMA is presented in Figure 6.

Compared to the CSII+CGM treatment classification, HCL significantly increased % TIR (between 3.9 – 10.0 mmol/L), with a mean difference (MD) of 8.6 (7.03 to 10.22). There was

no statistically significant difference between CSII+GCM and LGS/PLGS.

Figure 5. Network map of the outcome Time in target range (% between 3.9 and 10.0 mmol/l)



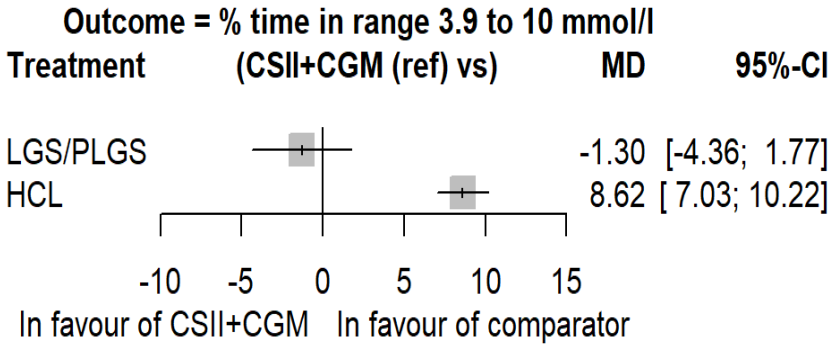


Figure 6. Results of the NMA of the outcome Time in target range (% between 3.9 and 10.0 mmol/l)

4.2.6 % time within range (>10.0 mmol/L) – Forest plot

Figure 7 shows the change from baseline in % time in hyperglycaemic range (> 10.0 mmol/L). Ware 2022 [56] and Boughton[48] reported BL and follow up % time in range as medians IQR without specifying the IQR for the change from BL, calculating IQR was problematical and not attempted. The studies of Benhamou [66] and Thabit [54] only reported net ES.

Figure 7. Change in % time in hyperglycaemic range (> 10.0 mmol/L) over treatment period in RCTs

STUDY	N	mean	SD	mean ± SD ‖ median -14 -12 -10 -8 -6 -4 -2 0 2	AGE yr	weeks	BL	ES
Kariyawasam HCL	17	NR	NR		2 to 6	6.0	NR	-5.01 (-6.21,-3.81)
Kariyawasam comp	17	NR	NR		2 to 6	6.0	NR	
Ware a HCL	34	-9.30	NR		5.6	16.0	32.2	-8.5 (-9.9,-7.1)
Ware a comp	35	-5.00	NR		5.6	16.0	36.7	
von dem Berge HCL	38	10.40	0.57		2 to 17	8.0	36.3	10.5 (8.09,12.91)
von dem Berge comp	38	-0.10	1.04		2 to 17	8.0	36.3	
Collyns HCL	19	NR	NR		7 to 13	4.0	NR	-11.2 (-14.8,-7.6)
Collyns comp	19	NR	NR		7 to 13	4.0	NR	
Thabit HCL	32	NR	NR		12 (±3.4)	12.0	NR	8.9 (5.9,11.8)
Thabit comp	33	NR	NR		12 (±3.4)	12.0	NR	
Ware b HCL	65	-8.00	2.70		13.1 (±2.6)	26.0	46.0	-7 (-12.5,-1.5)
Ware b comp	68	-1.00	2.60		13.1(±2.6)	26.0	47.0	
Collyns HCL	14	NR	NR		14 to 21	4.0	NR	-14 (-18.4,-9.55)
Collyns comp	14	NR	NR		14 to 21	4.0	NR	
Tauschmann HCL	46	-12.00	2.00		13 to 26	12.0	44.0	-10 (-13.2,-7.5)
Tauschmann comp	40	-2.00	2.35		11 to 36	12.0	44.0	
Stewart HCL	16	NR	NR		32 (±5)	4.0	NR	-0.1 (-4.2,4.0)
Stewart comp	16	NR	NR		32 (±5)	4.0	NR	
Thabit HCL	25	NR	NR		40 (±9.4)	12.0	NR	-9.6 (-13.0,-6.3)
Thabit comp	24	NR	NR		40 (±9.4)	12.0	NR	
Benhamou HCL	63	NR	NR		48.2 (±11.7)	12.0	NR	-6.8 (-9.7,-3.9)
Benhamou comp	63	NR	NR		48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-8.80	0.00		67	16.0	25.5	-8.5 (-10.9,-6.1)
Boughton comp	17	-4.10	0.00		67	16.0	25.5	
McAuley HCL	30	NR	NR		67.0	16.0	NR	-5.4 (-7.3,-3.5)
McAuley comp	30	NR	NR		67.0	16.0	NR	
Collyns HCL	59	NR	NR		7 to 80	4.0	NR	-12.1 (-16.8,-7.38)
Collyns comp	59	NR	NR		7 to 80	4.0	NR	

N = number of participants contributing data; yr = years; weeks = treatment duration; BL = mean baseline value ; ES = net effect size comparing reduction in % in range in HCL arm relative to control arm, n.b. the ES values reported were usually statistically adjusted. Benhamou and Thabit and only reported net ES. Median values have no error bars.

In all studies HCL reduced % time in hyperglycaemic range greater extent than in the comparator arms. Difference between arms (net effect size) was statistically significant in all cases ($P < 0.05$). The NHS Pilot study (described in section 4.3.1) reported an unadjusted reduction in hyperglycaemic range of ≥ 14 mmol/L (rather than 10 mmol/L) of 22.2 %.

4.2.7 % time within range (>10.0 mmol/L) – NMA

There were the same 13 estimates from 12 studies in this NMA as for the outcome TIR % between 3.9-10.0 mmol/L. The reference treatment class was CSII+CGM, where estimates >0 favoured CSII+CGM. The network map is presented in Figure 8 and the forest plot of the NMA is presented in Figure 9.

Compared to CSII+CGM, HCL significantly decreased TIR (% above 10.0 mmol/L), with a mean difference (MD) of -7.2 (-8.92 to -5.48). There was no statistically significant difference between CSII+GCM and LGS/PLGS.

Figure 8. Network map of the outcome Time in target range (% above 10.0 mmol/l)

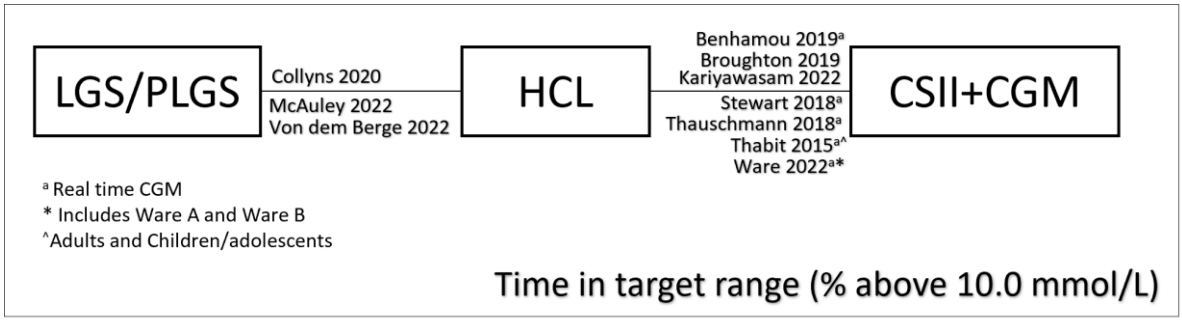
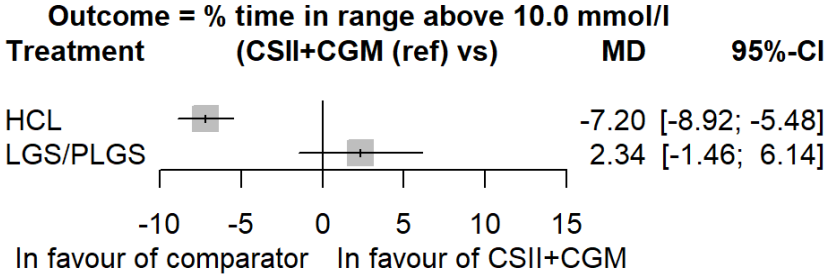


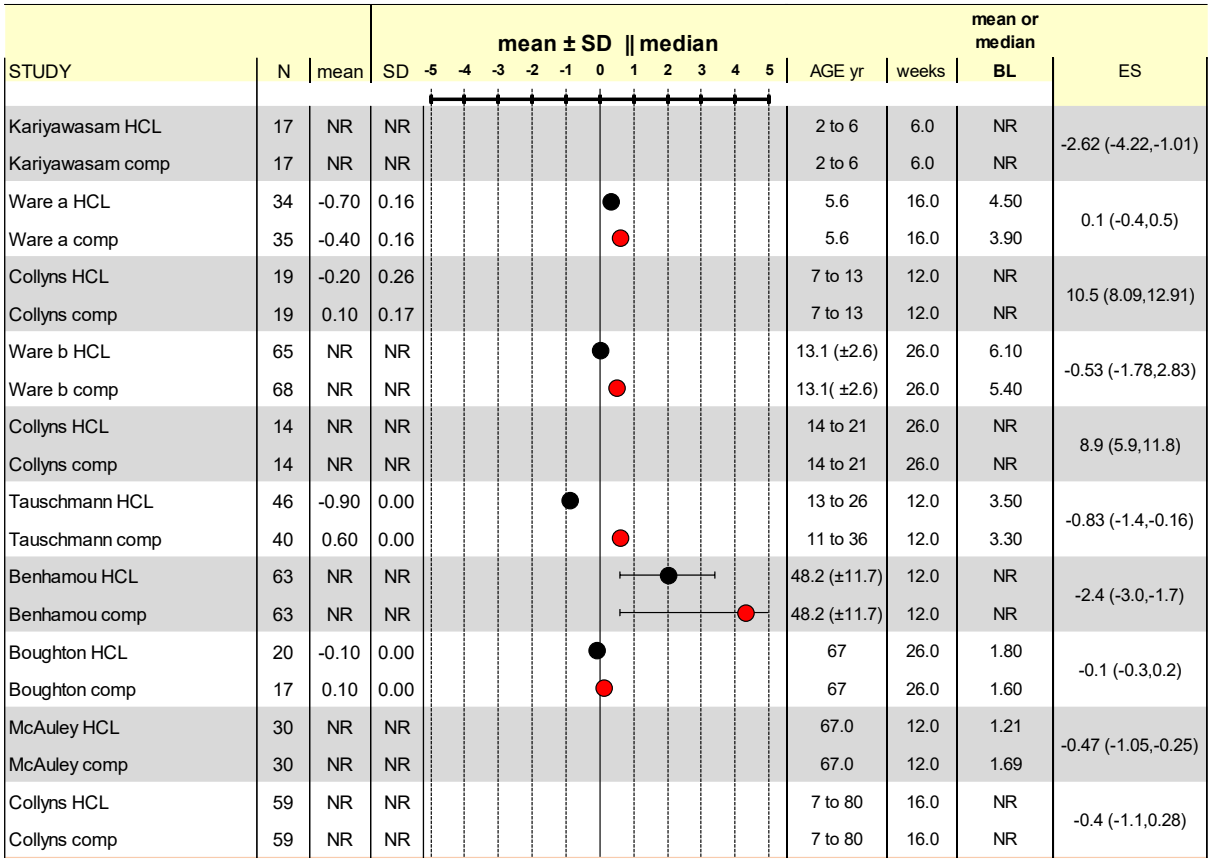
Figure 9. Results of the NMA of the outcome Time in target range (% above 10.0 mmol/l)



4.2.8 % time within range (<3.9 mmol/L) – Forest plot

Figure 10 summarises % time in hypoglycaemic range of <3.9 mmol/L. Because of skewed data results were mostly reported as medians with IQRs, only a few studies reporting mean ± sd. The plots show BL and follow up % time in specified range by each arm since this allows IQRs to be shown whereas reliably calculating IQR for BL vs. follow-up differences was problematical for most studies.

Figure 10. % time in hypoglycaemic range < 3.9 mmol/L



STUDY	N	mean	SD	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR	2 to 6	6.0	NR	-2.62 (-4.22,-1.01)
Kariyawasam comp	17	NR	NR	2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16	5.6	16.0	4.50	0.1 (-0.4,0.5)
Ware a comp	35	-0.40	0.16	5.6	16.0	3.90	
Collyns HCL	19	-0.20	0.26	7 to 13	12.0	NR	10.5 (8.09,12.91)
Collyns comp	19	0.10	0.17	7 to 13	12.0	NR	
Ware b HCL	65	NR	NR	13.1 (±2.6)	26.0	6.10	-0.53 (-1.78,2.83)
Ware b comp	68	NR	NR	13.1(±2.6)	26.0	5.40	
Collyns HCL	14	NR	NR	14 to 21	26.0	NR	8.9 (5.9,11.8)
Collyns comp	14	NR	NR	14 to 21	26.0	NR	
Tauschmann HCL	46	-0.90	0.00	13 to 26	12.0	3.50	-0.83 (-1.4,-0.16)
Tauschmann comp	40	0.60	0.00	11 to 36	12.0	3.30	
Benhamou HCL	63	NR	NR	48.2 (±11.7)	12.0	NR	-2.4 (-3.0,-1.7)
Benhamou comp	63	NR	NR	48.2 (±11.7)	12.0	NR	
Boughton HCL	20	-0.10	0.00	67	26.0	1.80	-0.1 (-0.3,0.2)
Boughton comp	17	0.10	0.00	67	26.0	1.60	
McAuley HCL	30	NR	NR	67.0	12.0	1.21	-0.47 (-1.05,-0.25)
McAuley comp	30	NR	NR	67.0	12.0	1.69	
Collyns HCL	59	NR	NR	7 to 80	16.0	NR	-0.4 (-1.1,0.28)
Collyns comp	59	NR	NR	7 to 80	16.0	NR	

Thabit and Benhamou did not report before and after values; Thabit presented ES as a ratio of medians, Benhamoou ES was reported as -2.4 (95% CI: -3.0 to -1.7).

The NHS Pilot study (described in section 4.3.1) did not report this outcome.

In both arms the mean or median % time in range was small (6% or less), the ES (difference between arms) was also small occasionally reaching statistical significance.

Figure 11 summarises % time in hypoglycaemic range of <3.0 mmol/L. Again study results were mostly reported as median with IQR, only a few studies reported mean ± sd.

Figure 11. % time in hypoglycaemic range < 3.0 mmol/L

STUDY	N	mean	SD	mean ± SD || median -0.40 -0.20 0.00 0.20 0.40	AGE yr	weeks	mean or median BL	ES
Kariyawasam HCL	17	NR	NR		2 to 6	6.0	NR	-0.44 (-0.96,0.08)
Kariyawasam comp	17	NR	NR		2 to 6	6.0	NR	
Ware a HCL	34	-0.70	0.16		5.6	16.0	0.80	0.02 (-0.1,01)
Ware a comp	35	-0.40	0.16		5.6	16.0	0.60	
von dem Berge HCL	38	-0.20	0.26		7 to 13	12.0	0.80	0.2 (0.04,0.36)
von dem Berge comp	38	0.10	0.17		7 to 13	12.0	0.80	
Collyns HCL	19	NR	NR		13.1 (±2.6)	26.0	NR	-0.2 (-.42,0.02)
Collyns comp	19	NR	NR		13.1(±2.6)	26.0	NR	
Collyns HCL	14	NR	NR		14 to 21	26.0	NR	-0.01 (-0.26,0.06)
Collyns comp	14	NR	NR		14 to 21	26.0	NR	
Boughton HCL	20	NR	NR		13 to 26	12.0	NR	0.0 (-0.1,0.1)
Boughton comp	17	NR	NR		11 to 36	12.0	NR	
McAulery HCL	30	NR	NR		48.2 (±11.7)	12.0	NR	-0.11 (-0.16,-0.05)
McAuley comp	30	NR	NR		48.2 (±11.7)	12.0	NR	
Collyns HCL	59	5.00	NR		67	26.0	NR	-0.1 (-0.31,0.11)
Collyns comp	59	5.00	NR		67	26.0	NR	

The mean or median % time in range was < 1.5% in both arms and ES values (HCL vs. comparator) reported were very small. This outcome was reported in the NHS Pilot study (described in section 4.3.1). The % times in range were reported as: baseline 0.36%; follow up

0.34%; providing a difference for HCL of -0.02 (95%CI : -0.01 to 0.2). A few studies reported alternative hypoglycaemic ranges (see Table 2) with similar results.

4.2.9 % time within range (<3.9 mmol/L) – NMA

There were 7 estimates from 7 studies that were included in this NMA. The reference treatment class was CSII+CGM, where estimates >0 favoured CSII+CGM. The network map is presented in Figure 12**Error! Reference source not found.** and the forest plot of the NMA is presented in Figure 13.

Despite a MD <0 for HCL compared to CSII+CGM, as the 95% CI crossed 0, there was no statistically significant difference between HCL and CSII+CGM, and similarly no statistically significant difference between CSII+CGM and LGS/PLGS.

Figure 12. Network map of the outcome Time in target range (% below 3.9 mmol/l)

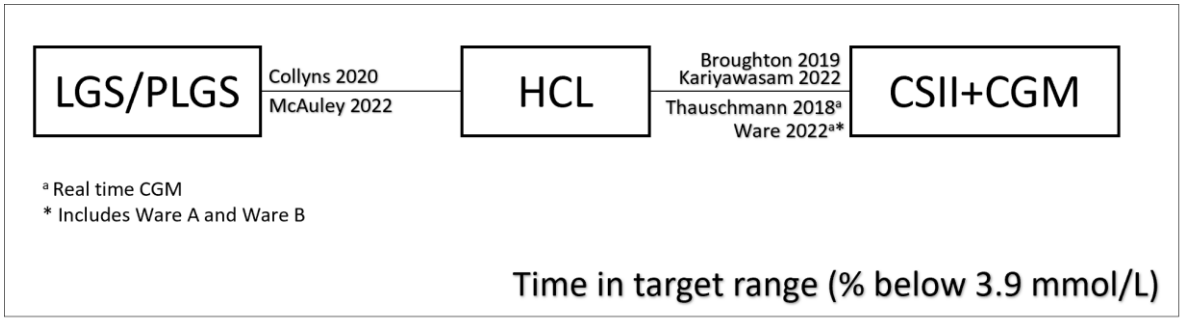
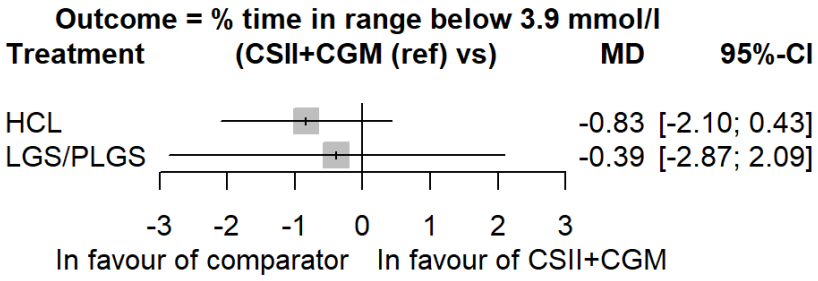


Figure 13. Results of the NMA of the outcome Time in target range (% below 3.9 mmol/l)



4.2.10 Observational studies (studies with no intervention other than HCL and or AHCL)

Nine observational studies are presented in Table 4 and provided outcomes indicating glycaemic performance in T1DM patients using HCL or AHCL (advanced HCL) systems. Two are NHS pilot studies, which are described in reports provided to the EAG (NICE, 17 June 2022) and seven are reported in published articles.[27, 60-65]

Table 4. Main characteristics of populations recruited in observational studies

Study	Population at recruitment / randomisation	Age description	N
NHS Pilot study adults. HCL (Report provided to EAG by NICE, 17 June 2022)	NHS services adults with Type 1 diabetes managed with an insulin pump and flash glucose monitor with an HbA1c ≥ 8.5% ; Age > 18 yr.	Adult median 40 (IQR: 28, 50).	640 (63 Lost to Fup)
Forlenza 2022 HCL [65]	Diag: ≥ 0.25 yr; Pump ≥ 3 months; HbA1c < 10%; total insulin ≥ 8 U/day; no severe hypo in last 3 months.	children; 2 to <7yr	46
Beato-Vibora 2021a "group 4" HCL (MM670G) [61]	T1DM for 29yr (±9·4) Preg: women excluded. Cross sectional study	Adult 38yr (±11)	43
Bassi 2022; 2 AHCLs (A=MM780G; B= Control-IQ) [60]	Diag: ≥ 1yr ; previous CSII or MDI; use of CGM : ≥ one-months' before and after starting the AHCL. Drop outs from AHCL before one month of use were excluded.	24.4 yr (±15.7)	A 51 B 39
Beato-Vibora 2021b AHCL MM780G [62]	HbA1c % 7.23 (± 0.86); Preg: women excluded	Adult 43 yr (±12)	52
Breton 2021 AHCLAHCL slim X2 pump with Control-IQ [63]	Users of the AHCL US in "Tandem's Customer Relations Management database"	Range 6 to 91 yr	7801
Carlson 2022 AHCL MM [64]	Diag: ≥ 2 yr ; T1D for, at least, 2 years. Minimum daily insulin ≥ 8 U; HbA1c % < 10 ; willingness to use device. Excluded if history of severe hypos , diabetic ketosis.	Adolescents and adults. 38.3 yr (±17.6)	157
Bergenstal 2021; HCL MM 670G; AHCL as but with updated software. X over study [27]	Diag: ≥ 1 year; Age 14 to 29 yr ; HbA1c 7·0% to 11·0% ; Excluded if ≥ 1 severe hypo.	14 to 29 yr	112
NHS Pilot study CYP HCL (Report provided to EAG by NICE, 17 June 2022)	Children or young people age 1 to <19 yr; TID for ≥ 1 yr; minimum of 2 prior HbA1c measures;	6.6 (±3.7) range 2 to 18.9 yr	251

Most observational studies employed similar inclusion criteria to those used in the RCTs. The NHS Pilot adult (described in section 4.3.1.1) and CYP (described in section 4.3.1.2) pilot studies were less narrow in recruitment than these and included adult participants that had poorer glycaemic control in terms of HbA11c and hyperglycaemia (% time above 10 mmol/L (reported separately for ranges 1 to 14 mmol/L and above 10 mmol/L) at baseline than the other observational studies.

The number of participants across these studies was greater than seen across the RCTs even when excluding the large survey study of Breton et al.[63] The adult pilot study accumulated >200 person years of HCL observation (more than twice that in RCTs) and the CYP pilot more than approximately 100 person years (the CYP pilot report was not clear about numbers of participants with missing data).

Outcome results reported in observational studies are summarised below in Table 5 and presented graphically in forest plots in which the change from baseline is compared with that seen in the HCL arm of the RCTs.

Table 5. Outcome results reported in observational (single arm) studies

NHS Pilot adult: HCL; median age 40 yr (29,50); N =540 FUP, 640 start (no FUP 63);Tx 6 months; 57 users discontinued use temporarily or permanently.

	HbA1c%	*% > 14 mmol/L*	*% TIR -10.0 mmol/L*	*% TIR <3.9 mmol/L [70mg/dl]*	*% TIR <3.0 nol/L [54mg/dl]*	*N hypo severe*	*DKA Event*
Inter Base	9.4 (0.8) N 456	37 N 428	34.2 N 440	2.1	0.36 N 419	0.05/PY	NR
Inter end	7.9 (0.8)	15.2	62.7	1.6	0.34	0.08 /PY	NR
DIFF (95% CI)	*-1.59 (-1.44,-1.74) P <0.0001*	*-22.2 (-20.4,-224.0) P <0.0001*	*28.5 (25.6,31.5) P <0.0001*	-0.5 (NR) P < 0.001	*-0.02 (-0.1,0.2) P 0.794*	*P 0.380*	*1 DKA-associated death*

NHS Pilot CYP: HCL; age 1 to 18 yr; N =251 ; Tx 6 months (3 month results also reported);

	HbA1c%	*% > 14 mmol/L*	*% TIR -10.0 mmol/L*	*% TIR <3.9 mmol/L [70mg/dl]*	*% TIR <3.0 mol/L [54mg/dl]*	*N hypo severe*	*DKA Event*
Inter Base	7.9	NR	48.7 (±15.3)	3.6 (±3.8)	NR	NR	NR

Inter end	7.21	NR	63.0 (±12.4)	2.4 (±2.2)	NR	NR	NR
DIFF (95% CI)	*-0.70 (-2.15, -0.15) P <0.001*	*NR*	*14.3 (15.9,12.4) P <0.001*	*-1.2 (-0.1.74,-0.82) P <0.001*	*NR*	*NR*	*NR*

Forlenza 2022 : [65] MiniMed™ 670G 2-6 yr ; N = 46 ; Tx 3 months

	% > 10 mmol/L	*% 3.9 to 10m mmol/L*	*% TIR < 3.9mmol/L*	*% TIR <3.0 mmol/L [54mg/dl]*	*% TIR <2.8 ol/L [50mg/dl]*	*N hypo severe*
Inter Base	41.0 (14.7)	55.7 (13.4)	3.3 (2.5)	0.7 (0.8)	0.5 (0.5)	10 during run in 0.824/100 user days
Inter end	33.0 (9.90	63.8 (9.4)	3.2 (1.6)	0.7 (0.6)	0.5 (0.4)	39 during HCL 0.841/100 user days
DIFF	*-8.0 P <0.001*	*8.1 P <0.001*	*-0.1 P 0.996*	*0 P 0.679*	*0 P 0.447*	*29 0.017/100 user days*

Beato Vibora 2021 [61] "Cross sectional study" ; HCL system MiniMed 670G with Guardian Sensor Group 4, N = 43 ; Age 38 yr((± 11) ; Tx unclear

	HbA1c% *mean sd*	*> 10 mmol/L* *mean sd*	*TIR 3.9-10.0 mmol/L* *mean sd*	*% TIR <3.9 mmol/ [70mg/dl]* *mean sd*	*% TIR<3.0 mmol/L [54mg/dl]* *mean sd*
Inter Base	NR	NR	NR	NR	NR
Inter end	7.0 (0.42)	27 (9)	71 (10)	1.9 (1.6)	0.5 (0.6)
DIFF	*NR*	*NR*	*NR*	*NR*	*NR*

Bassi 2022. [60] 2 AHCL systems: Minimed 780G and Control IQ; N= 51 & N = 39 ; age 24.4 (±15.7) ; Tx 1 month; Retrospective, propensity matching.

	> 10 mmol/L	*% TIR 3.9-10. mmol/L*	*% TIR <3.9 mmol/L [70mg/dl]*	*% TIR<3.0 mmol/L [54mg/dl]*
Mean DIFF (95%CI)	-5.7 (-7.8, -3.5)	14.6 (11.4,17.9)	-0.2 (-0.6,0.2)	-0.2 (-0.4,0.0)
Mean DIFF 780G	*-7.3 (-10.6,-4.1)*	19.1 (14.3,23.9)	*0.37 (-0.21,0.94)*	*-0.08 (-.28,0.12)*
Mean DIFF Control IQ	*-3.8 (-6.7,-1.0)*	*9.8 (5.9,13.7)*	*-0.68 (-1.23,-0.12)*	*-0.27 (-0.63,0.09)*

Beato vibora 2021 [62] AHCL system: prospective study. Medtronic 780G Advanced Hybrid Closed-Loop N = 52 ; age 43 (±12) yr ; Tx 3 months

	HbA1c% *mean sd*	*%* *> 10 mmol/L*	*% TIR* *3.9-10.0 mmol/L* *mean sd*	*% TIR <3.9* *mmol/L* *[70mg/dl]* *mean sD*	*% TIR<3.0* *mmol/L* *[54mg/dl]* *mean sd*	*Hypo* *Alarms* *per day* *mean sd*	*N hypo* *Severe* **mean sd*	*DKA* *nt *mean sd*

Inter Base	7.23 (0.86)	29.4 (15.1)	67.3 (13.6)	3.4 (3.4)	0.9 (1.2)		NR	NR
Inter end	6.67 (0.61)	16.8 (8.4)	80.1 (7.5)	3.1 (2.5)	0.7 (0.9)	3.5 (3.0)	0	0
DIFF	*P <0.001*	*P <0.001*	*P<0.001*	*P 0.562*	*P 0.127*	NR	NR	NR

Breton 2021 [63] AHCL: slim X2 in pump with Control-IQ; 4% Type 2DM ; Tx 1 year (retrospective survey) ; results based on N = 7801 T1DM

	> 10 mmol/L Median IQR	*% TIR 3.9-10.0 mmol/L Median IQR*	*% TIR<3.0 mmol/L [54mg/dl] Median IQR*
Inter Base	25.2 (18.2,31.0)	63.2 (49.8,75.1)	0.01 (0.00,0.35)
Inter end	19.7 (14.3, 24.2)	73.5 (64.4,81.6)	0.02 (0.00,0.4)
DIFF (95% CI)	*P <0.001*	*P <0.001*	*P <0.001*

Time in range 3.9 to 10 mM improved; time in hyperglycaemic improved, less hyperglcaemia; hypoglycaemic time worsened, more time hypoglycaemic but events were rare authors state "*Although there was a statistically significant increase (due to the very large sample size) in time". %* TIR > 10 mM was actually % TIR 10 mM to 14 mM ; % time >250 : base 8.3 (3.1,16.9) , 12 months 4.7 (2.0,9.6) *i.e. better(less hyper) at 12 months.*

Carlson : [64] MiniMed AHCL ; N = 157 ; age 14-21yr ; (N 39) , Tx 3 months

	% > 10 mmol/L	*% TIR 9-10.0 mmol/L mean sd*	*% TIR <3.9 mmol/L [70mg/dl]*	*% TIR<3.0 mmol/L [54mg/dl]*	*% TIR <2.8 mmol/L [50mg/dl]*	*N hypo non-severe*	*N hypo severe*	*DKA Event*

			mean sd	*mean sd*	*mean sd*			
Adults 22-75 yr (N 118)								
Inter Base	25.7 (10.2)	70.9 (9.8)	3.4 (3.0)	0.8 (1.1)	0.5 (0.7)	0	0	0
Inter end	22.6 (7.5)	75.1 (7.3)	2.3 (1.7)	0.5 (0.6)	0.3 (0.4)	0	0	0
DIFF(95% CI)	*-3.1 P<0.001*	*4.2 P<0.001*	*-1.1 P<0.001*	*-0.3 P 0.005*	*-0.2 P 0.006*	*0*	*0*	*0*
Adolescents14-21yr (N 39)								
Inter Base	34.3 (10.7)	62.4 (9.9)	3.3 (2.7)	0.9 (1.0)	0.6 (0.7)	0	1 *not device related*	*0*
Inter end	24.9 (5.7)	72.7 (5.6)	2.4 (1.8)	0.6 (0.6)	0.4 (0.5)	0		*0*
DIFF (95% CI)	*-9.6 P <0.001*	*10.4 P <0.001*	*-0.9 P 0.021*	*-0.3 P 0.106*	*-0.2 P 0.252*	0		*0*

Bergenstal 2021 [27] MiniMed 670G + previous software (HCL) and + updated software (AHCL).N 112; TX 12 weeks X-over (no washout);

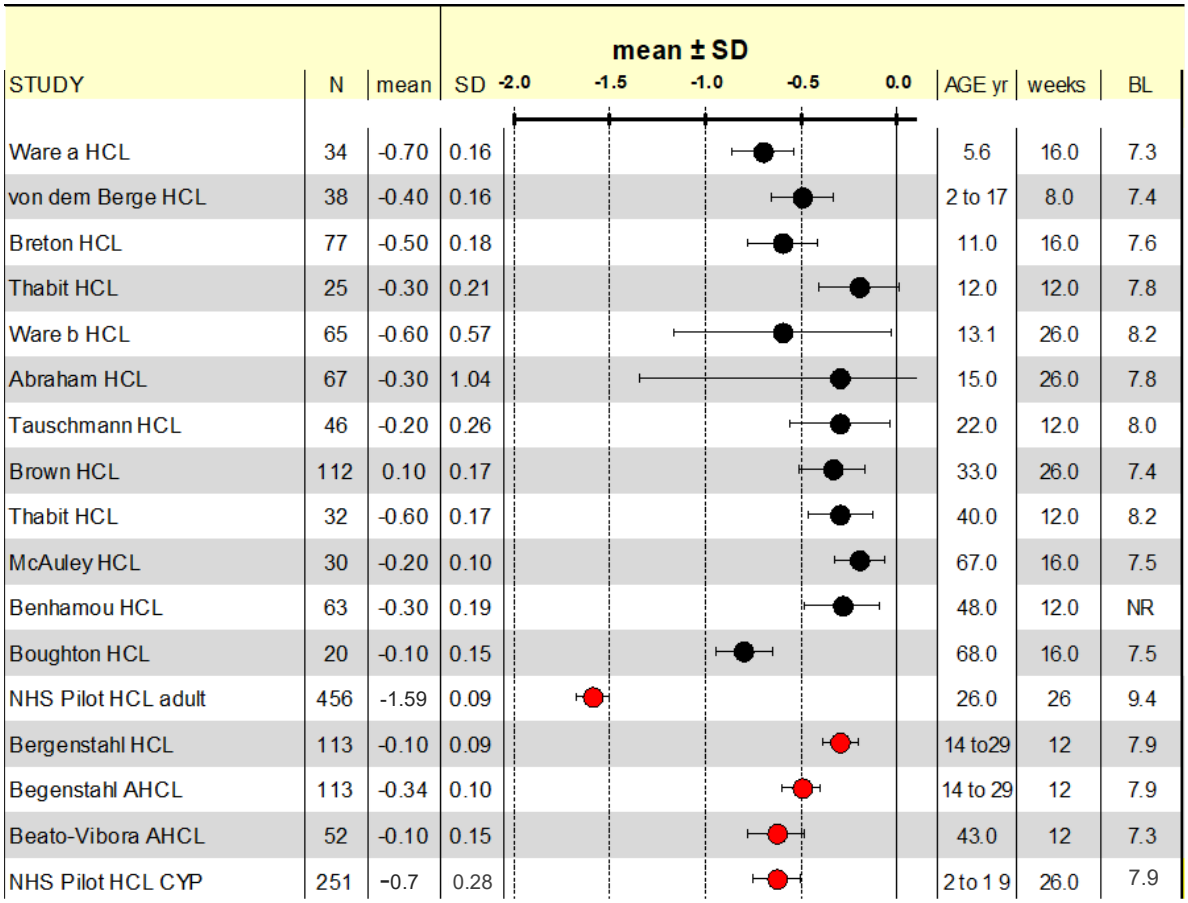
Co-primary outcomes	*Daytime > 10mmol/L [180mg/L]* *mean sd*		*All day % TIR<3.0 mmol/L [54mg/dl]* *mean sd*	
	HCL	AHCL	HCL	AHCL
Inter Base	42 (13)	42 (13)	0.46 (0.42)	0.46 (0.42)
Inter end	37 (9)	34 (9)	0.50 (0.35)	0.46 (0.33)

DIFF (95% CI) calc	-5	-8	0.4	0.0

Secondary Outcomes (all day)	*HbA1c %*		*% TIR >10.0 mmol/L mean sd*		*% TIR 3.9-10.0 mmol/L mean sd*		*% TIR<3.9 mmol/L [70mg/dl] mean sd*		*N hypo severe*	*DKA Event*
	HCL	AHCL	HCL	AHCL	HCL	AHCL	HCL	AHCL	HCL || AHCL	HCL || AHCL
Inter Base	7.9 (0.7)	7.9 (0.7)	41 (13)	41 (13)	57 (12)	57 (12)	2.3 (1.8)	2.3 (1.8)		
Inter end	7.6 (0.6)	7.4 (0.8)	34 (8)	31 8	63 (8)	67 (8)	2.1 (1.4)	2.1 (1.2)	0 || 1	0 || 0
DIFF (95% CI) calc	-0.3 (-0.13,-0.47)	-0.5 (-0.3,-0.7)	-7 (-9.8, -4.2,)	-10 (-12.8,-7.2)	6 (4.0,8.0)	10 (8.0,12.0)	-0.2 (-0.62, 0.22)	-0.2 (-0.60,0.2)	0 || 1	0 || 0

Figure 14 shows the change from baseline in HbA1c % experienced by HCL recipients reported in identified RCTs and observational studies. The range of change is narrow across RCTs and single arm trials (i.e. no intervention other than HCL and or AHCL). The improvement in HbA1c % level was much greater in the NHS Pilot study; the baseline level was considerably above than in all other studies so that there was a greater scope for improvement. In the NHS Pilot with children and young people (CYP) baseline HbA1c was lower (~7.8%) and benefit more modest (-0.7%).

Figure 14. Change in HbA1c % from baseline in study participants receiving HCL intervention

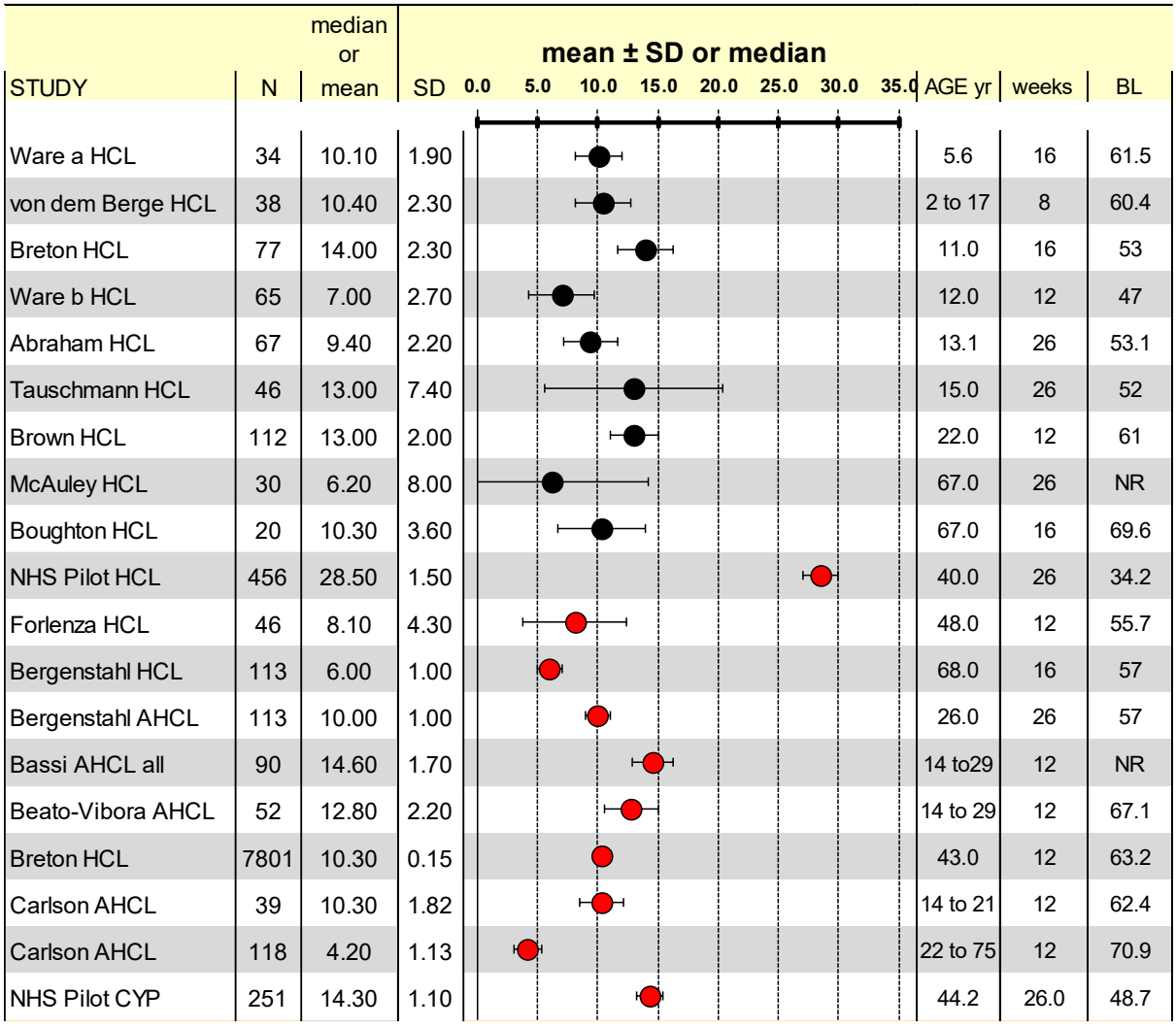


STUDY	N	mean	SD	AGE yr	weeks	BL
Ware a HCL	34	-0.70	0.16	5.6	16.0	7.3
von dem Berge HCL	38	-0.40	0.16	2 to 17	8.0	7.4
Breton HCL	77	-0.50	0.18	11.0	16.0	7.6
Thabit HCL	25	-0.30	0.21	12.0	12.0	7.8
Ware b HCL	65	-0.60	0.57	13.1	26.0	8.2
Abraham HCL	67	-0.30	1.04	15.0	26.0	7.8
Tauschmann HCL	46	-0.20	0.26	22.0	12.0	8.0
Brown HCL	112	0.10	0.17	33.0	26.0	7.4
Thabit HCL	32	-0.60	0.17	40.0	12.0	8.2
McAuley HCL	30	-0.20	0.10	67.0	16.0	7.5
Benhamou HCL	63	-0.30	0.19	48.0	12.0	NR
Boughton HCL	20	-0.10	0.15	68.0	16.0	7.5
NHS Pilot HCL adult	456	-1.59	0.09	26.0	26	9.4
Bergenstahl HCL	113	-0.10	0.09	14 to29	12	7.9
Begenstahl AHCL	113	-0.34	0.10	14 to 29	12	7.9
Beato-Vibora AHCL	52	-0.10	0.15	43.0	12	7.3
NHS Pilot HCL CYP	251	-0.7	0.28	2 to 1 9	26.0	7.9

Figure 15 shows a forest plot for % time in range (between 3.9 and 10 mmol/L). At baseline in most studies time in range was above 50%. In the NHS Pilot adult study baseline time in range was 34.2%; this likely reflects the broad inclusion of patients and indicates along with HbA1c baseline that these patients have poor glycaemic control prior to receiving HCL intervention. Similarly in the NHS CYP Pilot baseline control was poor (48.7%). In the adult NHS Pilot benefit from HCL was larger than in the other studies; the mean value at end of

follow-up was 62.7 % time in range; this compares fairly closely with values in other observational studies of 63.8% (Forlenza), 71% (Beato-Vibora cross sectional study), 80 % (Beato-Vibora prospective study) 63% and 67% (Bergenstahl (HCL and AHCL respectively). Similarly in the CYP Pilot the end of study TIR near that in other studies at 63%.

Figure 15. Change from baseline of %time in range (3.9 to 10 mmol/L)



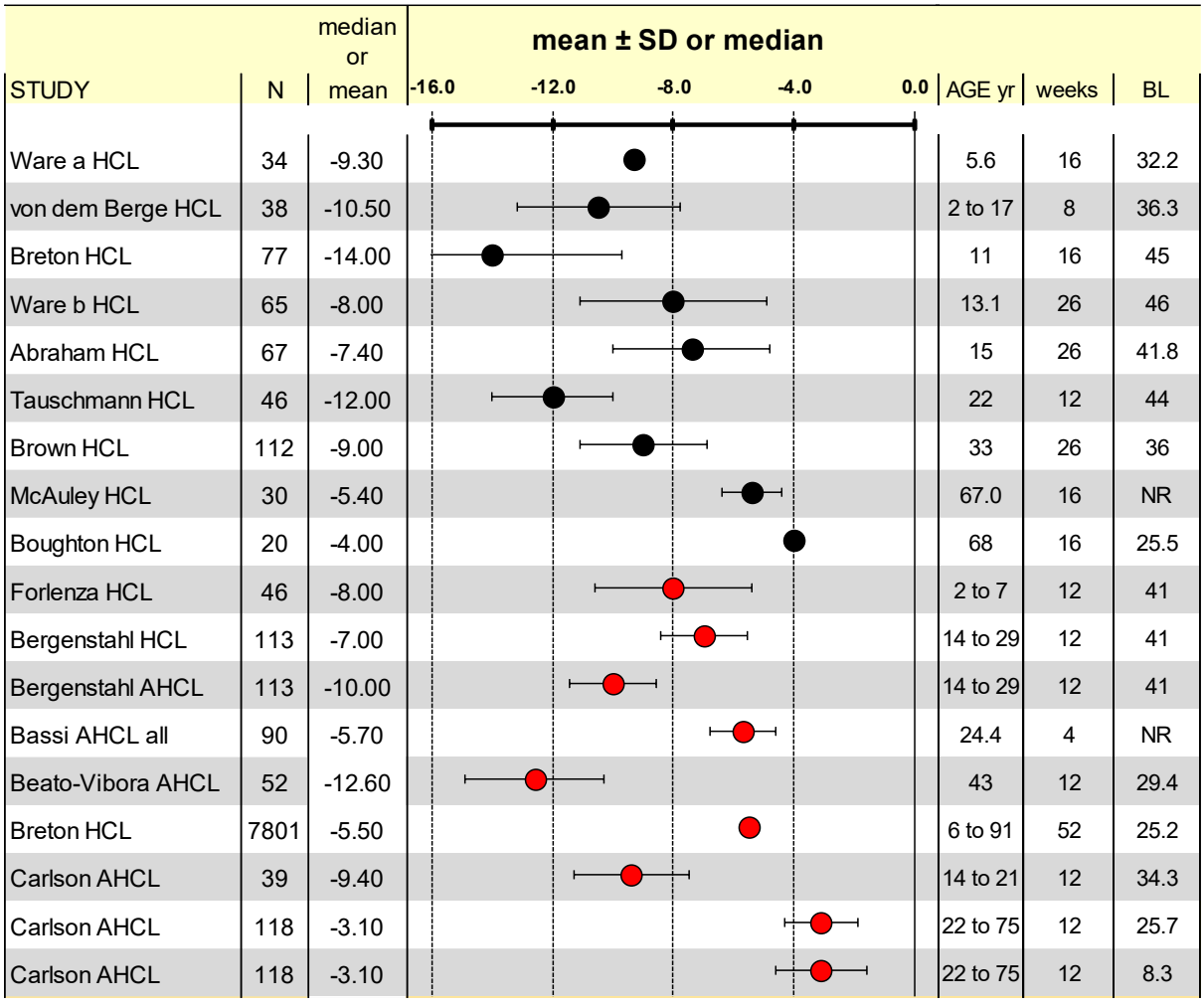
STUDY	N	median or mean	SD	AGE yr	weeks	BL
Ware a HCL	34	10.10	1.90	5.6	16	61.5
von dem Berge HCL	38	10.40	2.30	2 to 17	8	60.4
Breton HCL	77	14.00	2.30	11.0	16	53
Ware b HCL	65	7.00	2.70	12.0	12	47
Abraham HCL	67	9.40	2.20	13.1	26	53.1
Tauschmann HCL	46	13.00	7.40	15.0	26	52
Brown HCL	112	13.00	2.00	22.0	12	61
McAuley HCL	30	6.20	8.00	67.0	26	NR
Boughton HCL	20	10.30	3.60	67.0	16	69.6
NHS Pilot HCL	456	28.50	1.50	40.0	26	34.2
Forlenza HCL	46	8.10	4.30	48.0	12	55.7
Bergenstahl HCL	113	6.00	1.00	68.0	16	57
Bergenstahl AHCL	113	10.00	1.00	26.0	26	57
Bassi AHCL all	90	14.60	1.70	14 to29	12	NR
Beato-Vibora AHCL	52	12.80	2.20	14 to 29	12	67.1
Breton HCL	7801	10.30	0.15	43.0	12	63.2
Carlson AHCL	39	10.30	1.82	14 to 21	12	62.4
Carlson AHCL	118	4.20	1.13	22 to 75	12	70.9
NHS Pilot CYP	251	14.30	1.10	44.2	26.0	48.7

Median values have no error bars. RCTs shown include Abraham 2021[67] Brown 2019[68] Breton 2020 [69] details of these studies available in 9.4.

Figure 16 shows a forest plot of the change from baseline in the % time in the hyperglycaemic range of > 10 mmol/L. All studies reported an improvement from baseline; improvement ranged from (3.0% to 14 % reduction in % time in hyperglycaemic range). The NHS Pilot study did not report this outcome but did report unadjusted (uncorrected) % time

in range >14 mmol/L. At baseline the % time above 14 mmol/L was 37.4% and a further 26.6% of time was in the range between 10 and 14 mmol/L, indicating that at baseline the NHS Pilot study patients had a large % of time in hyperglycaemic state (~64% of time). Transfer to HCL resulted in large reduction of 22.6 % time above the 14 mmol/L range. The benefit of HCL in the range 10 to 14 mmol/L was more modest (a reduction in % time in range of 4%); thus these results suggest that HCL improved hypoglycaemia considerably in the upper range but that a substantial proportion remained slightly above the 10 mmol/L cut off.

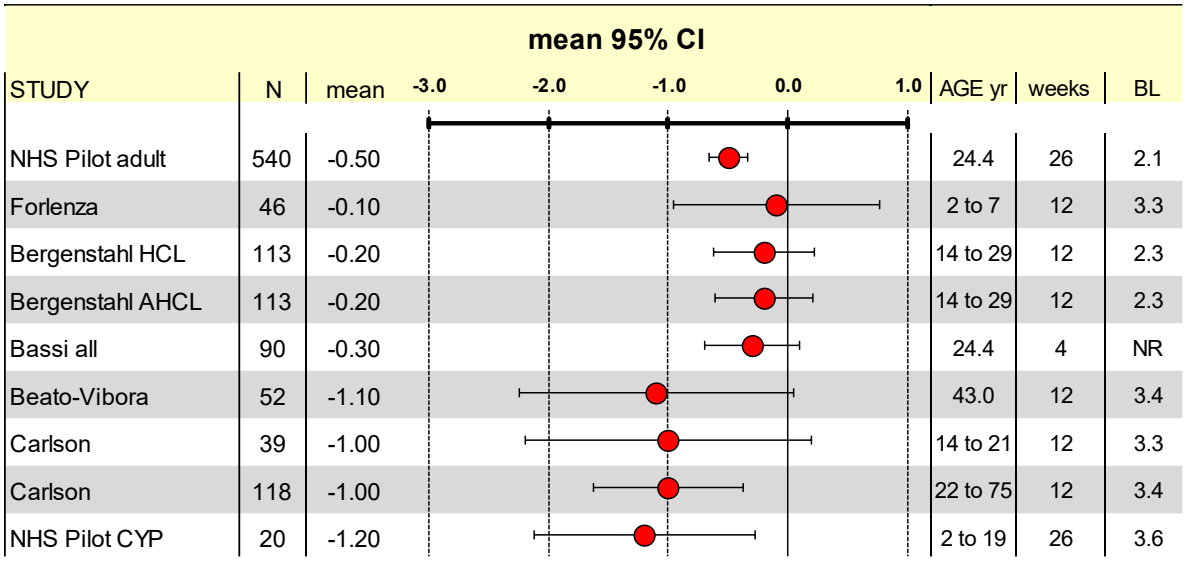
Figure 16. Change from baseline of %time in hyperglycaemic range (>10 mmol/L)



STUDY	N	median or mean	AGE yr	weeks	BL
Ware a HCL	34	-9.30	5.6	16	32.2
von dem Berge HCL	38	-10.50	2 to 17	8	36.3
Breton HCL	77	-14.00	11	16	45
Ware b HCL	65	-8.00	13.1	26	46
Abraham HCL	67	-7.40	15	26	41.8
Tauschmann HCL	46	-12.00	22	12	44
Brown HCL	112	-9.00	33	26	36
McAuley HCL	30	-5.40	67.0	16	NR
Boughton HCL	20	-4.00	68	16	25.5
Forlenza HCL	46	-8.00	2 to 7	12	41
Bergenstahl HCL	113	-7.00	14 to 29	12	41
Bergenstahl AHCL	113	-10.00	14 to 29	12	41
Bassi AHCL all	90	-5.70	24.4	4	NR
Beato-Vibora AHCL	52	-12.60	43	12	29.4
Breton HCL	7801	-5.50	6 to 91	52	25.2
Carlson AHCL	39	-9.40	14 to 21	12	34.3
Carlson AHCL	118	-3.10	22 to 75	12	25.7
Carlson AHCL	118	-3.10	22 to 75	12	8.3

Median values have no error bars.

Figure 17. Mean (95% CI) change from baseline in % time in range < 3.9 mmol/L



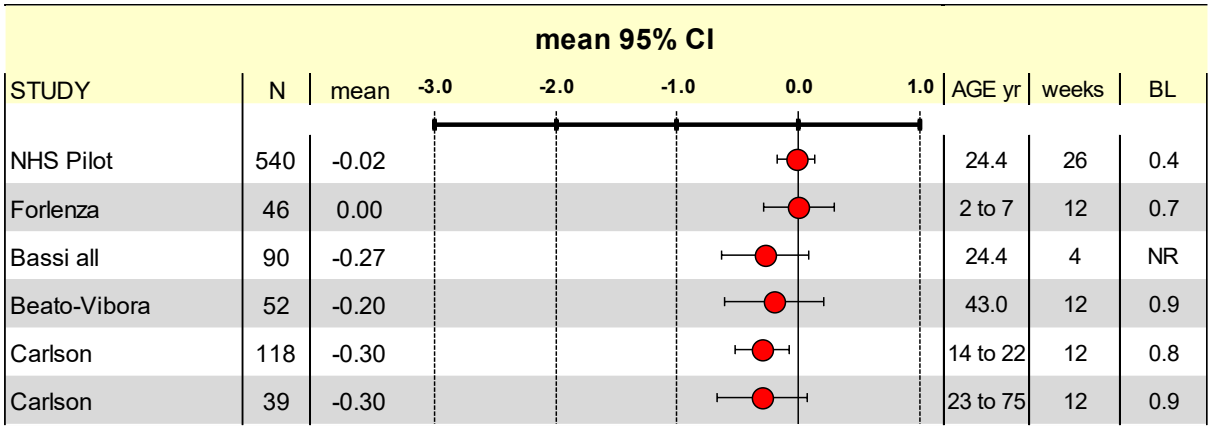
The change in % time in hypoglycaemic ranges (< 3.9 mmol/L and < 3.0 mmol/L) was reported in most observational studies.

Figure 17 shows the mean (95% CI) change from baseline in % time below 3.9 mmol/L; confidence intervals were wide. Both % time below 3.9 mmol/L at baseline (range 2.1% in the NHS Pilot adult study to 3.4%) and after HCL intervention were small, so that the resulting mean improvement was ~ -1% or less with CIs mostly crossing the null. The NHS Pilot adult study reported a change of -0.5% and an associated P value of <0.001. The CYP Pilot also reported a statistically significant improvement. Only in one other study (Carlson, adult patients) was the change statistically significant at P <0.05.

Several single arm studies reported other outcomes indicative of hypoglycaemic status, most commonly % time in range < 3.0 mmol/L. The results are shown in

Figure 18.

Figure 18. Mean (95% CI) change from baseline in % time in range < 3.0 mmol/L



Changes from baseline were < 1% and with one exception did not reach statistical significance. The large survey study by Breton et al., (T1DM N = 7801) reported medians and IQR of: before HCL 0.01 (IQR (0.00 to 0.35) and after 0.02 (IQR 0.00 to 0.400) with a resulting P value of <0.001. These authors considered this small worsening in hypoglycaemia during HCL likely to be clinically meaningless.

4.2.11 Summary of observational studies

The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range (3.9 to 10 mmol/L), and % time above range >10 mmol/L all improved on transfer to HCL (or to an AHCL) without any strong evidence that hypoglycaemia became more of a problem; however changes in hypoglycaemia were mostly underpowered in these studies; in the largest studies (NHS Pilot audit study in adults and very large survey study by Breton et al.,) there was no persuasive indication of deterioration in hypoglycaemic states.

The NHS Pilot adult audit study differed somewhat from most other studies in that it included a broader spectrum of patients. That these patients had a poor record of glycaemic control at baseline that was indicated by high HbA1c% and low % time in range (3.9 to 10 mmol/L) measures; at baseline the proportion hyperglycaemic participants was high as indicated by the % time > 10 mmol/L. Transfer to HCL resulted in larger improvements than observed in other studies likely partly due to the poorer starting status that would allow for greater scope for improvement. In the NHS Pilot study, the post HCL levels of measures of glycaemic control approached those seen for HCL groups in other studies (both RCT and single arm studies). The NHS Pilot studies in adults and in CYP may have enrolled patients atypical of the generality of UK T1DM population; however it is unlikely all UK T1DM patients need to transfer to better control systems because many may be achieving good control with their current practice; it appears likely that by recruiting patients with poor control the outcomes reported in the Pilot studies may reflect the sort of improvements in glycaemic control that may be close to a group that would require access to better systems. The discontinuation rate in the use of HCL (temporary or permanent) in the adult Pilot study was about 10%; there was no distinction made between permanent and temporary. Whether discontinuation would increase with time is unknown but from a CE perspective permanent discontinuation represents a wastage of device(s). Discontinuations were reported in some RCTs; in most cases in RCTs the observation time on treatment to short and numbers of participants too small to get a meaningful idea of discontinuation rates in thee studies.

4.2.12 Assumptions

Publication bias was visually assessed using a funnel plot and statistically assessed using Egger's test for each of the outcomes. All four funnel plots were symmetric, suggesting a lack of publication bias, as well as the p-values of Egger's test, all of which were $p>0.05$. Consistency and inconsistency were measured using node-splitting, which compares the Direct and indirect estimates of the network. Loop-consistency was not measured as the Networks for each outcome had no closed loops. Node-splitting concluded that there were no Issues with consistency in the models.

4.2.13 Subgroup and sensitivity analyses

Results of the subgroup and sensitivity analyses (as specified in the protocol) are presented in Table 6.

A subgroup analysis was performed where studies were categorised based on mean or median age of participants at baseline. Mean or median age less than 18 years were classified as "Children and young adults", and studies with mean age greater than or equal to 18 years were classed as "Adults").

<u>The following sensitivity analyses were performed:</u>

Removing the Stewart 2018 study which was done on pregnant women only from the analysis.

Removing the Benhamou 2019 study from the analysis as it was identified as a potential outlier for the outcome "% time in range 3.9 – 10.0 mmol/L" as the difference in arms was around 31, but larger than the remaining studies.

Compared to the overall results, there were no statistically significant changes to the results when removing pregnant participants (excluding Stewart 2018), or when removing the outlying study (Benhamou 2019).

When splitting the study estimates into adults (18+ years) and under 18's. There were no statistically significant subgroups when compared to the overall NMA results. When comparing the subgroups separately, for the outcome TIR % between 3.9-10 mmol/L, HCL was significantly statistically worse compared to CSII+CGM (MD = -2.76, 95% CI = -5.33 to

-0.19) in the under 18's, but not statistically significant in the 18+ group.

Table 6. Results of the subgroup and sensitivity analyses compared to the overall NMA results

	HbA1c %	%TIR 3.9-10	%TIR > 10	%TIR < 3.9	%TIR < 3.0
Overall results					
HCL	-0.28 (-0.34, -0.21)	8.66 (7.33, 9.99)	-7.20 (-8.89, -5.51)	-0.83 (-2.10, 0.43)	-0.14 (-0.40, 0.12)
LGS/PLGS	-0.06 (-0.22, 0.09)	0.44 (-2.36, 3.24)	2.25 (-2.40, 6.90)	-0.39 (-2.87, 2.09)	-0.16 (-0.56, 0.24)
Excluding Stewart 2018 (pregnant participants)					
HCL	NA	8.90 (7.63, 10.17)	-7.81 (-9.33, -6.30)	NA	NA
LGS/PLGS	NA	0.73 (-1.89, 3.34)	1.76 (-2.38, 5.91)	NA	NA
Excluding Benhamou 2019 (outlying study)					
HCL	-0.29 (-0.36, -0.22)	8.58 (7.09, 10.07)	-7.24 (-9.12, -5.36)	-1.04 (-2.71, 0.63)	-0.21 (-0.60, 0.18)
LGS/PLGS	-0.08 (-0.23, 0.80)	0.33 (-2.66, 3.32)	2.17 (-2.70, 7.04)	-0.60 (-3.55, 2.36)	-0.23 (-0.76, 0.31)
Adults (18+)					
HCL	-0.24 (-0.32, -0.15)	9.28 (7.44, 11.13)	-7.28 (-10.06, -4.51)	-0.37 (-0.95, 0.21)	0.00 (-0.10, 0.10)
LGS/PLGS	-0.01 (-0.24, 0.21)	2.85 (-0.88, 6.58)	-0.27 (-9.75, 9.22)	0.09 (-0.80, 0.99)	0.11 (-0.01, 0.23)
Under 18 years old					
HCL	-0.31 (-0.43, -0.20)	7.74 (6.87, 8.62)	-6.97 (-9.31, -4.63)	-1.10 (-3.43, 1.22)	-0.21 (-0.66, 0.24)
LGS/PLGS	-0.11 (-0.36, 0.13)	-2.76 (-5.33, -0.19)	3.33 (-1.95, 8.61)	NR	-0.41 (-1.20, 0.38)

4.2.14 Additional outcomes

4.2.14.1 Adverse events

Studies did not consistently report additional outcomes (see section 9.3 for list of additional outcomes reported in RCTs). In the Benhamou trial, authors observed one severe hypoglycaemia and one ketoacidosis occurring in two different patients during the extension phase. The ketoacidosis occurred while the patient was under closed loop (CL) and presented with an acute infection of the ear, whereas the severe hypoglycaemia occurred while the patient had temporarily switched to Open Loop treatment. In this study several device malfunctions were reported, including 21 events related to the pump (in seven patients), six events related to the sensor (four patients), and four events related to the handset (three patients).[47]

In the Ware study, seven severe hypoglycaemia events were reported in total (four in the closed loop group, three in the comparator group), two diabetic ketoacidosis events (both in the closed-loop group), and two non-treatment-related serious adverse events (broken ankle in the control group and hospital admission for gastroenteritis in the closed-loop group) occurred after randomisation. There were 23 reportable hyperglycaemia events (11 in the closed-loop group, 12 in the control group), which did not meet criteria for diabetic ketoacidosis. A total of 155 adverse events were reported (67 in the closed-loop group, 88 in the control group).[57]

Tauschmann's study reported one diabetic ketoacidosis presenting in the closed-loop group due to infusion set failure which was not related to the closed-loop therapy. There were two severe hypoglycemia in both groups. [53]

Thabit 2015 reported safety outcomes. In this study one episode of severe hypoglycaemia occurred in an adult participant during the intervention period when the closed-loop system was not in use because of loss of connectivity (low battery) and the participant was receiving insulin at the rate supplied by the study insulin pump. In the study involving children and adolescents, one adolescent participant had two severe hypoglycaemic episodes (seizures) during the intervention period; these episodes required third-party assistance but did not result in hospital admission. During the two episodes, the closed

loop system was not in use (the participant was using sensor-augmented pump therapy).[54] Seven adverse events were reported for seven (6%) of 112 participants during use of the 670G system and six events for six (5%) of 112 participants during use of the advanced hybrid closed-loop system (table 3). Severe hypoglycaemia occurred in one participant while using the advanced hybrid closed-loop system and none while using the 670G system. No cases of diabetic ketoacidosis were reported. Six cases of Hyperglycaemia was reported and that was in relation to infusion-set obstruction, and four cases were observed in the comparator group of adults. In children and adolescents, this was reported for two cases in the intervention group only. [27]

The FLAIR study reported two severe hypoglycemia events in the HCL. There were two hyperglycaemia events related to insulin pump issues (without diabetic ketoacidosis) in the HCL group.

The Boughton's study reported two events of severe hypoglycemia in SAP group. Four participants reported some adverse events in the HCL group and 7 participants in the SAP group.

The Kariyawasam's study reported a mean value of hypoglyceamic episodes 25.51 (5.42 SE) in the closed loop group and 48.19 (5.39 SE) in open loop group.

von dem Berge's study reported the median of Hypoglycaemic events (< 54 mg/dl), four in the intervention group and three in the comparison group.

Collyn's study reported five device related adverse events for each study arm.

Stewart study reported eight hypoglycemic events for the HCL group and 12.5 for the comparator (CGM+CSII) group.

Ware 2022 reported one serious adverse event of severe hypoglycemia that occurred during the

closed loop period.

Overall, the majority of the studies reported a low number of events for both trial groups. There was no clear difference between HCL vs comparator groups. Studies included a samll sample, were hetrogenious which limits a quantative synthesis.

4.2.14.2 Patient-Reported Outcomes and Perspectives

Tauschmann's study used the Pedatric Quality of Life Inventory (PedsQL) questionnaire which was administered to participants (participant version) and guardians of participants aged 17 years and younger (the parent proxy version) before and after the intervention period. The result showed –0·3 (95% CI: –4·1 to 3·4) a difference between groups regarding score of using PedsQL for assessing quality of life.

The FLAIR study, reported mean scores on the glucose monitoring satisfaction survey 2·76 points (SD 0·52) at screening, 2·65 points (0·63) at the end of the period using the HCL system, and 2·80 points (0·55) at the end of the period using the advanced HCL (p=0·0030 comparing HCL vs advanced HCL. The only two satisfaction subscales that changed and showed superiority of AHCL were emotional burden and behavioral burden[70]

Benhamou's study reported improved levels of satisfaction using the Diabetes Treatment Satisfaction Questionnaire score. The satisfaction improved significantly, with a DTSQ total score of 50.0 (Q1-Q3 48.5-53.5) at baseline in open loop, 65.0 (57-66.5) after the initial close loop period, and 60.0 (58.5-63) at the end of the extension period [47]

McAuley's recorded Hypoglycemia Fear Survey score. The total score was 7.5 (4–10) and 7.5 (5–10) for HCL and SAP therapy respectively. Difference between the two groups was not significant.

Wheeler's study compared technology satisfaction and sleep quality between AHCL vs. SAP + PLGM. overall treatment satisfaction was significantly higher for AHCL group compared to SAP+PLGM treated. There was no significant difference for anticipated worry of hypoglycaemia. Results showed no changes in the well-being index and hypoglycaemia fear/confidence were seen.

Several studies that used various tools and different survey approaches for technology satisfaction. Only one study (Benhamou), comparing an open loop to a closed loop system, found that user satisfaction had increased significantly. Other studies did not observe any significant changes.

4.2.1 Quantity and quality of research available

Of the 12 RCTs included in the analysis, 11 were quality assessed (the FLAIR RCT was considered as a single arm study therefore not presented in this section). Five were rated overall as having some concerns about their risk of bias, and three were rated overall as having a high risk of bias (von dem Berge, Collyns, Benhamou). Table 7 provides a visual summary of each domain. Risk of bias was noted for each domain as follows: high risk of bias was most common in relation to domain 2 (deviations from intended interventions). In this domain, 4/11 RCTs were deemed to be of low risk of bias (Tauschmann, Boughton, McAuley, Stewart); 5/11 had some concerns over risk of bias (Thabit, Ware, Kariyawasam, von dem Berge, Collyns), and 1/11 RCTs were deemed to be at high risk of bias in this domain (Benhamou).

In domain 1 (randomisation process), there were some concerns over risk of bias in 4/10 RCTs (Benhamou, Thabit, Kariyawasam, von dem Berge), either because there was no information available to answer the signalling questions for the domain (Benhamou, Thabit, von dem Berge); because of a lack of information on the randomisation process (Benhamou, Thabit, von dem Berge); issues with allocation concealment (Benhamou, Tauschmann, Thabit, Ware, Boughton, von dem Berge); or differences in the characteristics of participant groups at baseline (Bergenstal). The RCT by Collyns was deemed to be high risk of bias in relation to the randomisation process. The domains with the lowest risk of bias were in relation to missing outcome data (domain 3) and outcomes measurement (domain 4), where all 11 RCTs were considered to have low risk of bias for both domains.

In domain 5 (selection of the reported results), all but three RCTs were considered to have low risk of bias. Those that had some concerns over risk of bias were the studies by Benhamou, Boughton and von dem Berge).

Table 7. Risk of bias summary

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall

Benhamou (2021)	Some concern	High	Low	Low	Some concern	High
Tauschmann (2018)	Low	Low	Low	Low	Low	Low
Thabit (2015)	Some concern	Some concern	Low	Low	Low	Some concern
WareA (2022)	Low	Some concern	Low	Low	Low	Some concern
WareB (2022)	Low	Some concern	Low	Low	Low	Some concern
Boughton (2022)	Low	Low	Low	Low	Some concern	Some concern
Kariyawasam (2022)	Some concern	Some concern	Low	Low	Low	Some concern
McAuley (2022)	Low	Low	Low	Low	Low	Low
von dem Berge (2022)	Some concern	Some concern	Low	Low	Some concern	High
Stewart (2018)	Low	Low	Low	Low	Low	Low
Collyns (2021), Wheeler (2022)	High	Some concern	Low	Low	Low	High

4.3 External submissions

4.3.1 NHSE evidence

NHSE submitted two observational audit studies, the first audit was conducted in adults and the second in children and young people. The pilot studies were non-randomised studies with no control group with a before-after study design. The before-and-after design limits the scientific value of the evidence since there is a greater risk of bias due to lack of randomisation, lack of a true control, and selection bias

Additionally, the findings of the two pilots are interim results and potentially there do not give the full results.

4.3.1.1 NHS England Hybrid Closed Loop Pilot in Adults with Type 1 Diabetes

The study included adults with T1DM (n = 570 with complete follow-up data) from 31 diabetes centres across England that started HCL therapy. Inclusion criteria were use of an insulin pump and flash glucose monitoring and a HbA1c ≥69 mmol/mol. Routinely collected, anonymised data were submitted to a secure online tool. Outcomes included in the analysis were those with both baseline and follow-up data available. The primary outcome was HbA1c, other outcomes related to the scope included diabetes distress scores; and event rates (hospital admission, paramedic callouts and severe hypoglycaemia).

Participants had high HbA1c (9.4% or over; 78.9 mmol/mol). Participants in the pilot study had poorer glycaemic control in comparison to the National diabetes audit (Table 8).[71] The National Diabetes Audit shows that 16% of people with T1DM have an HbA1c over 86mmol/mol or 10%.[71] This indicates that the pilot study participants are within the 20% of poorest control population.

Table 8. Baseline characteristics of the Audit vs. the National Diabetes Audit [71]

Variable	Audit in Adults	National Diabetes Audit*
Age (years)	40**	43.4
Diabetes duration (years)	21	24.9
Gender (% male)	32.8**	42
Ethnicity (%)		
White	83.9	87.2
Asian	2.6	2.1
Black	1.2	0.9
Mixed	1.8	0.8
Other	0.7	1.0
Unknown	7.7	8.1
HbA1c (mmol/L)	78.8	63.5
HbA1c (%)	9.4	8.0
*On insulin pump; **median		

Mean HbA1c % declined from baseline to five months follow-up (mean change -1.5, 95% CI -1.4 to -1.6, $p < 0.0001$). Time below target range ≤3.9mmol/l showed some reductions with a mean change of -0.5, 95% CI 0.2 to 0.7 for 3-3.8 mmol/L %, and a mean change of -0.02, 95% CI -0.1 to 0.2. There are several points that require consideration:

1. Diabetes distress score measures were improved, however EQ-5D data measures were not collected. Therefore, utility measures are challenging to quantify.

2. The level and volume of patient education is not clearly defined. It is unclear if patients received structured education that may have improved glucose measures.
3. Patients enrolled in the study were on CSII therapy which is one of NICE criteria to switch to HCL. However, the length of pump therapy was not clear. NICE recommends the suspension of pump therapy when glycaemic improvements are not achieved.
4. Cost data were not provided.

4.3.1.2 NHS England Closed Loop Study in Children and Young People

The study recruited (*n* = 251) children and young people (under 19 years), with T1DM for at least a year and had two HbA1c measures prior to the start of HCL (baseline characteristics Table 9). Participants were recruited from eight centres across England. Participants with other medical conditions that have an impact on glucose measures and/or participants in other device evaluation trials were excluded. Outcomes (HbA1c, TIR, hypoglycaemia frequency) were assessed at baseline, three- and six-months follow up. The Hypoglycaemia Fear Survey was completed by participants aged 12 years or more and by parents of participants aged <12 years.

Table 9. Baseline characteristics of children and young people

Variable	Value
Age (years), mean (SD)	12.3 (3.5)
Diabetes duration (years), mean (SD)	6.6 (3.7)
Gender (% male)	58%
Ethnicity (%)	
White	89%
Asian	3%

Black	3%
Mixed	3%
Other	1%
HbA1c (mmol/L)	62.3 (12.1)
Time in range (%) 3.9-10mmol/L	48.7 (15.1)
Hypoglycaemia frequency (%)	3.6 (3.8)

At six months follow-up, HbA1c (mmol/L) was 7 mmol/L, 95% CI 5.8 to 8.2, $p < 0.001$. The improvement observed (0.6%) was slightly above the clinically meaningful change (0.5%). This was accompanied by improvements in time in range (mean difference -14.3, 95% CI -15.9 to -12.4, $p < 0.001$), and hypoglycaemia (mean difference -1.2, 95% CI 0.82 to 1.74, $p < 0.001$). There are several points that require consideration:

1. Pre-HCL treatments (such as pump and CGM) were not clearly described.
2. Extent of severe hypoglycaemia that may affect the Hypoglycaemia Fear Survey was not described.
3. Parental/carer EQ-5D data was not collected.
4. The level and volume of patient education was not clearly defined.
5. Cost data were not provided.

4.3.2 Medtronic submission clinical effectiveness

The Medtronic submission compared the (Advanced) Hybrid Closed Loop Systems with Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). They described a number of studies and edited extracts of their report are included in the box below:

1. Carlson et al.'s study [64] assessed safety and change in glycemia in adolescents and adults with type 1 diabetes (T1D) during the Medtronic Safety Evaluation of the Advanced Hybrid Closed Loop (AHCL) System. Both the run-in period and study phase involved use of the AHCL study device that included the MiniMed 670G insulin pump (version 4.0 algorithm) with CGM system (the Guardian™ Sensor [version 3] glucose sensor and Guardian Link [version 3] transmitter). This 3-month trial with a total 14,134 days of AHCL Auto Basal and Auto Correction use had no device-related SAEs and no serious or unanticipated device-related effects. There were no episodes of severe hypoglycemia or DKA during the Auto Basal and Auto Correction-enabled study phase. Glycemic outcomes of this study demonstrated reduced A1C and increased overall (24-h day) TIR in adolescents and adults using the AHCL system, when compared with a run-in period of SAP, PLGMs or automated basal insulin delivery use.

2.Da Silva et al. 2022,[72] in a report from 4120 users, analysed the safety and outcomes results of the MiniMed™ 780G system, which includes an advanced hybrid closed loop (AHCL) algorithm that provides both automated basal and correction bolus insulin delivery in real-world settings. An improvement was reported over standard of care based on the on-going trial (NCT03959423) which was confirmed by real world evidence: 80% of the first 4120 AHCL users have reached glycaemic targets, i.e., TIR >70% and a GMI <7.0%.

3. Vigereski et al. 2022 [73] analysed safety and effectiveness outcomes of individuals using the MiniMed™ 780G system with the no-calibration Guardian™ 4 sensor during the first three months of use. Data is based on the published poster. There is inadequate data on participant history.

4. The FLAIR study [27] compared the existing MiniMed 670G system with the new Medtronic advanced hybrid closed-loop system in adolescents and young adults with type 1 diabetes in a crossover trial at seven academic-based endocrinology practices (USA, and one each in Germany, Israel, and Slovenia). Both the MiniMed 670G and AHCL systems consisted of the same Medtronic 670G insulin pump and Guardian Sensor 3 continuous glucose monitor, with only the software differing between systems. The AHCL system was found to induce a greater reduction in hyperglycaemia during the day without an increase in hypoglycaemia than did the MiniMed 670G system. Time in the target glucose range increased from 57% to 67% with use of the advanced hybrid closed loop system compared with 57% to 63% with use of the 670G system.

5. For the comparison between AHCL to SAP 1 PLGM in a two-sequence crossover study in New Zealand, 59 participants (35 females), mean age 23.5 years, were recruited. AHCL improved %TIR 3.9–10.0 mmol/L (70–180 mg/dL) compared to SAP. There was one episode of mild diabetic ketoacidosis in the study, which occurred in the SAP 1 PLGM treatment period due to possible infusion set occlusion and a concurrent viral infection. There were no episodes of severe hypoglycaemia in the study.[49]

6. Petrovsky et al.'s study [74] described a structured initiation protocol of the MiniMed 670G HCL system in individuals with type 1 diabetes on MDI. This non-randomized single-centre study was conducted in

Doha, Qatar, and enrolled individuals aged 7–18 years with type 1 diabetes > 1 year, on MDI with SMBG, with or without RT-CGM or isCGM, with no prior pump experience, and with an HbA1c level < 12.5%. An improvement in TIR was observed after 3 days in Auto Mode, TIR continuously improved over time until reaching a plateau after 2 months. The authors reported that the improved clinical outcomes observed in the study were achieved in a safe manner, with no events of DKA, or severe hypoglycemia, and with no hospital admission, similar to the MiniMed 670G ~~pivotal~~ trials.

7. In an abstract Slover's et al [75] evaluated whether the MiniMed™ 780G AHCL system may be effective in adult individuals with T1D naive to CSII and CGM technologies. Report shows people with T1DM naive to CSII and CGM technologies who switched directly to AHCL improved their glycaemic control but there is no further information on participant history and intervention details.

4.3.2.1 Medtronic submission clinical effectiveness: EAG critique

The Carlson's study [64] was undertaken in the US context. The result on the extended study phase has not be published except in an abstract.

Da Silva's study reported data based on an ongoing trial of the MiniMed™ 780G AHCL system and it is the first report of outcomes.[72] There is a lack of demographic data, such as users' duration of diabetes and previous therapies. The results are limited by the follow-up duration of the cohort with a mean of 54 ± 32 days. There is some concern about reliability. The usability can only be inferred from the high percentage of time spent in AHCL and the low number of AHCL exits.

Medtronic suggest that there is consistent effectiveness of the MiniMed™ 780G system in current users (over 20,000 in June 2022), reporting improvements in performance, safety and usability compared to MiniMedTM 670G reducing the burden of people living with T1D. It seems these results are based on the same source as the ongoing trial. The source and history of participants is not clear.

Vigersky et al., 2022 reported safety and effectiveness outcomes following transition of participants to the MiniMedTM 780G system with the GuardianTM 4 sensor (NCT03959423).[73] The results relate to the US population. It is not clear whether they used the GuardianTM 4 System (GuardianTM 4 sensor plus GuardianTM 4 transmitter) or just the GuardianTM 4 sensor. The data is based on a poster presentation, and no more data was available about the patients.

The main issue with Arrieta et al., 2022 it is not clear whether patients with T1DM were on different previous treatments.[76] The only treatment information that was available is the percentage of MiniMedTM 780G system users, for two different age groups of people. Outcomes were analysed for three cohorts of users; cohort 1 (post-AHCL), cohort 2 (longitudinal), cohort 3 (pre- vs. post-AHCL). This study is related to several different countries' populations and results show differences with adults with T1DM in NHS England.

Choudhary et al., 2022 [77] is a retrospective analysis of CareLink™ (Medtronic, Northridge, California) data from people with Type 1 diabetes in the UK and was conducted to determine the real-world effectiveness of sensor-integrated pump therapy with the MiniMed Paradigm Veo or MiniMed 640G systems. Comparisons of SAP vs LGS, SAP vs PLGM, and LGS vs LGM was undertaken. There is not an HCL arm in this study. The initial analysis was based on treatment groups of different sizes and durations of treatment. The reasons for using SAP therapy without any suspension mode activated, and for switching to low glucose suspend, were not available. The analysis was purely descriptive, and no formal statistical comparison has been done.

The FLAIR study,[27] a randomized crossover trial conducted between June 3 and Aug 22, 2019, recruited 113 adolescents and young adults with type 1 diabetes. It was undertaken in the UK. The study period was only 3 months long; thus, it' is not possible to determine the sustainability of observed benefit over a longer period of time.

Collyn's et al.'s study [49] demonstrated a significant improvement in TIR, with no increase in hypoglycaemia for AHCL compared with SAP 1 PLGM during 4-week. The short study period limits the impact sustainability assessment. The age range of included participants is wide and no stratified data has been reported based on the age group.

Petrovski et al.'s study [74] assessed the use of a 10-day structured initiation protocol for MiniMed 670G HCL system in individuals with type 1 diabetes on MDI therapy. It was a single centre study with a small sample size for investigating clinical outcomes of using HCL for patients on MDI with SMBG, with or without RT-CGM or isCGM, with no prior pump experience.

Reported data in Farabi et al.'s study [78] was a systematic evaluation of the relationship between routine, unstructured physical activity, and glucose variations across wake and sleep periods for multiple days in young adults with T1DM in their natural home/work environment. This study is limited by the lack of a control group. The study did not have any exclusion criteria based on patients' history. There are also factors that can affect glucose levels such as structured physical exercise, which have not been considered in this study.

4.3.3 Dexcom submission clinical effectiveness

Dexcom compares HCL with SAP. This is based upon the results of one systematic review and network meta-analysis [79] and eight RCTs.[56, 57, 68, 69, 80-83] The review was based on 52 RCTs, including 3,975 participants, for T1D. Comparators were SAP (rt-CGM + CSII) and intermittently scanned glucose monitoring with CSII (FGM + CSII). The results of the NMA indicated that in terms of HbA1c reduction, there is no significant difference between CGM + CSII with a mean difference (MD) of −0.36 (95% CI: −0.90, 0.19). When simultaneously considering HbA1c and severe hypoglycaemia, integrated systems as well as MDI + CGM, appeared to provide the highest composite ranking in cluster analysis of surface under the cumulative ranking curve (SUCRA) values. Despite finding the most favourable results for HCL, it should be noted that the study authors recommended that "If only one technology is desired or practical, then CGM appears most favourable from composite ranking of A1c, hypoglycaemia, and QoL".[79]

All of the eligible trials included SAP as the main comparator; there were no studies that compared HCL with FGM + CSII. They described a number of studies and edited extracts of their report are included in the box below:

The iDCL Trial Research Group conducted several feasibility and pilot studies of the Control-IQ system and in 2019, Brown and colleagues published results of a 6-month randomised trial of this system.[68] A multicentre (MC) RCT conducted across several centres in the US evaluated a total of 168 patients who were randomly assigned in a 2:1 ratio to either the: Control-IQ system (n=112; HCL group) or control group (n=56; SAP therapy).

Breton and colleagues conducted a 16-week, RCT across four paediatric diabetes centres in the US.[69] A total of 101 patients were randomly assigned in a 3:1 ratio to either the: Control-IQ system (n=78; HCL group) or control group (n=23; SAP therapy). Patients in both groups attended follow-up visits at 2, 8, and 16 weeks.

Kanapka et al. (2021) further evaluated the efficacy and safety of the Control-IQ system in the same cohort of children aged 6-13 years with a 12-week extension phase.[83] A total of 100 patients who completed the 16-week RCT were entered into the extension phase and monitored for a further 12 weeks (a total of 28 weeks follow-up).

Ware et al. (2022) recently published a study with the aim of assessing the efficacy and safety of the Cambridge HCL algorithm in children and adolescents with T1D.[57] This study was a parallel, RCT conducted across seven UK and five US paediatric diabetes centres. A total of 133 patients were randomly assigned in a 1:1 ratio to either the: CamAPS FX system (n=65; HCL group) or control group (n=68; SAP therapy with or without glucose sensor). Patients in both groups attended follow-up visits at 13 and 26 weeks.

Some studies reported results of RCTs across different ski camps. Breton and colleagues' study was a multi-site, parallel, RCT conducted across two ski camps (5-day ski camp; ~5 hours skiing/day) in the US.[84] A total of 32 adolescents were randomised in a 1:1 ratio to either the: UVA AP system (n=16; HCL group) or control group (n=16; RM-SAP therapy. Ekhlaspour et al. conducted the first superiority trial of the Control-IQ system in children and adolescents aged 6-18 years under real-world conditions.[81] The study was a multisite, parallel, RCT conducted across three ski camps (2-day ski-camp; ~5 hours skiing/day) in the US. A total of 48 participants were randomised in a 1:1 ratio to either the: control-IQ system (n=24; HCL group) or control group (n=24; RM-SAP therapy).

Forlenza et al. conducted a 3-day home-use superiority trial in the 24 school children aged 6-12 years that participated in the 48-hours ski camp trial above.[82] The study was a multisite, parallel, RCT conducted during three days of home use at two clinical sites in the US. A total of 24 school children were randomly assigned in a 1:1 ratio to either the: Control-IQ system (n=12; HCL group) or control group (n=12; SAP therapy).

Ware et al.(2022), in a different study, aimed to evaluate the efficacy and safety of longer-term use of the Control-IQ system in young children using a larger sample size compared with previously conducted trials.[56] The study was a MC, cross-over, RCT conducted across diabetes centres in Europe over 16 weeks. A total of 74 children were firstly randomly assigned in a 1:1 ratio to either the: Control-IQ system (n=39; HCL group) or the control group (n=35; SAP therapy). As the trial used a cross-over design, participants

received their assigned initial therapy for 16 weeks and then crossed over to the second trial therapy after a wash out period of 1−4 weeks. Patients in both groups attended a follow-up visits every 4 weeks.

Boughton et al. recently conducted one of the only multinational study of HCL use specifically in older adults.[80] The study adopted a MC, randomised, cross-over (two-period) design across diabetes clinics at three UK centres and one Austrian centre. A total of 37 older adults were firstly randomly assigned in a 1:1 ratio to either the: CamAPS FX system (n= 20; HCL group) or control group (n= 17; SAP therapy). As the trial used a cross-over design, participants received their assigned initial therapy for 16 weeks and then crossed over to the second trial therapy after a wash out period of 4 weeks. Patients in both groups attended a follow-up visits every 4 weeks.

Overall, all studies, except Breton et al. (2020) [69] reported a statistically significant between-group difference in HbA1c (%) reduction in favour of HCL compared with SAP systems. Although statistical significance between systems was not reached in Breton et al.(2020),[69]. Also, all studies reported a statistically significant between-group difference in TIR (70–180 mg/dL) in favour of HCL compared with SAP systems.

The median number of hypoglycaemic events across trial periods was reported in two studies (Brown et al. 2019 and Breton et al. 2020).[68, 69], although statistical significance was not reached between groups. The difference in the median number of hypoglycaemic events per week in the iDCL study (Brown et al. 2019) was approaching statistical significance.[68]

The iDCL trial [68] included a number of PRO measures to assess user experience with diabetes technology and the impact of HCL and SAP system use on QoL. Total Diabetes Distress Scale [DDS] scores were significantly higher (less favourable) in the SAP compared with the HCL group at 3 months (P=0.04) but not at 6 months (P=0.30). Total Hypoglycaemia Fear Survey [HFS-II] scores showed no significant differences between the SAP and HCL group at 3 or 6 months. the HFS subscale scores also did not differ between study groups. However, scores on the two factors of the behaviour subscale (including a “maintain high blood glucose” and “avoidance” factor) were examined and showed lower (more favourable) scores in the HCL group on items, reflecting tendencies to maintain higher blood glucose level in certain situations to avoid hypoglycaemia (mean: 25) compared with the SAP group (mean: 35).

4.3.3.1 Dexcom submission clinical effectiveness: EAG critique

The EAG has some concerns about the results of the existing network meta-analysis.[79] Performance bias is challenging to asses because of impracticability of blinding

participants and clinicians to the devices being compared. Inconsistent reporting of TIR outcome made it impossible to meta-analyse this outcome.

The EAG has not managed to source the result reported in the submission from the iDCL trial because in this study multiple daily insulin injections were used by 35 (21%) patients.[68] The authors reported more unscheduled contacts in the closed loop group, which was attributed to the use of an investigational device, and the insulin pumps used by the control group did not have a feature to suspend insulin for predicted hypoglycaemia, which might have an effect on the amount of continuous glucose monitor–measured hypoglycaemia.

Breton's and Kanapka's study was similar to iDCL, with 21% of patients in the closed loop group and 17% in control group who had used MDI.[83] The amount of hypoglycaemia at baseline was unrepresentatively low in both treatment groups, which, in addition to the fact that most of the patients in the control group used a pump with a predictive low-glucose suspend feature, limited the ability of the trial to assess the effect of the closed-loop system on hypoglycaemia. On the other hand it's not possible to assess the sustainability of the treatment effect over a longer period because the trial period was only 4 months.

The EAG has some concerns about participants' characteristics. They came from a more advantaged socioeconomic background, and had more experience with diabetes technology, which may have a better effect on glycaemic control.

The EAG has some concerns about the monitoring method used because the researchers used remote monitoring that might have improved the glycemia compared to real world control. In addition, they reported an error in the software. Small sample size and the different context of the UK cause some concerns regarding generalisability.[81] There are some concerns about Forlenza et al.'s study.[82] because that study it was possible to achieve better control than could be seen in the real world. This occurred because a high degree of physician oversight was provided to both groups through continuous remote monitoring by a paediatric endocrinologist. This may have biased both the experimental and control groups, thereby limiting generalizability. There is risk of selection bias because subjects had enrolment HbA1c values of <7.5% on average in both groups, which may further limit generalizability.

There are some concerns about the generalisability of Ware et al.'s study on 'Closed-Loop Control in Very Young Children with Type 1 Diabetes'.[56] Highly motivated participants in closed-loop studies, and the crossover design, may limit the generalizability of these findings, because growth and development are rapid in very young children and may have affected trial results. Furthermore, additional exclusion criteria that were unrelated to diabetes applied to participants at sites in Germany, which potentially affected the reported treatment effect.

There are also concerns about the generalisability of Boughton et al.'s study [80] results because they enrolled participants that might not be fully representative of the general population of older adults with type 1 diabetes owing to the requirement for insulin pump therapy and the low baseline HbA1c. There was little ethnic diversity in the study population. The study participants had a relatively high level of educational attainment and might have had a higher level of technological proficiency than an age matched population which might limit generalisability of the results.

4.3.4 CamDiab submission clinical effectiveness

CamDiab presented 10 studies as clinical effectiveness evidence. They described a number of studies and edited extracts of their report are included in the box below:

Boughton et al.'s study [80] tested the hypothesis that use of the Cambridge closed-loop algorithm in older adults with type 1 diabetes is safe and improves glucose control compared with sensor augmented pump (SAP) therapy. The study was a multicentre, multinational, crossover design contrasting 16 weeks of hybrid closed-loop insulin delivery with 16 weeks of sensor augmented pump therapy in 38 participants at three centres in the UK (Cambridge, Manchester, and Birmingham) and one centre in Austria (Graz). The result shows HCL algorithm is safe, and significantly improves glycaemic control compared with sensor-augmented pump therapy, without increasing hypoglycaemia in older adults with type 1 diabetes. The time spent in the target glucose range (3·9–10·0 mmol/L) with closed-loop in this study population was high at 80%, and the 8·6 percentage point additional time in range compared to SAP therapy equates to an additional 2 h each day in target glucose range. Results show improvement in glycaemic control with closed-loop without any increase in hypoglycaemia and in the context of a population with tight glycaemic control at baseline (baseline HbA1c 7·4%; 57 mmol/mol).

Bally et al.'s randomised, crossover study,[85] recruited 31 adults (aged ≥18 years) attending diabetes clinics at Cambridge, UK and Graz, Austria. Participants were randomly assigned to receive either day-and-night closed-loop insulin delivery followed by usual pump therapy with blinded CGM, or vice versa. The results of the study show day-and-night hybrid closed-loop insulin delivery significantly improved overall glucose control while reducing hypoglycaemia progressively by 50–75% at lower glucose thresholds compared with usual insulin pump therapy. The findings of increased time spent in the glucose concentration target range, reduced hypoglycaemia, and decreased glycaemic variability were similarly observed during night-time and daytime periods. These outcomes were achieved without change in total insulin delivery.

Leelarathna et al.'s study [86] adopted a prospective multinational three-center randomized crossover design on seventeen adults with type 1 diabetes on insulin pump therapy over the 7-day home phase and 1-day stay at the clinical research facility.

Stewart et al. conducted a randomized, two-period crossover study in pregnant women with T1D to evaluate the safety, efficacy, and longer-term feasibility of day-and-night closed-loop insulin delivery versus SAP therapy.[52] Participants were randomly assigned to either 4 weeks of closed-loop (intervention) insulin delivery or 4 weeks of real-time CGM and CSII without the closed-loop system (SAP control) with a 1- to 2- week washout period before crossed to the alternate phase. No difference was found in the primary outcome of percentage of time in the target glucose range (63–140 mg/dL) during closed-loop and SAP therapy (62.3 vs. 60.1%, absolute difference 2.1% [95% CI 24.1 to 8.3]; P = 0.47). No episodes of severe hypoglycemia occurred. The mean (SD) HbA1c was 6.6% (2.8) (48.5 mmol/mol [7.5]), 6.4% (2.7) (46.3 mmol/mol [5.6]), and 6.3% (2.7) (45.9 mmol/mol [5.5]) at baseline, end of closed-loop, and end of SAP therapy, respectively.

Three studies by Tauschmann et al.'s reported results of a day-and-night closed-loop home trial in adolescents with type 1 diabetes under free-living conditions.[53, 87] One study is a randomized, two-period crossover design comparing automated closed-loop insulin delivery with sensor-augmented pump therapy over two 21-day periods in 12 subjects from paediatric diabetes clinics in UK.[87] Results show no serious adverse events or severe hypoglycemic episodes were observed during either study period. The proportion of time that sensor glucose was in the target glucose range of 3.9 to 10.0 mmol/L (primary end point), was increased during closed loop delivery compared with control period (P , 0.001). The mean glucose level was significantly lower with closed loop use (P = 0.001) as was the time spent above the target glucose range (P , 0.001).

The study extended findings from previous home trials in children and adolescents which were limited by a shorter intervention period. One of the previous trials was a prospective, single-centre, randomized crossover design contrasting automated closed-loop insulin delivery and sensor augmented pump therapy over 7 day.[88] Results show the proportion of time that the sensor glucose level was in the target glucose

range of 3.9– 10.0 mmol/L, significantly increased during closed-loop (P , 0.001). Closed-loop insulin delivery significantly reduced the mean glucose level (P = 0.028) and the time spent above target glucose level (P = 0.005) without increasing the time spent in hypoglycemia. No serious adverse events or severe hypoglycemic episodes were observed during either study period.

The Tauschmann's study published in 2018 was a randomised, parallel design in multiple centres,[53] from the UK and the USA for comparing day-and-night hybrid closed-loop (closed-loop group) or sensor-augmented pump therapy (control group) during free living over 12 weeks. The study reported a 10·8 percentage point increase in time with glucose concentrations within the target glucose range across all age groups. This improvement resulted from a reduction of time spent in hyperglycaemia without change in total insulin delivery. The researchers observed a lower amount of bolus insulin and a higher amount of basal insulin in the closed-loop group than in the control group. Post randomisation, no severe hypoglycaemia occurred in either study group.

Ware and colleagues (2022) [56] evaluated the efficacy and safety of longer-term use of the Control-IQ system in young children in an OL, MC, cross-over, RCT conducted across diabetes centres in Europe over 16 weeks. A total of 74 children were firstly randomly assigned in a 1:1 ratio to either the: Control-IQ system (n=39; HCL group) or the control group (n=35; SAP therapy). As the trial used a cross-over design, participants received their assigned initial therapy for 16 weeks and then crossed over to the second trial therapy after a wash out period of 1−4 weeks. Patients in both groups attended a follow-up visits every 4 weeks. The primary outcome was the between treatment difference in the % TIR of 70−180 mg/dL.

In a separate study, Ware et al. (2022) [57] adopted an open-label, multicentre, multinational, one-period, randomised design comparing hybrid closed-loop insulin delivery with insulin pump therapy, with and without glucose sensor, over 6 months. Participants were recruited from diabetes outpatient clinics at seven UK and five US paediatric diabetes centres. 133 eligible participants were randomly assigned to treatment (65 to the closed-loop group and 68 to the control group). Study reported a difference in efficacy between the two closed-loop system hardware configurations using the same algorithm, with an 11 ·5 mmol/mol (1 ·05%) reduction in HbA 1c in the CamAPS FX cohort compared with the control, and no reduction in HbA 1c in the FlorenceM cohort. No treatment effect in the cohort using the FlorenceM hardware was observed, contrasting with a treatment effect observed in the CamAPS FX cohort which used more reliable components and a factory-calibrated glucose sensor.

4.3.4.1 CamDiab submission clinical effectiveness: EAG critique

For Boughton et al.'s study [80] there are some concerns about generalisability of the results to the wider population of older adults with type 1 diabetes because there was little ethnic diversity in the study population. In the supplementary material, it is mentioned that the

study participants had a relatively high level of educational attainment and might have had a higher level of technological proficiency than an age matched population which might limit generalisability of the result.

For Bally et al.'s study [85] there may be some concerns around the duration of the study (for 4 weeks, in the order assigned at randomisation, with a 2–4 week washout period in between). This might have been insufficient to assess long-term compliance. Some exclusion criteria, such as participants with hypoglycaemia unawareness, have restricted assessment of the closed-loop system to those who might benefit greatly. The heterogeneity of sensor use in the control period might have confounded the reported glycaemic outcomes.

Leelarathna et al.'s study results are based on the a small sample size and a relatively short study duration.[86] In this study, the system used was an early generation closed-loop system (which was not a commercially available product). Some failures were observed using closed loop during the home phase because of unavailability of CGM data, a non-operational laptop, and unreliable Bluetooth communication between pump and the computer. All of these limitations could have affected the results.

Stewart et al.'s study included pregnant participants who had had intensive insulin treatment (either MDI or CSII), with equal numbers of pump and MDI users.[52] There are some concerns about duration of study (the short 4-week duration may have been insufficient for optimal closed loop training, particularly for device-naïve participants and those with less-advanced self-management skills). It was the prototype version of the closed-loop system, which had frequent errors, and reduced the time that closed-loop was operational.

One of Tauschmann et al.'s 2016 studies included a small sample size and the need to carry multiple devices during the closed-loop intervention, in addition to the study duration cause concerns about the finding.[87] Another study by Tauschmann et al. cause the same concerns, and also mention that the intervention was a prototype version of a closed-loop system and there was some restriction in use of this system during strenuous exercise.[88]

The main concerns about Tauschmann et al. 2018 [53] were the number of devices comprising a hybrid closed-loop system, which increased the risk of device and connectivity problems.

This issue resulted in more frequent non-protocol contacts to address technical issues. Another concerns is about systematic exclusion of participants with HbA1c outside the range of 7·5–10·0% and other groups, such as those with an impaired awareness of hypoglycaemia or a history of recurrent severe hypoglycaemia.

Ware et al. 2022 (Cambridge hybrid closed-loop algorithm in children and adolescents with type 1 diabetes) [57] used two different glucose sensors in the two closed-loop hardware configurations, although both have been shown to be similarly accurate in the hypoglycaemic range (glucose <3·9 mmol/L), it needs to be considered for interpreting the results. A prespecified analysis has been done to compare the entire closed-loop group with the control group, rather than each closed-loop system separately; the findings should be interpreted with caution.

The EAG's main concerns about the other Ware et al. 2022 study (Closed-Loop Control in Very Young Children with Type 1 Diabetes) is the generalisability of data.[56] Insulin-pump use was a prerequisite for trial participation and sensor use at enrolment was higher than average. Glycated haemoglobin level of less than 11.0% (97 mmol per mole) was required for trial participation, which potentially limited access to enrolment. Also, children from ethnic minorities were underrepresented. Investigators were free to adjust insulin therapy according to clinical judgment before randomization, which may have affected baseline characteristics. Research participants in closed-loop studies tend to be highly motivated, which may also limit generalizability. A crossover design was used, but because growth and development are rapid in very young children, this may have affected trial results. Additional exclusion criteria that were unrelated to diabetes applied to participants at sites in Germany, which potentially affected the reported treatment effect.

4.3.5 Tandem submission clinical effectiveness

Tandem presented three recent pieces as clinical effectiveness evidence in their submission. They described a number of studies and edited extracts of their report are included in the box below:

One of them is a poster that was presented at the Australian Diabetes Conference.[89] Of the two papers presented, one has been through peer review and is published online in Diabetes Technology &

Therapeutics [90] and the other is a version before peer review that has been submitted to the Diabetes Care journal.

Singh's study (presented as a poster) [89] reported analysis of 71,686 people with type 1 diabetes from the United States who on boarded to Control-IQ technology between August 2020 and February 2022. They reported stratified data based on the prior therapy and age group. The result show by using Control-IQ technology, GMI reflected clinically significant glycemic improvement (7.1%, [6.8-7.5], p<0.001).

Glycemic improvements were also demonstrated by prior therapy: prior MDI users at baseline = 8.2% [7.2-9.5] to 7.2% [6.9-7.6] at post, p<0.001; prior pump users = 7.5% [6.9-8.3] to 7.1% [6.8-7.5], p<0.001), and by age group: pediatrics at baseline = 8.2% [7.3-9.3] to 7.5% [7.1-7.9] at post, p<0.001; adults = 7.7% [7.0-8.8] to 7.1% [6.8-7.5], p<0.001; and older adults = 7.3% [6.8-8.0] to 7.0% [6.7-7.2], p<0.001.

Forlenza et. al.'s pending publication (approved) [90] includes 5,575 patients who were covered by Medicare insurance (over age 65) or Medicaid insurance (disadvantaged youth) in the United States in a real-world retrospective analysis to assess glycemic control outcomes with CIQ use among Medicare and Medicaid-beneficiaries with any type of diabetes and those with T2D with either type of insurance. Glycemic outcomes were calculated for all participants who had at least 30 days of CGM data with ≥75% CGM availability before and after Control-IQ initiation. In this cohort 806 users who transitioned from multiple daily injection (MDI) therapy to CIQ therapy had a higher baseline GMI at 7.9% and saw a significant decline in Glucose Management Indicator (GMI)* [91] to 7.1% (difference of -0.8%; p<0.0001).Across all age groups TIR was also significantly increased without significant change in level 1 or level 2 hypoglycemia. The results show significant reduction in GMI in the Medicare group by 0.3%, in the Medicaid group by 0.4%. There was also significant improvement in TIR in the Medicare group by 10%, in the Medicaid group by 14%, and in the T2D subset by 8%.

Kovatchev et al.'s submitted publication (supplied to the EAG in the Tandem submission) is a retrospective analysis of 2,329,166 days (6,381 patient-years) of CGM and insulin therapy data for 19,354 individuals with Type 1 Diabetes in the United States, during 1-month PLGS (Basal-IQ technology) use followed by 3-month AID use (Control-IQ technology). They included 19,354 US-based individuals with Type 1 Diabetes who were using a PLGS system (Basal-IQ technology) and then updated their insulin pumps to AID (Control-IQ technology). The results show that on AID, TIR increased by 12 percentage points study; time >180 mg/dL decreased by 12 percentage points in this observational study, time <70 mg/dL decreased by 0.9, 0.4, and 0.2 percentage points, respectively, and HbA1c decreased by 0.33%, 0.4%, and 0.4%.

* GMI = 3.31 + 0.02392 × [mean glucose in mg/dL]. The average glucose is calculated over the entire time a customer used a Tandem pump in accordance with the guidelines above.

4.3.5.1 Tandem submission clinical effectiveness: EAG critique

Assessing quality of study and results based on the Singh's poster is not possible because there is not enough data about history of patients or a description of the intervention and comparator. [89]

In Forlenza et. al.'s pending publication (approved),[90] 500 users were affected by Type 2 diabetes while most patients had Type 1. In this cohort study there were 806 users who transitioned from multiple daily injection (MDI) therapy to CIQ therapy. There is reliance on GMI as a surrogate for biological HbA1c data because of lack of follow up for this data. There is concern about generalizability of results because of the need to have uploaded device data by user. Those device users who did not upload their data would not be represented. The analyses were performed using a reporting dashboard of real-world data, which is a limitation because predetermined analyses existing within the dashboard tools were used.

In Kovatchev et. al.'s study, GMI is used as a proxy for HbA1c. Analysed data are based on a retrospective real-world database. The observation period is too short (one month on Basal-IQ technology followed by 3 months on Control-IQ technology). No access to related variables which might have affected the result, such as sociodemographic features, or duration of diabetes. There is concern about generalisability of data because the participant population in the study were early adopters of diabetes technology, already using PLGS before transitioning to AID when it became available for home use.

4.4 Assessment of effectiveness

4.4.1 Summary of information

The clinical evidence identified 12 randomised controlled trials that compared HCL to CSII+CGM or SAP therapy.

Studies were heterogeneous in terms of population, age groups, gender, RCT design (parallel cross over), numbers of participants and variable adjustment methods for determining MD between intervention and comparators. Studies did not consistently describe comparators. Cross-over studies did not provide data at different cross-over time points.

Overall, the HCL arm of RCTs achieved improvement in HbA1c %, time in in range (3.9 to 10 mmol/L), and hyperglycaemic levels. Comparator arms also showed improvements but this was less than that observed in the HCL arm. Irrespective of type of intervention used in the comparator arms, these outcomes were statistically superior in the HCL arm vs. control arm. Available evidence from the RCTs suggests that these gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration.

The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range, and % time above range all improved on transfer to HCL (or to AHCL) without any strong evidence that hypoglycaemia became more of a problem; however changes in hypoglycaemia were mostly underpowered in these studies; in the largest studies (NHS Pilot and survey study by Breton et al.,) there was no persuasive indication of deterioration in hypoglycaemic states.

The inclusion of RCTs was based on the presence of a relevant comparator arm, the inclusion of at least 90% HCL recipients in the intervention arm, and the reporting of outcome measures applicable to NMA. The aim of the RCTs was generally to demonstrate improvement of glycaemic control with use of HCL. The study by Stewart of pregnant women included only 16 participants followed for 4 weeks; the population, study design and outcomes in this study were clearly different from other studies so that transitivity in NMA including Stewart is threatened.

There were relatively few studies, they were of small size encompassing a total of ~450 HCL recipients followed for between 4 and 26 weeks accumulating approximately 110 person years of observation. Inclusion criteria applied for the studies were relatively narrow and most participants had reasonably good glycaemic control at entry, as indicated in most of those studies reporting baseline TIR (3.9 to 10 mmol/L) at greater than 50% (range 47% to 62%), and baseline HbA1c at between 7% and 8%. There was considerable heterogeneity across studies regarding the age of participants, some studies presented results stratified by age groups. The relevance of the RCT populations and outcome measure results for the decision problem is debatable and not easy to judge.

The quality of studies assessed according to Cochrane criteria (Table 7) was associated with some concern.

In the HCL arm of RCTs the intervention achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10 mmol/L, and in hyperglycaemic levels. Control arms also showed improvement but this was less than that seen with HCL. Irrespective of type of intervention used in the control arms these outcomes were statistically superior in the HCL arm vs. control arm. Available evidence from the RCTs suggests that these gains in glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration. The NHS adult Pilot study differed somewhat from most other studies in that it included a broader spectrum of patients. These patients had a poor record of glycaemic control at baseline was indicated by high HbA1c% and low % time in range (3.9 to 10 mmol/L) measures; at baseline the

proportion hyperglycaemic participants was high as indicated by the % time above 10 mmol/L. Transfer to HCL resulted in larger improvements than observed in other studies, likely partly due to the poorer starting status. In the NHS Pilot study the resulting levels of measures of glycaemic control after HCL intervention approached those seen for HCL groups in other studies (both RCT and single arm studies). The discontinuation rate in the use of HCL (temporary or permanent) in the Pilot study was about 10%; whether this would increase with time is unknown but from a clinical evidence perspective represents a wastage of device(s).

4.4.2 Discussion

The evidence on closed loop systems has been based largely informed by short duration studies, small number of participants and some uncertainty of the methodological quality of included studies. Closed loop systems have been previously reviewed and showed effectiveness in in treating patients with type 1 diabetes.[92] In this review, the HCL arm of RCTs achieved improvement in HbA1c %, time in in range (3.9 to 10 mmol/L), and hyperglycaemic levels. Comparator arms also showed improvements but this was less than that observed in the HCL arm. Irrespective of type of intervention used in the comparator arms, these outcomes were statistically superior in the HCL arm vs. comparator arm. In the NHS Pilot study, the post HCL levels of measures of glycaemic control approached those seen for HCL groups in other published studies (both RCT and single arm studies). The 2022 Scottish Health Technologies Group (SHTG) [25] found significant improvements in mean percentage time in range for people with type 1 diabetes using a closed loop system compared to other insulin-based therapy. We found similar trends to the SHGT work. However, it should be noted that the scope of the SHGT group differs from this work. Our NMA synthesis demonstrated a significant decrease in TIR (% above 10.0 mmol/L), increase in % TIR (between 3.9 – 10.0 mmol/L), and a decrease in HbA1c % showing superiority of HCL in comparison to other treatments.

Evidence suggest that such technologies have the potential to improve the lives of people with type 1 diabetes and their families. People seem to report a better quality of life,

diabetes burden and quality of sleep and less anxiety with technologies.[93] The study by Wheeler showed no significant improvements in the anticipated worry of hypoglycaemia in children, parents and adults. Studies included in this review used various tools to assess technology satisfaction. Only one study (Benhamou), that compared an open loop and closed loop system, found that user satisfaction had increased. In the other studies, the difference between the HCL group and comparator was not statistically significance. RCTs included in this review reported a low number of adverse events for both treatment groups. Although some reports of hypoglyceamia were identfied in the included studies, we did not identfify any clear trends and differences between HCL vs comparator. It is worth noting that the studies included in this review are of short duration. The REPOSE study assessed the relative effetivenss of CSII therapy in comparison to MDI over 24 months. Adverse events (such as DKA) were higher at the initiation of therpay and reduced over time. Therefore, it is important to assess the long term adverse events to allow for an adjustment period in people with type 1 diabetes.

5 Systematic review of existing cost-effectiveness evidence

5.1 Methods for assessing cost effectiveness evidence: Key questions

What is the cost effectiveness of hybrid closed loop systems (HCL) for managing glucose in people who have type 1 diabetes mellitus (T1DM), and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

Other questions:

1. What is the cost effectiveness of hybrid closed loop systems for managing glucose in pregnant women who have T1DM?

2. What is the cost effectiveness of hybrid closed loop systems for managing glucose in children who have T1DM and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood

glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

3. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, an extreme fear of hypoglycaemia, and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

4. What is the cost effectiveness of hybrid closed loop systems for managing glucose in people who have T1DM, with diabetes related comorbidities that are at risk of deterioration, and are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections?

5.2 Systematic review of existing cost-effectiveness evidence

As per protocol, a systematic review of existing cost-effectiveness evidence surrounding HCL was commenced using the following methods.

5.2.1 Study identification

A comprehensive search of the literature for published economic evaluations was performed in a range of relevant bibliographic databases in April 2021, and updated in April 2022. The database searches were developed using search strings applied in the previous technology assessment on integrated sensor-augmented pump therapy systems (DG21)[35] as the basis for selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections, and other systematic reviews for lines relating to pregnancy.[36-38] The search was informed by the strategy developed for the clinical effectiveness review (see section 4.1.2) and established economic terms based on the CRD NHS EED filter.[94] A date limit in 2014 was applied for each database, based on the search dates for DG21.[35] The search was limited to English language to reflect the inclusion criteria. Full details of the search strategies are provided in Appendix 1 (see section 9.1).

The following databases were searched, from 2014: MEDLINE ALL (via Ovid); Embase (Ovid); EconLit (EBSCO); HTA database (CRD); International HTA database (INAHTA); EconPapers (RePEc); AHRQ website; CADTH website; SBU website; Cost-Effectiveness Analysis (CEA) registry; and School of Health and Related Research Health Utilities Database (ScHARRHUD).

The reference lists of included studies and results of the clinical effectiveness search were also checked.

Records were exported to EndNote X9, where duplicates were systematically identified and removed.

An additional, scoping search for hypoglycaemia and health-related quality of life (HRQoL) in MEDLINE ALL (via Ovid) was conducted from 1st January 2020 to 10th June 2022 for studies on hypoglycaemia and quality of life in people with diabetes. The search was limited to 2020 onwards because searches for a recent economic report for NG17,[95] were undertaken in May 2020.[96] The targeted search included terms for hypoglycaemia and HRQoL, and used a recognised search filter (Arber 2017 FSF1 - sensitivity maximising health utilities search filter [97]). The full search strategy is provided in Appendix 1: Record of searches – Cost effectiveness (see section 9.1.2).

Additionally, the Hypo RESOLVE website was checked.[98]

Potentially relevant literature identified during the systematic review of economic evaluations and sent by topic experts was also examined for relevance.

127 records were retrieved and sifted by the health economists.

5.2.1.1 Inclusion and exclusion of relevant studies

Studies that satisfied the following criteria were included in the review:

Population:

People who have T1DM who are having difficulty managing their condition despite prior use of continuous subcutaneous insulin infusion and self-monitoring of blood glucose or glucose monitoring (real time continuous glucose monitoring or flash glucose monitoring) and multiple daily injections.ab

T1DM subpopulations included within:

- Pregnant women and those planning pregnancies (excluding gestational diabetes).
- Children (5 years and under, 6 – 11 years, 12 - 19 years).
- People with extreme fear of hypoglycaemia.
- People with diabetes related complications that are at risk of deterioration.

For the purpose of this review, difficulty refers to not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below, not maintaining at least 70% time in range of 3.9 -10 mmol/l, or repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life.

Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.

Intervention:

Hybrid closed loop systems

Comparators:

- Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated).
- Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion.

For women with type 1 diabetes who are pregnant/planning pregnancy comparators also included:

- Real time continuous glucose monitoring with multiple daily insulin injections.
- Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections.
- Self-blood glucose monitoring with continuous subcutaneous insulin infusion.

Outcome measures:

- Cost and cost-effectiveness outcomes (costs for each treatment technology, direct medical care costs, incremental cost-effectiveness ratios (ICER) e.g. cost per quality-adjusted life year (QALY) gained).

Study design:

- Studies comprising an economic evaluation (cost analysis, cost-consequence analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis), and any model-based economic evaluation involving direct comparison between HCL and non-integrated CGM and CSII therapy in T1DM.

Other inclusion criteria:

- Full text reports published in English Language
- Abstracts (only if they are companion publications to full text included studies or contain extractable numerical data)

Papers that fulfilled the following criteria were excluded:

Studies evaluating automated insulin delivery systems which only suspend insulin delivery when glucose levels are low/ are predicted to get low.

Non-human studies, letters editorials and communications, and articles not available in the English language.

Methods

The searches were developed and run by our information specialists (Anna Brown and Rachel Court). Sifting was undertaken by 2 reviewers. Mary Jordan lead the review sifting abstract and titles of all identified studies while Felix Achana and Lena Al-Khudairy acted jointly as second reviewer. Results between 1st and respective 2nd reviewer were then compared and anomalies resolved through discussion or where this was not possible by recourse to the full team of reviewers. Full text of the result of the first sift were obtained and screened using the same process.

Data extraction and quality assessment

As per the protocol, it was intended that information was extracted by one reviewer (MJ) using a pre-piloted data extraction form for full economic evaluation studies, and reporting quality of studies included in the systematic review would be assessed against the Consolidated Health Economic Reporting Standards (CHEERS)[99] and the Philips' checklist,[100] respectively. Where search results rendered this process unnecessary, quality appraisal was undertaken narratively guided by the criteria detailed in these checklists.[99, 100]

Data synthesis

Narrative synthesis of findings and assessment of study quality is presented, with recommendations for future economic models discussed.

Results

The literature search identified 745 records through electronic database searches and other sources. After removing duplicates, 516 records were screened for inclusion. On the basis of title and abstract, 497 records were excluded. The remaining 19 records were included for full-text screening. A further 13 articles were excluded at the full-text stage mainly due to incorrect intervention/comparator,[101-105] incorrect study design,[106] abstract/poster presentation only,[107-109] or further duplication identified.[110-112]

The literature search (Figure 19) identified six studies which were included in the review.[25, 113-117]

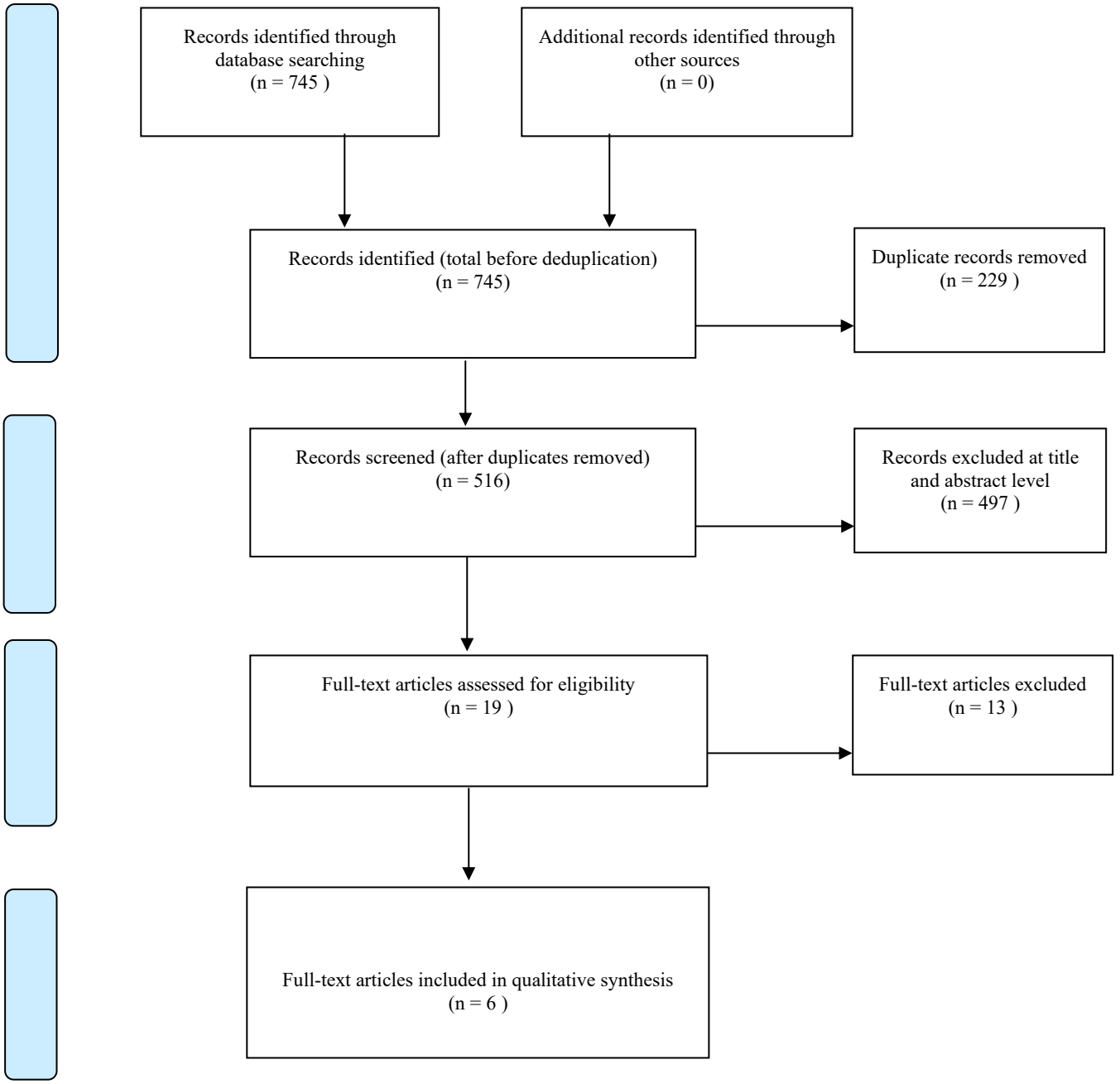


Figure 19. Search strategy flow diagram

5.2.1.2 Summary of the economic analyses undertaken

In this section, we summarise the economic analyses retained and discuss the approach taken and relevance in assessing HCL compared with CGM/FGM and CSII in adults with type 1 diabetes.

The first four studies use the IQVIA CORE Diabetes Model (CDM) to conduct their economic evaluations, whereas the study in the SHTG report [25] uses the Sheffield type 1 diabetes model. Both the IQVIA CORE Diabetes Model and the Sheffield type 1 diabetes model are validated models that employ Monte Carlo methods to estimate the cost effectiveness of diabetes related technologies including HCL systems. The study presented in the CADTH report [113] is a budget impact analysis and was conducted using a customized Microsoft Excel tool.

Jendle et al., 2019 [114]

Jendle et al., 2019[114] used the CDM to assess the cost effectiveness of the MiniMed™ 670G HCL system versus CSII in people with T1DM in Sweden.

Baseline cohort characteristics, and both treatment effect on HbA1c and rate of SHEs for the HCL system, were taken from a single arm before/after clinical study.[118, 119] Other clinical inputs were either assumed or derived from the literature and costs obtained from a variety of published sources.

All costs included in the model were reported in 2018 Swedish krona (SEK). The analysis was conducted from a Swedish societal perspective, over a lifetime horizon, with future clinical and economic costs discounted at a rate of 3% per annum. A human capital approach to costing lost productivity was used. Results were presented in terms of an incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life year (QALY) gained. Authors undertook scenario analyses around the costs of HCL, costs of comparator, rate of SHEs, impact of fear of hypoglycaemia (FoH) and cost effectiveness in poorly controlled patients (HbA1c ≥7.5%).

The base-case deterministic results showed that the MiniMed 670G HCL system when compared with CSII had an ICER of SEK 164,236 (1 SEK = £0.082) per QALY gained. This resulted from an increase of 1.90 QALYs but higher overall costs despite lower cumulative incidence of diabetes-related complications and reduced productivity losses.

The results of the scenario analyses showed that the ICER was most sensitive to assumptions relating to the impact of FoH on quality of life, treatment comparator costs, and reductions in SHE rates.

While the study added to the literature on the cost effectiveness of HCL systems by conducting a cost effectiveness analysis of the MiniMed 670G system in Sweden, the authors acknowledged and discussed the limitations associated with the analysis.

Roze et al., 2021 [116]

Roze et al., 2021[116] used the CDM to assess the cost effectiveness of the MiniMed™ 670G HCL system versus CSII in people with T1DM in the UK.

Baseline cohort characteristics, and both treatment effect on HbA1c and rate of SHEs for the HCL system, were taken from a single arm before/after clinical study.[118, 119] Other clinical inputs were either assumed or derived from the literature and costs obtained from a variety of published sources.

All costs included in the model were reported in 2018 British pound sterling (GBP). The analysis was conducted from a UK health care system perspective, over a lifetime horizon, with future clinical and economic costs discounted at a rate of 3.5% per annum. Results were presented in terms of an ICER expressed as cost per QALY gained.

Base-case deterministic results showed use of the MiniMed™ 670G HCL system led to an increase of 1.73 QALYs compared to CSII, with higher total lifetime direct costs of GBP 35,425. This resulted in an ICER of GBP 20,421 per QALY gained.

Sensitivity analyses showed sensitivity of the ICER to assumptions surrounding glycemic control and quality of life benefits associated with reduction in FoH.

Authors ultimately concluded that in the UK, over patient lifetimes, use of the MiniMed™ 670G HCL system is likely to be cost-effective relative to the continued use of CSII in people with T1D, particularly those with fear of hypoglycemia and poor glycaemic control at baseline. The main contribution to knowledge was that unlike the previous analysis of the MiniMed 670G in Sweden [114] that considered a societal perspective, Roze et al., 2021 adopted a UK health care system perspective.

Serne et al., 2022 [117]

Serne et al., 2022[117] used the CDM to determine the cost effectiveness of the MiniMed™ 670G HCL system versus IS-CGM with MDI or CSII in people with T1DM. The study extended the evidence base on the cost effectiveness of the MiniMed 670G HCL system by conducting a study in Netherlands.

Baseline cohort characteristics, and treatment effect data for the IS-CGM with MDI/CSII, were taken from a prospective observational real-world cohort study (FUTURE) in Belgium.[120] Treatment effect for the HCL cohort was sourced from a retrospective analysis of patients transitioning from SAP to the MiniMed 670G in the US.[121]

A societal perspective was taken for the analysis, over a lifetime time horizon, with future costs specific to the Netherlands discounted at 4% and clinical outcomes at 1.5% per annum. All direct and indirect costs included were reported in 2020 Euros, with a human capital approach taken to calculate cost of lost productivity.

Use of the MiniMed 670G HCL system increased mean QALYs by 2.231 versus IS-CGM in the deterministic base-case. Total mean lifetime costs were also higher in the HCL cohort, at EUR 13,683, resulting in an ICER of EUR 6133 per QALY gained.

Sensitivity analyses highlighted ICER results were sensitive to assumptions around SHE rates and the quality of life benefit associated with reduced FoH.

Some discussion of the limitations of data sources for this economic analysis was provided by authors. They concluded that use of the MiniMed 670G system is likely to be cost-effective relative to IS-CGM plus MDI or CSII for adults with long-standing T1DM based in the Netherlands.

Jendle 2021 [115]

Jendle 2021 [115] use the CDM (version 9.0) to evaluate the long-term cost-effectiveness of the MiniMed 780G advanced hybrid closed-loop (AHCL) system against isCGM plus MDI CSII in people with T1D in Sweden.

Baseline characteristics and treatment effect data for the IS-CGM with MDI/CSII cohort were taken from a the FUTURE clinical trial in Belgium,[120] with an assumed treatment effect applied for the HCL cohort based on Collyns et al., 2021.

The cost effectiveness analysis was conducted from a societal perspective projected over patients' lifetimes with results presented in Swedish Kroner (SEK), although no cost year was explicitly stated. Future clinical and cost benefits were discounted at 3.0% per annum and results presented in terms of an ICER expressed as cost per QALY gained.

Use of the MiniMed 780G system was associated with an improvement of 1.95 QALYs versus isCGM plus MDI or CSII. Clinical benefits accrued due to reduced incidence and delayed time to onset of diabetes-related complications. Total costs were estimated to be SEK 727,408 producing an ICER of SEK 373,700 per QALY gained.

Jendle et al. (2021) contributed to the literature by showing that the MiniMed 780G system is expected to be cost-effective versus isCGM plus MDI or CSII for the treatment of T1D in Sweden, at a willingness to pay threshold of SEK 500,000 per QALY gained.

SHTG (2022) [25]

The study in the 2022 Scottish Health Technologies Group (SHTG) report used the Sheffield type 1 diabetes model to examine the clinical and cost effectiveness of closed loop systems and the artificial pancreas for the management of type 1 diabetes. In particular, the study compared closed loop systems with five comparator interventions i.e. SMBG + MDI, CGM + MDI, isCGM + MDI, CSII+MDI and CSII + CGM.

The baseline characteristics and treatment effects for the simulation cohort were obtained from a 2017 Scottish type 1 diabetes cohort study and a network meta-analysis (NMA) of the published literature. The cohort study was a nationally representative sample of individuals living with type 1 diabetes in Scotland.

The analysis adopted a healthcare payer perspective with patients' lifetimes as the time horizon. The indirect costs associated with lost work productivity due to diabetes morbidity were not included and all the other costs were expressed in GBP. The costs and

utilities were discounted at 3.5% p.a. following the NICE methods of technology appraisal guidance.

The base case results showed that the ICERs of closed loop systems vs SMBG+MDI, CGM+MDI and isCGM + MDI were £44,920, £58,996 and £79,664 per QALY gained respectively. The SHTG found that closed loop systems had the highest costs and QALYs compared with CSII + rtCGM. The deterministic sensitivity analyses showed that the findings were sensitive to changes in the assumed effects on hypoglycaemia and the per event disutility value associated with non-severe hypoglycaemic events, whereas the results of the probability sensitivity analysis were very similar to the base case results.

The main limitation of the study was that it relied on an algorithm to convert improvements in percentage time in range to measures of reduction in HbA1c which potentially resulted in inaccurate estimates. Nevertheless, the fact that the study used a nationally representative simulation cohort for Scotland meant that the findings were generalisable to the population unlike the results of the other identified economic studies that used baseline data for different countries. Furthermore, unlike the previous analyses in the literature that considered either the MiniMed 670G or the MiniMed 780G compared with isCGM+CSII or CSII alone, the study provided a more comprehensive analysis of closed loop systems in general compared with multiple configurations of the comparator technologies.

CADTH 2021 [113]

The study in the 2021 Canadian Agency for Drugs and Technology in Health (CADTH) report had three objectives. First, it extended the evidence base by estimated the financial impact of introducing HCL systems for individuals with type 1 diabetes using a budget impact analysis. Second, it assessed the perspectives, experiences and expectations of individuals living with type 1 diabetes as well as their carers. Third, it assessed the ethical aspects associated with the use of HCL systems.

The analysis was conducted from the perspective of the Canadian publicly funded healthcare system with a time horizon of 3 years. The base case results of the budget

impact analysis showed that an additional $823 million would be needed to reimburse HCL systems for the eligible population. In particular, an additional $131 million would be needed in year 1, an additional $271 million in year 2 and an additional $421 million in year 3. The scenario analyses showed that the results were sensitive to changes in the population of eligible individuals. In particular, increasing the HCL coverage levels to 100% translated to an increase of $916 million needed to finance the provision of HCL systems. The results were also sensitive to changes in the price of CGM and the uptake of HCL systems among the users of MDI.

The main limitation of the analysis was that the epidemiological measures used to inform the budget impact analysis i.e. the prevalence of type 1 diabetes, the annual incidence of type 1 diabetes and the population growth rate were proximate measures derived from the literature and may thus not have been accurate. These measures were obtained from a 2014 report but the cost estimates for the base case were for 2020. The study also made several assumptions on the coverage levels of insulin-pump use, glucometers, CGM and SMBG test strips which had an impact on the accuracy of the results.

5.2.1.3 Characteristics of retained studies

The characteristics of the six retained studies are summarised in following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). Five of these studies were economic evaluations of hybrid closed loop systems, whereas one was a budget impact analysis that aimed at estimating the financial impact of reimbursing HCL systems for individuals with type 1 diabetes. The economic evaluation studies compared the cost effectiveness of hybrid closed loop systems with various diabetes management technologies such as isCGM+MDI, CSII and SMBG among others. Four studies used the IQVIA CORE Diabetes Model to conduct their analyses (Jendle et al., 2019;[114] Jendle et al., 2021;[115] Roze et al., 2021;[116] Serne et al., 2022 [117]), while the study in the SHTG report [25] used the Sheffield type 1 diabetes model. Of the six studies, two were conducted in Sweden (Jendle et al., 2021; Jendle et al., 2019) and one each in the

UK (Roze et al., 2021), Netherlands (Serne et al., 2022), Scotland (SHTG, 2022 [25]) and Canada (CADTH, 2021).

The studies modelled their outcomes over patients' lifetimes and reported their outcomes as cost per QALY gained except from Roze et al., 2021 and the study in the CADTH report that considered a healthcare payer perspective.[113] All the studies discounted their costs and outcomes in line with their national guidelines. An interesting point to note, however, is that there was substantial heterogeneity in the choice of baseline cohort data as well as the data for the treatment effects. For instance, Serne et al., 2022 used different data sources for both the treatment effects and the simulation cohort. Moreover, the data was not for Netherlands. Similarly, the studies by Roze et al., 2021 and Jendle et al., 2019 used a baseline simulation cohort comprising individuals from the USA yet the studies aimed at informing long-term cost effectiveness for the UK and Swedish populations respectively. Jendle et al., 2021 despite being conducted in Sweden used simulation cohort data sourced from a Belgium study. It is only the Study in the SHTG report [25] that used baseline data for its population of interest.

In order to characterise uncertainty in the base case results, all the included studies performed several one-way sensitivity/scenario analyses. The studies that employed the IQVIA CORE Diabetes Model and the study in the SHTG report that used the Sheffield type 1 diabetes model further conducted probabilistic sensitivity analyses and presented the results in the form of cost effectiveness acceptability curves (CEAC). An interesting point to note is that the base case results were found to be very sensitive to the severe hypoglycaemic rates (SHE) and changes in the assumptions relating to the quality-of-life benefit associated with reduced fear of hypoglycaemia (FOH) in four out of the five cost effectiveness studies.[25, 115-117] Furthermore, the CEAC showed that HCL systems are expected to be cost effective compared with the comparator technologies at various hypothetical willingness-to-pay thresholds.

5.2.1.4 Quality assessment of the modelling methods and economic analyses

Structure

The budget impact analysis contained in the CADTH report [113] was conducted using a customised Microsoft Excel tool and it utilised several epidemiological measures obtained from the literature such as the prevalence of type 1 diabetes, incidence rates and population growth rates to estimate the market size and coverage levels of HCL systems in Canada. Financial projections were then made using these measures by adjusting the base year HCL costs over a 3-year time horizon.

The structure of the models used in the cost effectiveness studies was judged to be of good quality. The studies clearly stated their decision problem/research question, the viewpoint of their analyses and their modelling objectives, which were coherent with the decision problem. Both the IQVIA CORE Diabetes Model and the Sheffield type 1 diabetes model are validated models for evaluating diabetes technologies. The studies that used the IQVIA CORE diabetes Model described the model as one with a complex semi-Markov model structure with interdependent sub-models, so more thorough, easier access to its reported features would be of benefit to the intended audience. None of the studies clearly showed the illustrative model structure, which depicted the clinical pathway for T1DM, although references were given to previous publications which outline this. The model is capable of capturing both long- and short-term clinical complications and costs associated with T1DM and has been extensively validated for use in this condition since inception.[122, 123]

The Sheffield type 1 diabetes model is discussed more extensively by the study in the SHTG report [25] unlike the IQVIA CORE Diabetes Model studies that merely provide brief descriptions. The model also has a Markov model structure with several sub-models. The first Markov model predicts mortality in each cycle and is characterised by two states i.e. alive or dead. If a particular individual is alive, then the individual can develop microvascular complications or cardiovascular disease and can experience severe or non-severe hypoglycaemic events. A five-state model for nephropathy (i.e. no nephropathy, microalbuminuria, macroalbuminuria, end stage renal disease and death from end stage renal disease), a three-state neuropathy model (no neuropathy, neuropathy and amputation) and a five-state model for retinopathy (i.e. no retinopathy, background retinopathy, proliferative retinopathy, macular oedema and blindness) is used to capture

the progression of microvascular complications. A key difference between the STHG study that used the Sheffield type 1 diabetes model and the studies that used the IQVIA CORE Diabetes Model is that the SHTG study used a published algorithm to model cardiovascular disease and convert improvements in time in range to reductions in HbA1c, which was deemed to be a more relevant outcome measure. The algorithm assumed the form of a multivariable model where the 5-year risk of cardiovascular disease was dependent on several individual characteristics including duration of diabetes, age, systolic blood pressure, HbA1c levels, previous cardiovascular disease, presence of macroalbuminuria and cholesterol levels.

Data

All the studies required data to undertake the economic analyses. For the cost effectiveness studies to be conducted, both clinical and cost information as well as baseline characteristics for the simulation cohorts had to be inputted into the analytical models prior to the simulation process. The cost effectiveness analyses also required data on the disutilities associated with diabetes related complications as well as data on the utility benefits due to the reduction in the fear of hypoglycaemia (FOH), which were largely obtained from the published literature. The budget impact analysis in the CADTH report [113] used national statistics to inform the key epidemiological measures (i.e. the prevalence of type 1 diabetes, the annual incidence of type 1 diabetes and the population growth rate) and cost data required to estimate the market size and the amount of money needed to reimburse HCL systems.

Two studies i.e. Serne et al., 2022 [117] and Jendle et al., 2021[115] obtained their baseline data and data for the treatment effect of their comparators from a prospective cohort study conducted in Belgium [120] but used different data sources for their intervention treatment effects. The study by Serne et al., 2022 obtained the treatment effect for the intervention from a retrospective US based study of patients transitioning from SAP to the MiniMed 670G HCL system,[121] whereas the study by Jendle et al., 2021 obtained the intervention treatment effect from a randomised crossover trial conducted in New Zeeland that comprised type 1 diabetes patients using the MiniMed 780G HCL system (Collyns et al., 2021 [49]). It is, however, not clear how the treatment effect was elicited as

this is not explicitly stated in the text. Furthermore, the New Zealand study reported the treatment effects of the MiniMed 780G system on time in range. Yet time in range was not one of the outcomes of interest in Jendle et al., 2021.

The study by Roze et al., 2021 [116] and that by Jendle et al., 2019 [114] obtained their baseline data from a study similar to the one used by the Serne et al., 2022 for the intervention treatment effect,[118, 119] but Roze et al., 2021 used a network meta-analysis of the literature to obtain the treatment effects, whereas Jendle et al., 2019 sourced the treatment effects from the simulation cohort. Similar to Roze et al., 2021, the study in the SHTG report conducted a network meta-analysis of the published literature so as to get estimates of the treatment effects but unlike Roze et al., 2021, the baseline characteristics were sourced from a 2017 Scottish type 1 diabetes cohort study.

The relevant cost inputs were obtained from the published literature, and they reflected the perspective of each study as reported. Where suitable resource use data were not available e.g. for treatment mix of the comparator, limitations were acknowledged and authors justified the assumption of using a more conservative approach to costing. An important point to note is that the methods used to identify the relevant information sources were not clearly stated although justifications for the chosen data sources were made and appropriate references provided. It was not clear if quality appraisal of the studies serving as data sources was undertaken and to the best of our knowledge, the studies did not undertake systematic reviews to identify the studies reporting key inputs. With respect to the risk equations underlying clinical progression within the validated models (i.e. the IQVIA CORE Diabetes model and the Sheffield type 1 diabetes model), the sources and choice of source where multiple options were available were not provided or justified. Appropriateness of these sources for use within the specific decision problem cannot, therefore, be assessed.

Uncertainty

The budget impact analysis presented in the CADTH report [113] included scenario analyses where universal HCL coverage was assumed. All the five cost effectiveness studies also conducted several deterministic analyses by varying key input parameters to

reflect lower and upper limits, or by making changes to input parameters if multiple sources of information were available to assess the impact on the base-case ICER, and/or to determine the key drivers of the economic model. It was unclear in some analyses whether the sensitivity analyses were exhaustive as no tornado plots were reported. However, results were presented for all sensitivity and scenario analyses.

Four out of the five cost effectiveness studies i.e. Serne et al., 2022,[117] Roze et al., 2021,[116] SHTG, 2022,[25] and Jendle et al., 2019 [114] noted that there was a substantial negative relationship between reducing the utility benefit for the HCL users due to an expected relatively lower FOH compared with the users of the comparator technologies and the incremental QALY gain. To the best of our knowledge, however, 'best-case' and 'worst-case' analyses were not undertaken. It appears that probabilistic sensitivity analyses were performed as CEAC were presented showing the probabilities at which the HCL systems under investigation were likely to be cost effective at various willingness-to-pay thresholds. This was, however, not explicitly stated in the texts.

Assumptions

The studies made several assumptions depending on the type of economic analysis being undertaken. There was significant overlap between studies about the assumptions made, likely due to the homogeneous nature of the economic analyses. For instance, the budget impact analysis in the CADTH report assumed particular figures for the epidemiological measures needed to estimate the market size and financial impact of reimbursing HCL systems. The study also assumed that the reimbursement would be limited to the eligible population but explored this assumption in a scenario analysis by varying the population coverage levels.

All the cost effectiveness analyses except from the study in the SHTG report [25] assumed that their findings were generalisable to their target populations despite using baseline data for other countries. The studies also used short-term simulation data to make long-term projections over patients' lifetimes. The study in the SHTG report used an algorithm to convert improvements in time in range to reductions in HbA1c and assumed that the converted measures compared favourably with their actual estimates. In order to

show that HCL systems were cost effective compared with their comparator technologies, the majority of the cost effectiveness analyses assumed a utility benefit to the HCL users due to the expected greater reduction in diabetes related complications for this group compared with the other technologies.

Discussion

The systematic review identified six studies containing economic analyses of HCL systems. Of the six studies, five were cost effectiveness analyses comparing HCL systems with various diabetes management technologies, whereas one was a budget impact analysis that estimated the financial impact of reimbursing HCL systems over a three-year time horizon. There were two studies conducted in Sweden [114, 115] and one study each in the United Kingdom,[116], Netherlands,[117] Scotland,[25] and Canada.[113] These studies were assessed using the CHEERS and Phillips checklists where applicable.

According to the assessment, four studies were identified as cost effectiveness analyses in their titles i.e. Jendle et al., 2021,[115] Serne et al., 2022,[117] Roze et al., 2021,[116] and Jendle et al., 2019.[114] The other two studies i.e. the study in the SHTG report [25] and the one in the CADTH report [113] did not have the phrase, 'cost effectiveness analysis' or other similar terminology in their titles that would have identified them as economic evaluations but upon further scrutiny of the studies, however, we noted that the SHTG report contained a cost effectiveness analysis in addition to a systematic review and network meta-analysis, while the CADTH report contained a budget impact analysis in addition to a review of the perspectives of HCL users and their carers as well as the ethical considerations of using HCL systems.

All the studies except from the one in the SHTG report [25] had structured abstracts containing information on the background, methods, study perspective, results and conclusions. Although the study in the SHTG 2022 report did not contain an abstract, it had several sections with the relevant information that would normally be found in an abstract. The overall objective of Jendle et al., 2021 was to evaluate the long-term cost effectiveness of the MiniMed 780G HCL system (i.e. Advanced Hybrid Closed Loop System) compared with isCGM+MDI or CSII. The study in the SHTG report examined

the clinical and cost effectiveness of closed loop systems and the artificial pancreas for the management of type 1 diabetes compared with the current diabetes management options. Serne et al., 2022, Roze et al., 2021 and Jendle et al., 2019 assessed the cost effectiveness of the MiniMed 670G HCL system compared with CSII but differed in the way the comparator intervention was configured. Serne et al., 2022 considered the users of isCGM+MDI or CSII, whereas Roze et al., 2021 and Jendle et al., 2019 considered only CSII users.

All the cost effectiveness studies noted that hybrid closed loop systems were cost effective over the lifetime compared with their comparator interventions. This inference was, however, subjective as the studies chose arbitrary willingness to pay thresholds. For instance, despite both Jendle et al., 2021 and Jendle et al., 2019 being conducted in Sweden, Jendle et al., 2019 found the MiniMed 670G HCL system to be associated with an ICER of SEK 164,236 per QALY gained and was thus cost effective at a threshold of SEK 300,000 per QALY gained. Jendle et al., 2021, on the other hand, showed that the MiniMed 780G HCL system was associated with an ICER of 373,700 per QALY gained and was cost effective at a willingness to pay threshold of SEK 500,000 per QALY gained. If a threshold of SEK 300,000 per QALY gained had been used instead, then the MiniMed 780G HCL system would not have been cost effective. The results in Serne et al., 2022 showed that the MiniMed 670G HCL system had an ICER of EUR 6133 per QALY gained compared with the comparator technology and was thus cost effective at willingness to pay thresholds of EUR 20,000, EUR 50,000 and EUR 80,000 per QALY gained. Roze et al., 2021 noted that the MiniMed 670G HCL systems had an ICER of GBP 20,421 per QALY gained which was below GBP 30,000 per QALY gained. The study in the SHTG report [25] noted that closed loop systems were not cost effective compared with CGM+MDI, SMBG+MDI and CGM+MDI since their ICERS were GBP 58,996, GBP 44,920 and GBP 79,604 per QALY gained respectively and they were all above a threshold of GBP 30,000 per QALY gained. If the study had considered a willingness to pay threshold of GBP 80,000 per QALY gained, then closed loop systems would not have been found to be cost effective in all these pairwise comparisons. This

therefore calls for economic evaluations to be undertaken with better justification for the chosen willingness to pay thresholds.

While the IQVIA CORE Diabetes model and the Sheffield type 1 diabetes model are both suited to conduct economic analyses of diabetes management technologies allowing for both deterministic and probabilistic sensitivity analyses to be undertaken; the four studies that use the IQVIA CORE Diabetes model [114-117] are limited in the sense that the model considers only life expectancy, quality adjusted life expectancy, cumulative incidence and time to onset of long-term complications as the outcomes of interest. These outcome measures are, however, sufficient in eliciting the population health gains (or health losses by extension) that are associated with the various diabetes management technologies.

The IQVIA CORE Diabetes model uses time, time in state and diabetes dependent probabilities to simulate progression of diabetes and diabetes related complications with both diabetes and non-diabetes mortality accounted for. The model allows for both clinical and cost data to be inputted directly into the model or for the default parameters to be used instead. The studies identified in this review used the literature to obtain this information. The clinical data includes baseline characteristics such as age, sex, duration of diabetes, total daily insulin dose and HbA1c levels as well as data on the disutilities associated with diabetes related complications. The cost data includes the cost of insulin pumps and accessories e.g. infusion sets and reservoirs, sensors, transmitters, serters, batteries, self-monitored plasma glucose testing, the direct costs of diabetes related complications and the indirect costs if a societal perspective is adopted. The Sheffield type 1 diabetes model used by the study in the SHTG report [25] is also limited in the sense that it relies on published data from outside the United Kingdom to define risk of long-term complications. Furthermore, this risk largely depends on HbA1c ignoring the effects of the other risk factors and could thus introduce bias in the results when evaluating interventions that affect other factors besides HbA1c (Thokala et al., 2013). Given that our objective is to provide evidence to NICE on the cost effectiveness of hybrid closed loop systems in general and our scope is not limited to the interventions that only affect HbA1c, we find the IQVIA CORE Diabetes model to be more appealing than the Sheffield type 1 diabetes model.

A major limitation of most of the cost effectiveness studies is that their findings might not be generalisable. This is because the studies did not use baseline characteristics and treatment effects data for their target populations. The studies relied on studies conducted in the USA for the treatment effects of the MiniMed 670G HCL system, a prospective cohort study conducted in Belgium for the simulation data and treatment effects of isCGM+MDI or CSII as well as a randomised crossover trial in New Zealand for the treatment effect of the MiniMed 780G HCL system despite some controversy around the elicitation of the treatment effect. It is only the SHTG study that used data for its study setting. The assumption made by these studies was that the simulation cohorts despite being for the USA, Belgium and New Zealand were representative of Netherlands, Sweden and the United Kingdom, which is a rather strong assumption. Furthermore, the chosen data sources had varying study designs with different identification assumptions which potentially affected the validity of the results. To extend these studies, therefore, cost effectiveness analyses with appropriate simulation cohorts are needed. Our study does this by using real world data for the United Kingdom to serve as the simulation cohort. We also extend the SHTG study that used the Sheffield type 1 diabetes model to simulate Scottish data by using the IQVIA CORE Diabetes model which obviates some of the limitations of the Sheffield type 1 diabetes model.

6 Companies' submissions of cost effectiveness evidence

6.1 Medtronic submission economics

The Medtronic submission used the iQVIA Core Diabetes Model, henceforth the iQVIA CDM and as described in more detail in section 6.2.1.4 below, to compare the AHCL 780G Minimed pump with the CSII using the 640G Minimed pump. Two comparisons were made with CSII+CGM, the first compared to rtCGM using the Guardian sensor and transmitter and the second compared to isCGM using the Freestyle Libre sensor.

HCL was associated with an HbA1c reduction of 0.8% and both CSII+rtCGM and CSII+isCGM with no change. Thereafter a common annual worsening of the iQVIA default of 0.045% was applied.

The change in HbA1c was derived from the Collyns et al [49] Medtronic funded open label RCT two sequence cross over study of HCL compared to SAP+PLGM. Collyns et al used the HCL 670G Minimed pump, revising the operational mode to implement SAP+PLGM. Collyns et al report a mean baseline of 9.3mmol/l with this improving to 8.5mmol/l in the AHCL arm and worsening slightly to 9.5mmol/l in the PLGS arm, equivalent to approximately a 7.5% HbA1c at baseline and 7.0% HbA1c for AHCL and 7.6% HbA1c for PLGS.

No difference in NSHE was assumed, though it can be noted that time below 3.9mmol/l improved from a baseline of 3.1% to 2.1% for HCL.

Both HCL and CSII+rtCGM were assumed to have no SHEs. For the comparison with CSII+isCGM annual rates of SHEs not requiring medical assistance and requiring medical assistance of 0.65 and 0.25 were stated as being sourced from Östenson et al [124].

Patient population characteristics at baseline were taken from Collyns et al, with a mean age of 23 years, a duration of diabetes of 13 years, a baseline HbA1c of 7.6% and 42% male.

Total annual technology costs were [redacted] for A/HCL 780G, [redacted] for CSII+rtCGM and £3,516 for CSII+isCGM. Other costs were largely sourced from NG17.

For the comparison of 780G with CSII+rtCGM the company estimated totals of 13.89 QALYs and 13.67 QALYs respectively yielding a net gain of 0.21 QALYs. Total costs of £253,583 and £259,400 were estimated, yielding a net cost saving of £5,816 hence dominance for HCL 780G over CSII+rtCGM. A scenario analysis using the net HbA1c gain of 0.3% from the Isganaitis study roughly halved the gain to 0.12 QALYs but net savings of £4,765 persisted so HCL 780G remained dominant over CSII+rtCGM.

For the comparison of HCL 780G with CSII+isCGM the company estimated totals of 13.89 QALYs and 13.19 QALYs respectively yielding a net gain of 0.69 QALYs. Total costs of £253,583 and £240,526 were estimated, suggesting a net cost of £13,057 and an

ICER of £18,672 per QALY. The scenario analysis using the net HbA1c gain of 0.3% from the Isganaitis study slightly reduced the estimated gain to 0.61 QALYs and net costs increased to £14,758 resulting in an ICER of £23,873 per QALY.

The EAG makes the following observations.

- The results of Collyns et al are for AHCL compared to PLGS rather than for HCL compared to CSII+CGM.
- Östenson et al [124], the reference for SHE rates for CSII+CGM, does not specify that patients with T1DM were on CSII+isCGM. The only treatment information that is available is the types of insulin that were received, with 8% receiving only long acting insulin, 65% both short and long acting insulin and 27% receiving other types of insulin. There is no obvious reason why the SHE rates are specific to CSII+isCGM and do not include other regimens such as MDI.
- The ERG is unable to source the annual SHE rates not requiring medical assistance and requiring medical assistance of 0.65 and 0.25 from Östenson et al who reported a mean annual SHE rate of 0.7 among those with T1DM.
- It appears that the iQVIA CDM default quality of life values were used throughout. These relate to T2DM patients with a quality of life value of 0.752 when having no complications, rather than the 0.839 for T1DM patients. Additional survival may have been undervalued.
- The sensors and transmitters for the Guardian system within the costing of the 780G system and CSII+rtCGM were costed at the anticipated April 2023 list price rather than the current list price.
- Both CSII+rtCGM and CSII+isCGM were costed as using the Medtronic 640G pump. There may be a range of other pumps that can be used within both CSII+rtCGM and CSII+isCGM, the costs of which may differ from the Medtronic 640G.
- The sensors and transmitters for a CSII+rtCGM assumed the Guardian system. There may be a range of other sensors and transmitters that can be used, the costs of which may differ.

6.1.1 Dexcom submission economics

Dexcom compares HCL with SAP, also using the iQVIA CDM. This is based upon the results of the six month iDCL trial as reported in Brown et al,[68] where T1DM patients were randomised 2:1 between HCL using the t:slim X2 insulin pump with Control-IQ Technology and SAP. For SAP patients either remained on their existing pump or if on MDI were initiated on pumps with LGS suspended during run in. While not explicit, this suggests that SAP may have been, or largely have been, LGS.

HCL was associated with a 0.34% reduction in HbA1c compared to 0.01% for SAP, and an adjusted net effect of -0.33%. Thereafter a common a common annual worsening of the iQVIA default of 0.045% was applied.

To estimate the number of NSHEs Dexcom uses the number of days with at least one reading below 3.0mmol/l (54mg/dL): 129 among the 112 patients in the HCL arm and 72 among the 56 patients in the SAP arm. These correspond to annual NSHE event rates of 2.30 and 2.57 respectively.

The HFS was also collected in the iDCL survey. In addition to applying the TTO quality of life function of Lauridsen et al [19] the company also used the HFS1-ws to EQ-5D function to estimate an additional annual quality of life benefit of 0.0424.

No SHEs were observed during the iDCL and none were assumed for the base case.

Patient population characteristics were largely drawn from Brown et al, with a mean patient age of 33 years, a duration of diabetes of 16 years, a baseline HbA1c of 7.4% and 50% being male.

For the base case it appears that HCL was assumed to be the same cost as SAP. Given the modelled benefits HCL dominated SAP, saved £3,744 over the patient lifetime due to reduced costs of complications and yielded an additional 1.034 QALYs. Sensitivity analyses suggested that HCL would have to have a net annual cost compared to SAP of £1,171 for the ICER to rise to £20,000 per QALY, and of £1,667 for the ICER to rise to £20,000 per QALY.

The ERG makes the following observations.

- The supplementary material of Brown et al reported mean weekly NSHE rates of 5.3 for HCL patients and 5.2 for SAP patients, these falling to 3.3 and 4.3 respectively at 6 months with a net adjusted effect of -1.1. It is unclear whether these are actual NSHEs or periods below range. The weekly rates at 6 months correspond to annual rates of 172 and 224 and a difference of 52, which is similar to the difference of 57 implied by the net adjusted effect estimate.
- The Dexcom estimated NSHEs as the number of days with at least one measurement below 3.0mmol/l (54mg/dL). It seems more usual for a given period of time below 3.0mmol/l to be used as a proxy for NSHEs.
- The EAG thinks that it is invalid to use both the Currie et al HFS1-ws to EQ-5D function and the Lauridsen et al NSHE quality of life function to estimate the quality of life effects of NSHEs.[19, 23] Only one should be used to avoid double counting as reviewed in greater detail in section 6.2.1.6 below. It is also not clear from the Dexcom submission if the HFS1-ws or HFS2-ws was inputted to the function of Currie et al. For these reasons the EAG thinks this aspect of the modelling should be excluded. Dexcom provided this scenario which reduced the net gain from 1.034 QALYs to 0.150 QALYs.
- HCL and SAP may be able to use different sensors and pumps. It may not be valid to assume no additional cost of HCL compared to SAP.
- It can also be noted that during the 6 month trial Brown et al report the following unscheduled visits, which might suggest an additional annual unscheduled visit during the first year for HCL compared to SAP even if device update related visits are excluded.

Table 10: Brown et al: Unscheduled visits

Unscheduled visits	HCL (N=112)	SAP (N=56)
Study supplies-related	41 (37%)	6 (11%)
Device update process/logistics	14 (13%)	0 (0%)
Device issue-related	9 (8%)	1 (2%)
Device training-related	6 (5%)	0 (0%)

Diabetes management-related	1 (1%)	3 (5%)
Review/change device configuration setting	1 (1%)	3 (5%)
Consent-related	1 (1%)	1 (2%)
Device data-related issue	2 (2%)	0 (0%)
Protocol/procedural training-related	1 (1%)	0 (0%)
Total (more than 1 reason possible per visit)	68 (61%)	13 (23%)

6.1.2 Tandem submission economics

The Tandem submission referenced the Dexcom submission economics, and provides no additional cost effectiveness estimates.

6.1.3 Camdiab submission economics

Camdiab presented two cost effectiveness modelling exercises, one based upon the Dan05 study among patients aged 6 to 18 years using the [redacted] and the other based upon the KidsAP02 study among patients aged 1 to 7 years using the [redacted]

6.1.3.1 Camdiab Dan05 study economics

The Dan05 trial, reported in greater detail in Ware et al [57], compared HCL using the CamDiab algorithm with usual care, 3 months prior pump use being an inclusion criterion. It recruited 133 children with a mean age of 13 years, a mean duration of diabetes of 6.3 years, 43% male and a mean baseline HbA1c of 8.2% in the HCL arm and 8.3% in the control arm.

At 6 months HbA1c had fallen to 7.6% and 8.1% respectively, with an adjusted net effect of -0.32%. Time below 3.9mmol/l remained the same in the HCL arm at 6.1% but increased from 4.9% to 5.4% in the control group. Ware et al note that there were seven SHEs, four of which were in the HCL arm and 3 in the control arm, and 2 DKA events, all in the HCL arm.

The Dan05 study was complicated by the HCL arm being split between FlorenceM using the Medtronic 640G pump and CamAPS FX using the Dana RS pump. Due to problems

with the FlorenceM, HbA1c results were based upon the CamAPS FX subset of the HCL arm.

In a post hoc analysis of the HCL CamAPS FX group (N=21) against its control (N=25) baseline HbA1c was 7.9% for CamAPS FX compared to 8.0% for control. At 6 months this had fallen to 6.8% and 7.9% respectively, with an adjusted net effect of -1.05%. Time below 3.9mmol/l rose from 8.6% to 10.8% for CamAPS FX compared to falling from 8.7% to 6.3% for control, with an adjusted net effect of +3.13%.

The ERG makes the following observations:

[redacted]

Table 11: Dan05 EQ-5D values

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Table 12: Dan05 severe hypoglycaemic events

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n.r.: not reported				

[redacted]

† [redacted].

[redacted]

Table 13: Dan05 unscheduled contacts and visits

	[redacted]		[redacted]	
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

6.1.3.2 Camdiab KidsAP02 study economics

The KidsAP02 cross-over trial, reported in greater detail in Ware et al [56], compared HCL using the CamDiab algorithm and DanaRS pump and Dexcom transmitter with SAP. It recruited 74 children with a mean age of 5.6 years, a mean duration of diabetes of 2.6 years, 58% male and a mean baseline HbA1c of 7.3%. During the closed loop period HbA1c fell to 6.6% in the treatment arm compared to 7.0% in the control arm, a mean adjusted difference of 0.4%. Median time below 3.5 mmol/l was 2.6% and 2.4% respectively, with a mean adjusted difference of +0.04%, while median time below 3.0 mmol/l was 1.0% and 0.9% respectively, with a mean adjusted difference of +0.02%. There was one SHE in the CamDiab arm and none in the SAP arm.

[redacted]

[redacted]

The ERG makes the following observation.

- [redacted]

6.1.4 Summary of companies' economic modelling

The inputs and outputs of the companies' economic modelling are summarised below.

Table 14: Company submission economics summary: Baseline characteristics and inputs common to both arms

	Medtronic	DexCom/Tandem	CamDiab Dan05	CamDiab KidsAP02
Baseline characteristics				
Mean age	23.5 (7.0)	33 ±17	[redacted]	[redacted]
Male %	42%	50%	[redacted]	[redacted]
Duration diabetes	13 (10.2)	16	[redacted]	[redacted]
HbA1c	7.6% (0.9)	7.4% ±0.9	[redacted]	[redacted]
Costs of hypoglycaemic events				
NSHE	£0	£0	[redacted]	[redacted]
SHE non-medical	£489	£4.35	[redacted]	[redacted]
SHE medical	£2,358	£1,544	[redacted]	[redacted]
Disutilities hypoglycaemic events				
NSHE daytime	..	-0.004	[redacted]	[redacted]
NSHE night time	..	-0.008	[redacted]	[redacted]
SHE non medical	-0.0137	..	[redacted]	[redacted]
SHE medical	-0.0578	..	[redacted]	[redacted]
SHE any daytime	..	-0.047	[redacted]	[redacted]
SHE any night time	..	-0.051	[redacted]	[redacted]

Table 15: Company submission economics summary: Model clinical inputs and outputs

Company	Medtronic	DexCom/Tandem	CamDiab Dan05	CamDiab KidsAP02
Model	iQVIA CDM	iQVIA CDM	[redacted]	[redacted]

Regime	HCL	CSIIrtCGM	CSIIisCGM	HCL	SAP	[redacted]	[redacted]	[redacted]	[redacted]
Pump	780G	640G	n.r.	T:slim X2	n.r.	[redacted]	[redacted]	[redacted]	[redacted]
Clinical effects									
HbA1c	-0.8%	0.0%	0.0%	-0.33%	0.00%	[redacted]	[redacted]	[redacted]	[redacted]
NSHE	..	..	..	2.30	2.57	[redacted]	[redacted]	[redacted]	[redacted]
SHE non-medical	0	0	0.65	0	0	[redacted]	[redacted]	[redacted]	[redacted]
SHE medical	0	0	0.25	0	0	[redacted]	[redacted]	[redacted]	[redacted]
SHE total	0	0	0.90	0	0	[redacted]	[redacted]	[redacted]	[redacted]
QoL direct effect	..	..	..	+0.0454	0	[redacted]	[redacted]	[redacted]	[redacted]
Annual cost	[redacted]	[redacted]	£3,516	£0	£0	[redacted]	[redacted]	[redacted]	[redacted]
Results									
LY undiscounted	42.79	41.67	41.67	42.59	42.27	[redacted]	[redacted]	[redacted]	[redacted]
LY discounted	20.57	20.34	20.34	20.62	20.54	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	13.89	13.67	13.19	14.12	13.08	[redacted]	[redacted]	[redacted]	[redacted]
Net vs comp.		0.21	0.70		1.03		[redacted]		[redacted]
Costs	£253,583	£259,400	£240,526	£86,341	£90,085	[redacted]	[redacted]	[redacted]	[redacted]
Net vs comp.		-£5,816	£13,057		-£3,744		[redacted]		[redacted]
ICER vs comp.		Dominant	£18,672		Dominant		[redacted]		[redacted]

[redacted]

n.r.: not reported

6.2 Independent economic assessment

6.2.1 Methods

6.2.1.1 Patient population

The key baseline characteristics are drawn from the 2019-20 National Diabetes Audit subgroup of those on pump therapy. For the scenario analyses that uses the adult NHSE pilot data, the baseline characteristics are taken from the pilot.

Table 16: Baseline characteristics

	National Diabetes Audit		NHSE adult pilot	
	Mean	s.d.	Mean	s.d.
Age	43.4	17.8	40	16.3
Duration diabetes	24.8	15.6	21	11.8
HbA1c	8.0	1.1	9.4	2.0
Male	42%	n.a.	33%	n.a.
Race				
White	97%	n.a.	96%	n.a.
Black	1%	n.a.	1%	n.a.
Asian	2%	n.a.	3%	n.a.

Other baseline characteristics needed as inputs to the iQVIA CDM are taken from NG17, these largely being derived from the Repose trial of pumps against MDI as reported in Heller et al [125]. It can be noted that these characteristics relate to a slightly more poorly controlled group of patients, their baseline HbA1c being 9.1% at baseline. Patients were excluded if they had used a pump in the last three years, and among those randomised to pump therapy a 0.85% improvement was observed which brings it into line with that of the National Diabetes Audit pump subgroup. Unfortunately, in common with the HCL trials the Repose trial did not report changes in other baseline characteristics that might have been affected by pump adoption, such as SBP. The other baseline characteristics are reported in appendix 9.2.

6.2.1.2 Treatment options to be evaluated

The cost effectiveness analysis considers the three comparators within the EAG NMA:

- CSII+CGM non-integrated
- LGS/PLGS
- HCL

CSII+CGM is not separately evaluated as CSII+rtCGM and CSII+isCGM. Based upon feedback from the Diabetes Technical Network the balance is assumed to be 10% CSII+rtCGM and 90% CSII+isCGM for adult patients[‡], though this may underestimate CSII+isCGM use. The EAG scenario analysis that applies the NHSE adult pilot data CSII+CGM applies 100% CSII+isCGM due to prior use of CSII+isCGM being reported as a requirement.

6.2.1.3 Framework: methods of synthesis

HbA1c effects

The EAG base case applies the results of the NMA. The EAG also presents scenarios restricting the NMA evidence base to adult trials and applying the mean change of the NHSE adult pilot.

Table 17: EAG HbA1c (s.e) changes

	NMA	NMA adult	NHSE pilot adult
HCL	-0.28% (0.033%)	-0.24% (0.043%)	-1.50% (0.051%)
PLGS	-0.06% (0.079%)	-0.01% (0.115%)	..
CSII+CGM	0.00%	0.00%	..

The base case assumes that the HbA1c effect endures for the model time horizon of 50 years. Scenarios of durations of 5 years, 10 years and 20 years are presented.

[‡] Paediatric patients may have a higher rtCGM proportion of around 25%, in part due to higher Omnipod use.

NSHE and SHE rates

NSHE rates were not reported in the trials. As reviewed in more detail below, where they were reported they were typically based upon proxies such as the number of periods of 20 minutes or more spent below 3.0mmol/l. The EAG presents a brief review of the literature on NSHE and SHE rates before presenting scenario analyses that estimate NSHE and SHE rates based upon estimates in the literature coupled to the EAG NMA results for time below range.

The SHTG report estimated NSHEs from Donnelly et al [126]: a randomly drawn sample of 267 T1DM and T2DM insulin treated patients in Tayside during 2001. These patients were asked to record their hypoglycaemic events for one month. Among the T1DM patients (N=94), who had a mean age 41 years, a mean duration of diabetes 10 years, were 49% male and had a mean HbA1c of 8.5%, the numbers of NSHEs and SHEs were 327 and 9 respectively, suggesting per patient average annual rates of 42 for NSHEs and 1.15 for SHEs. The SHTG assumed that these rates apply to MDI+SMBG as is reasonable given the 2001 data and that patients were advised to check their blood glucose 2-4 times daily with a portable glucose meter. The SHTG coupled these with reductions of 50% for HCL from [127], 35% for MDI+rtCGM from Beck et al [128], 25% for MDI+isCGM from Bolinder et al [129] and an assumption of 30%, the midpoint of the MDI+rtCGM and MDI+isCGM values, for CSII+CGM. This implies annual NSHE rates of 21 for HCL and 29 for CSII+CGM.

Note in passing that the 1.15 annual average for SHEs of Donnelly et al is an order of magnitude greater than the 0.115 annual rate for SHEs requiring NHS resource use that Leese et al [4] estimated across all T1DM patients in Tayside (N=977), average age 33, average duration diabetes 17 years, 57% males and a mean 7.92% HbA1c. These estimates if taken together suggest that only 10% of SHEs require NHS attention which is somewhat less than the EAG base case of 37.9% as summarised in section 833910208.499.833910208.499 below.

McAuley et al [127], sponsored by JDRF Australia, compared HCL using the Medtronic 670G with MDI+SMBG or CSII+SMBG over six months among 120 T1DM patients, mean age 44 years, mean duration diabetes 24 years, 47% male and a mean of 7.4%

HbA1c. In the HCL group (N=61) there were 8 SHEs, of which 4 were attributed to the study device, while in the control group (N=59) there were 7 SHEs. These correspond to annual SHE rates of 0.26 and 0.24 respectively, a ratio of 111%, but when only including SHEs attributable to HCL annual SHE rates of 0.13 and 0.24 respectively, a ratio of 55%. Unfortunately, McAuley et al do not specify how SHEs were attributed to device or other causes. Turning to the time below range, both HCL and control showed improvements over the course of the trial. The net effects favoured HCL with the percentage time below range improving by 2.0%, 0.8%, 0.6% and 0.4% for 3.9 mmol/l, 3.3 mmol/l, 3.0 mmol/l and 2.8 mmol/l respectively. Applying these net changes to the end of trial control arm time below ranges of 3.8%, 1.4% 0.9% and 0.6%, the ratios of time below range[§] that result are 47%, 43%, 33% and 33%. These ratios may be subject to quite considerable rounding error but show some alignment with the 55% SHE ratio that excludes SHEs not attributable to HCL. But it must be acknowledged that this in turn begs the question of how to handle SHEs not attributable to HCL in the HCL arm for any comparison with the control arm.

In a similar vein the RCTs of HCLs that reported SHEs and ratios of time below range are presented below. Few papers reported NSHEs and those that did used proxies:

- Kariyawasam et al [130] used the number of events below 3.9mmol/l
- Brown et al (Brown, 2019 #132} and Breton et al [69] used the median numbers of events of at least 15 minutes ≤ 3.0 mmol/l
- Abraham et al [67] used the median numbers of events of at least 20 minutes ≤ 3.0 mmol/l

The median weekly NSHE rates at end of trial reported by Abraham et al of 2.1 for control and 1.1 for HCL are notably different from the numbers of moderate hypoglycaemia events reported in the supplementary appendix of 7 and 13 respectively. The former imply annual event rates of 57 for HCL and 109 for control, while the latter imply annual event rates of 0.21 and 0.38. But the ratios of these events are similar at

[§] While a percentage of e.g. 0.9% may at first sight seem small it corresponds with an hourly 1.5 per week.

53% and 55%, which are also quite similar to the ratios of the time below range as reported below.

Table 18: RCTs NSHE and SHE rates and ratios and time below range ratios

Lead author	Abraham	Brown	McAuley	Ware	Boughton	Breton	Ware	Benhamou	Tauschmann	Thabit	Thabit	Kariyawasam
Published	2021	2019	2020	2022	2019	2022	2022	2019	2018	2015a	2015b	2021
Study wks	26	26	26	26	16	16	16	12	12	12	12	6
Comparator	Mixed	CSII*	Mixed	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*	CSII*
Age	15	33	44	13	68	11	5.6	48	22	40	12	8.2
Dur. diabetes	7.7	17	24	6.5	38	5.2	2.6	28	12	21	4.7	5.5
Male	44%	50%	46%	43%	57%	50%	58%	38%	49%	55%	56%	47%
HbA1c base	7.75%	7.40%	7.80%	8.25%	7.45%	7.7	7.35%	7.60%	7.90%	7.60%	7.80%	7.25%
NSHEs annual												
Comparator	109.2	26.0	n.r.	n.r.	n.r.	31.2	n.r.	n.r.	n.r.	n.r.	n.r.	24.5
HCL	57.2	20.8	n.r.	n.r.	n.r.	20.8	n.r.	n.r.	n.r.	n.r.	n.r.	13.0
Ratio	52%	80%	..	..	..	67%	..	..	..	..	..	53%
SHEs annualised												
Comparator	0.00	0.00	0.24	0.00	0.38	0.00	0.00	0.19	0.20	0.00	0.00	0.00
HCL	0.00	0.00	0.26	0.06	0.00	0.00	0.04	0.32	0.17	0.13	0.35	0.00
Ratio	100%	100%	111%	..	0%	100%	..	167%	86%	..	..	100%
Excl. non attr.			0.13									
Ratio			55%									
Time ratios												

≤ 3.9 mmol/l	54%	61%	47%	110%	94%	78%	102%	44%	79%	81%	83%	50%
≤ 3.5 mmol/l	n.r.	n.r.	n.r.	n.r.	100%	n.r.	102%	n.r.	84%	n.r.	n.r.	n.r.
≤ 3.3 mmol/l	44%	n.r.	43%	n.r.	n.r.	n.r.	n.r.	35%	n.r.	n.r.	n.r.	n.r.
≤ 3.0 mmol/l	50%	97%	33%	n.r.	100%	77%	102%	n.r.	n.r.	n.r.	n.r.	56%
≤ 2.8 mmol/l	50%	n.r.	33%	n.r.	n.r.	n.r.	n.r.	29%	118%	45%	47%	n.r.
Mixed comparators: Abraham: CSII+CGM and MDI+CGM, McAuley: CSII+SMBG and MDI+SMBG. Others CSII* was in conjunction with CGM												

For individual studies, the reductions in time below range tend to be similar across the thresholds though Brown et al and Thabit et al do not follow this pattern.

Among the papers that report NSHEs there is a reasonable if imperfect correspondence between the reduction in NSHEs and the reduction in time below range. But there is a degree of circularity in this due to the definition of NSHEs not being symptomatic events but the number of times patients fell below a mmol/l threshold for at least a given amount of time.

Rates of SHEs are low but vary between the papers even for just their HCL arms. There is no obvious pattern between comparator and HCL, or with the time below range ratios.

Turning to rates of NSHEs within the two main quality of life studies reviewed in more detail in section 6.2.1.6 below, Gordon et al [131] and Currie et al [23], NSHEs were defined symptomatically with Gordon et al relying upon trial data and Currie et al relying upon postal questionnaire 3 month recall data with a 31% response rate. Gordon et al did not report NSHE rates. Currie et al reported an annualised symptomatic NSHE rate for the T1DM subset of 37.6 which given that the surveys were in 2000 and 2006 probably related mainly to MDI. This needs to be read in conjunction with the reported annual SHE rate of 1.47 and the 31% response rate. But the 37.6 annual NSHE rate corresponds quite closely to the 42 annual NSHE rate reported in Donnelly et al [126] from which the SHTG inferred annual NSHE rates of 21 for HCL and 29 for CSII+CGM. This in turn corresponds quite closely with the common 20.8 annual NSHE rate for HCL reported in Brown et al and Breton et al.

Due to there being no direct RCT evidence of the effects of HCL upon NSHEs the EAG does not include NSHE effects in its base case. Given the range of reported SHE rates the EAG also does not include SHE effects in its base case.

For NSHEs the EAG presents a scenario analysis that couples the 20.8 annual NSHE rate for HCL of Brown et al and Breton et al with the EAG NMA time below 3.0 mmol/l net effect estimates, the weighted mean of the end of trials' time below 3.0 mmol/l for the

CSII+CGM and the assumption that the number of NHSEs is proportionate to the time below 3.0 mmol/l. Scenarios of annual NSHE rates of 57.2 and 13.0 for HCL are presented.

For SHEs the EAG adopts the same approach in exploratory scenarios that assumes SHE rates are proportionate to time below 3.0 mmol/l. Note that this is not saying that the threshold for SHEs is 3.0mmol/l, only that the best measure of whatever is the appropriate threshold for SHEs is likely to be itself proportionate to time below 3.0mmol/l. Coupled with the annual SHE rate for HCL of 0.26[**] as reported in McAuley et al, chosen due to it being a 26 week study and a reasonable midpoint, results in the following estimates.

Table 19. EAG estimates of NHSEs and SHEs for main scenario analysis

	Time below 3.0mmol/l				
	NMA net	Absolute	Ratio	NSHEs	SHEs
HCL	-0.14%	0.46%	100%	20.8	0.26
PLGS	-0.16%	0.44%	96%	19.9	0.25
CSII	Reference	0.60%	130%	25.9	0.32

The annual SHE rates correspond reasonably closely with the NHSE adult pilot annual rates of 0.21 at baseline and 0.34 at six months.

[**] These are reasonably similar to the 0.20 annual SHE rate for CSII+CGM that was applied in the DG21 assessment of sensor augmented pump therapy for T1DM patients. The mean annual SHEs of 0.1855 for rtCGM and 0.1358 for isCGM of NG17 suggest an annual rate of around 0.14. The second year annual SHE rate of 0.30 for those on pumps in the Repose trial is also reasonably aligned with this, bearing in mind that CGM was not a requirement.

6.2.1.4 Treatment pathways and modelling

Treatment pathway

The treatment pathway assumes that patients remain on a single treatment option throughout: CSII+CGM, PLGS or HCL.

Modelling of HbA1c effects: iQVIA Core Diabetes Model summary

In line with DG21 and NG17 the EAG uses the iQVIA CDM to model the micro and macro vascular complications of diabetes and patients' overall survival. This decision is in part due to its availability to the EAG at the start of the DAR process, but is mainly due to precedents with NG17 noting:

"*The previously published IQVIA CDM (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*."

There is also the benefit of a direct comparability with most of the industry submissions' economic modelling. But it should be borne in mind that the SHTG modelling used the Sheffield model.

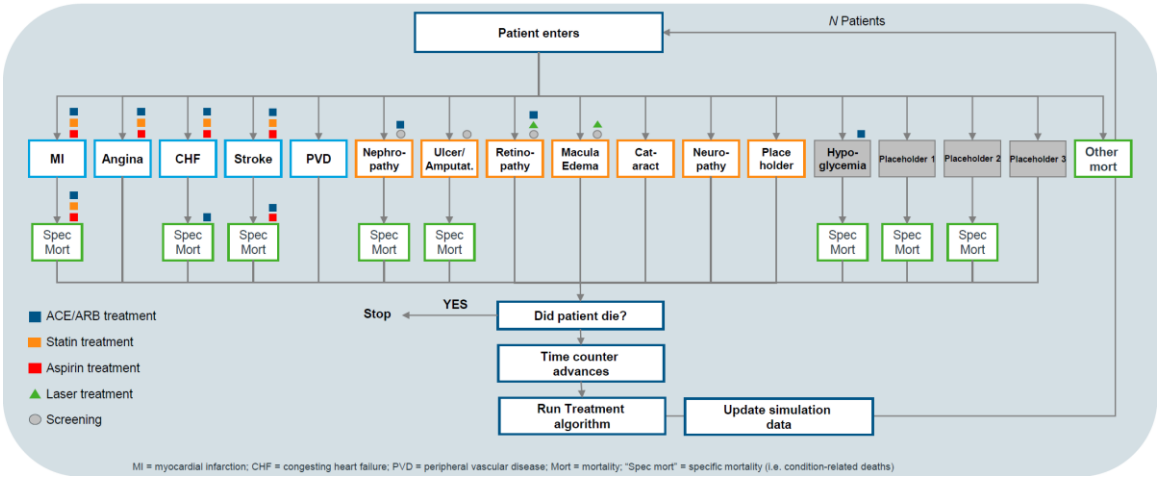


Figure 20: iQVIA CDM structure[††]

In brief, as shown in the model diagram above, the iQVIA CDM predicts the progress of patients with T1DM over their lifetime, modelling the incidences of the 11 macro and micro vascular complications the likelihoods of which are affected by T1DM. The default and recommended setting are to sample 1,000 patients from the patient characteristics and run each of these patients through the model 1,000 times.

The iQVIA team has advised the EAG that for modelling a T1DM cohort only the non-specific mortality approach should be use as per the diagram above, and not the combined approach of the T2DM UKPDS 62 and UKPDS 82 studies. Given the event specific mortality, to estimate the non-specific mortality by age, "Other Mort" in the diagram, the EAG adjusts UK life table data to remove deaths due to the ICD10 codes for CVD, cerebrovascular disease and renal failure as presented in appendix 9.6. The iQVIA modelling team have indicated that removal of deaths due to the ICD10 codes for hypertension may also be reasonable and the EAG presents this in a scenario analysis. The iQVIA CDM team indicate that for T1DM this approach requires that the non-combined modelling of mortality be selected.

Modelling of HbA1c effects: iQVIA Core Diabetes Model validation work

Both Palmer et al [122] and McEwan et al [123] presented model validation work for previous versions of what was then the IMS CDM. McEwan et al is the more recent paper, probably used a more recent version of the CDM and with the DCCT/EDIC study has a study with a large number of patients and a long follow up and is consequently preferred by the EAG. But only Palmer et al reported validation work around overall survival, and the EAG turns to this at the end of the review.

[††] Diagram courtesy of the iQVIA CDM team

McEwan et al modelled the internal validity of what was then the CDM version 8.5 in predicting events for the DCCT cohort with follow-up of 5.0 to 6.5 years and the EDIC cohort with follow-up of 17 to 30 years.

Table 20: DCCT and EDIC events: Observed vs modelled

		Trial observed			CDM v8.5 modelled		
Study	Event	Treat.	Control	Net	Treat.	Control	Net
DCCT	Retinopathy	23	91	-68	18	91	-73
N=1,441	Neuropathy	7	28	-21	8	30	-22
5.0-6.5 yrs FU	Microalb.	55	103	-48	72	105	-33
	Albuminuria	9	9	0	6	10	-4
DCCT/EDIC	CV events	25	38	-13	38	43	-5
N=1,226	Retinopathy	153	356	-203	200	211	-11
17-30 yrs FU	Neuropathy	66	178	-112	101	83	18
	CVD	66	100	-34	115	118	-3
	ESRD	7	14	-7	26	23	3

Validation is reasonable for the DCCT study, suggesting that the CDM is relatively good at modelling events over a medium time horizon. But given the lifetime modelling of most cost effectiveness analyses the validation for the DCCT/EDIC study is the more relevant. McEwan et al reported the relative risks of events for the CDM compared to the trial, but for cost effectiveness modelling the differences in the absolute numbers of events are the more relevant metric. It is not reported why McEwan et al group CV events given the CDM model structure, but this may have been due to trial reporting necessitating this.

The control arm of the DCCT/EDIC is now obsolete. Concentrating upon the DCCT/EDIC intensive treatment arm, the iQVIA CDM overestimated all events for the treatment arm, this being most serious for ESRD for which the model estimate was 26 compared to the observed 7: more than triple the observed at 371%. But CV events, retinopathy, neuropathy and CVD were also overestimated, the modelled incidences being 152%, 131%, 153% and 174% respectively of those observed in the trial. The EAG

presents a scenario analysis that reduces these costs proportionately to their overestimation as reported in McEwan et al. This mainly affects the costs of eye and renal complications due to their high annual costs. This scenario does not address the effects of any possible overestimation of eye and renal complications upon quality of life and overall survival.

It can be noted that Palmer et al also examined the observed versus the modelled incidences of ESRD over time and found a very good correspondence with data from 1,075 US T1DM patients recruited prior to the age of 18 years, a 25 year cumulative incidence of 9.1% observed compared to 8.9% modelled. It is unclear whether this model validation was internal, using a study used to construct the CDM, or external, trying to model the outcomes of a study not used in the construction of the CDM.

It is particularly important to model ESRD correctly within the CDM due to its large effect upon quality of life, a disutility of 0.164 for haemodialysis and 0.204 for peritoneal dialysis compared to a patient with no complications, and its very large ongoing annual cost of £34,613 for haemodialysis and £31,139 for peritoneal dialysis. The effects of the modelled ESRD upon QALYs, costs and the ICER bear particular scrutiny.

Unfortunately, McEwan et al did not report the corresponding survival percentages. Any modelled differences in overall survival may drive the ICER to a somewhat greater extent than the modelled differences in vascular events and albuminuria. This somewhat limits the usefulness of the validation exercise for assessing the reasonableness of using the CDM for economic assessments. This may also be the reason for the incidence of ESRD being modelled as higher in the treatment arm than in the control arm, the reverse of that observed. Time spent with ESRD would have been a better comparison, but data for this comparison may not have been available for the trial.

Turning back to Palmer et al, they reported the observed overall proportion surviving compared to that modelled for a cohort of 142 US T1DM patients in the Joslin clinic who were all recruited prior to the age of 21 years.

Table 21: Joslin clinic survival: Observed vs modelled

	Observed	Modelled
At 4 years	99%	99%
At 10 years	97%	95%
At 15 years	96%	87%
At 20 years	88%	79%
At 25 years	81%	70%

Again, the observed values and the CDM modelled values were reasonably aligned in the medium term but diverged somewhat in the longer term. This may argue for exploring the effect that shorter time horizons have upon the ICER, and if modelling children or adolescents keeping a weather eye on the considerably longer time horizons that have to be modelled to effect a lifetime time horizon.

The Mount Hood challenges invite diabetes modellers to test their models against long term follow up data in competition with other modellers. The EAG has identified the 1st, 4th, 5th, 8th and 9th challenges as being published in peer reviewed journals, but of these only the 4th held in 2004 reported validation data on model performance for T1DM patients.

The Mount Hood 4 Modelling Group [132] reported the results for two models that attempted to replicate the DCCT for the primary prevention cohort at 9 years, CORE and Archimedes‡‡. Only the micro-vascular complications that could be compared with published DCCT data were presented, results for the Archimedes model being very similar to those of the CORE model.

Table 22: 4th Mount Hood Challenge: CORE model T1DM results

	DCCT			CORE		
Arm	Control	Intense	Net	Control	Intense	Net

‡‡ A third model, EAGLE, attempted to reproduce results for the secondary prevention cohort.

Microalbuminuria	27.3%	16.0%	-11.3%	27.7%	14.9%	-12.8%
Back. retinopathy	52.2%	14.3%	-37.9%	39.4%	14.4%	-25.0%
Periph. neuropathy	63.2%	27.7%	-35.5%	64.0%	25.0%	-39.0%

The CORE model estimated 9 year cumulative incidences for the intensive care arm quite well, but estimates for the control arm were more variable. This caused the net estimates of microalbuminuria to be closely aligned, peripheral neuropathy to be reasonably aligned and background retinopathy to be poorly aligned with those of the DCCT. Within the above it should be borne in mind that the control arm of the DCCT is obsolete and that only the intensive treatment arm has any relevant today.

The above may appear critical of the validity of the iQVIA CDM as longer time horizons are modelled. It is almost inevitable that uncertainty around modelled outputs will increase as the time horizon extends and that observed values will diverge to some extent from that modelled. While the validation work suggests a less than perfect correspondence between the model and real life, the availability of the validation work is a strength. Much of the economic modelling presented to NICE within other workstreams such as STAs relies upon short term trials extrapolated to lifetime horizons for which no parallel validation work is possible. It should also be borne in mind that the iQVIA CDM continues to evolve.

The ability of the iQVIA CDM to reliably simulate a T1DM paediatric population is an open question, being affected by both the longer duration that is required for a lifetime horizon and the degree to which the risk equations of the model relate to a paediatric population. A key source for T1DM model inputs appears to be the DCCT/EDIC trial which recruited patients between 13 and 39 years, with a mean baseline age of 27 years and a standard deviation of 7.1 years. If normally distributed this would imply that of the 1,441 recruited at baseline around 24 (2%) would have been up to 12 years, 40 (3%) between 13 and 15 years and 80 (6%) between 16 and 18 years: a total of 144 (10%) being up to 18 years of age at baseline. At close of the DCCT the mean age had increased to 33 years while at EDIC 18 years follow up it had risen to 52 years meaning that the

great majority of the DCCT/EDIC data will relate to an adult population. An alternative to the EDIC CVD model in the iQVIA CDM is the Pittsburg CVD model, this being based upon Epidemiology of Diabetes Complications Study (EDC) which recruited 658 subjects with childhood onset of diabetes before the age of 17 years and has followed them up for 22 years. If modelling a younger population this suggests at a minimum exploring the effect of the Pittsburg CVD model. The EAG remains uncomfortable simulating a paediatric population using the iQVIA CDM but presents a scenario of this in appendix 9.5.

Modelling of HbA1c effects: HbA1c progression

The iQVIA CDM default for HbA1c progression is an annual 0.045% worsening. This is drawn from the DCCT/EDIC trial as reported in Nathan et al [133]. The DCCT trial compared intensive therapy with conventional therapy among 1,441 patients with T1DM. A primary prevention cohort with a duration of diabetes of 1-5 years had to have no history of hypertension, cardiovascular disease, neuropathy requiring treatment or retinopathy. A secondary intervention cohort could have a duration of diabetes of 1-15 years had to have at least one microaneurysm on one eye. Intensive therapy included MDI with a minimum of three daily injections or CSII with patient specific HbA1c goals. Conventional therapy was standard of care in the 1980s, typically one or two daily injections and SMBG or urine testing, with the only HbA1c goal being the avoidance of values over 13.5%. EDIC provided long term follow up to the DCCT. After DCCT and prior to enrolment in EDIC all in the conventional therapy arm were offered training in intensive therapy. The DCCT was a controlled trial, the EDIC observational.

Tabulated data suggests that at the end of the DCCT for the intensive therapy arm the median HbA1c was 7.2%. Figure 1 of Nathan et al is reproduced below, the values being taken from the graph.

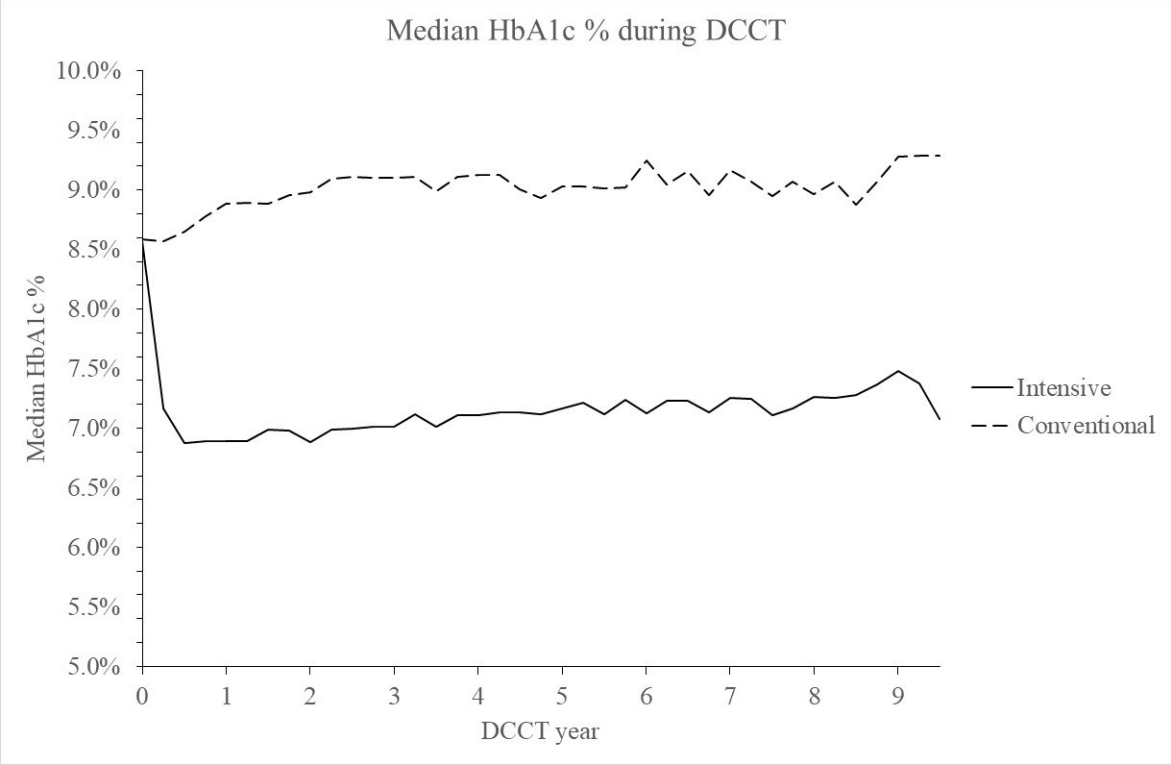


Figure 21: Median HbA1c during the DCCT trial

The reasons for downturn at the end of intensive therapy are unclear, the graphed value appearing to be below the reported 7.2% for the end of the DCCT phase. Values prior to this also appear slightly higher than 7.2%.

The EAG estimates that in the intensive therapy arm median HbA1c at 6 months was 6.88% while at 9 years it was 7.48% which suggests an annual worsening of 0.07%. Applying the stated end of DCCT value of 7.2% suggests and annual worsening of 0.04% which is reasonably aligned with 0.045% default of the iQVIA CDM. But this ignores the long term EDIC follow up as graphed below.

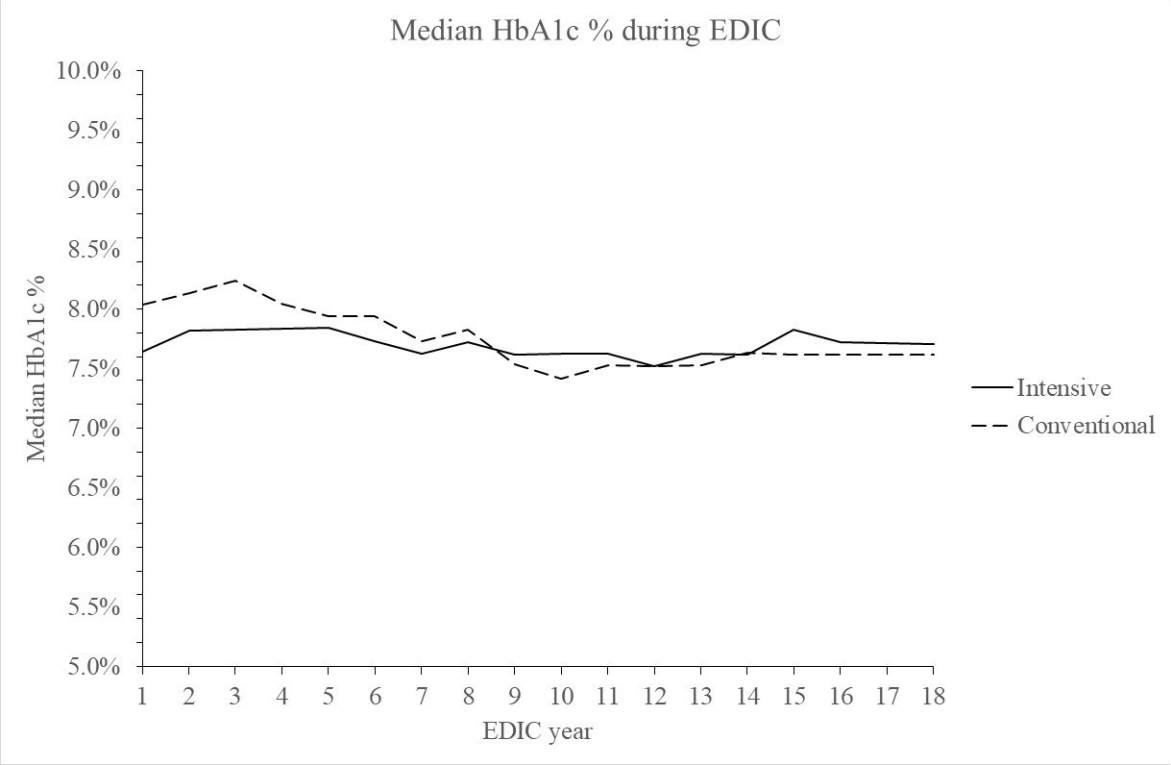


Figure 22: Median HbA1c during the EDIC extension trial

The EAG estimates that for those initially on intensive therapy who continued on it during EDIC at EDIC baseline the median HbA1c was 7.64% and at 18 years was 7.71% which suggests little to no annual worsening during EDIC. Nathan et al tabulate an end of EDIC value of 8.0%. which over the course of EDIC might suggest an annual worsening of 0.02% in the intensive care arm.

Combining the tabulated 8.0% end of EDIC value with the EAG estimates of a 6 month DCCT of 6.88% suggests an annual worsening over the 26.5 years[§§] of 0.042% which is aligned with the iQVIA CDM value of 0.045%.

It should be noted that both the DCCT and the EDIC are relatively old and of questionable relevance to the current appraisal. The DCCT control arm is obsolete. There

[§§] Ignoring the intervening training period.

was a slight upwards trend among the intensive care arm during the DCCT but this may have reflected "trial fatigue", or the incidence of hypos, or in the early years concern about retinopathy and "glycaemic re-entry". Follow-up in the DCCT intensive care arm was intensive with frequent visits. This intensity of follow-up was not carried through to EDIC which could account for any general worsening during EDIC rather than it being due to any underlying disease progression. It can also be noted that when the DCCT control group moved to EDIC and transferred to the intensified insulin regime they saw an initial fall in their HbA1c but no general upwards trend thereafter.

Turning to the UK National Diabetes Audit 2019-20 the median HbA1c by age among those with T1DM is shown below.

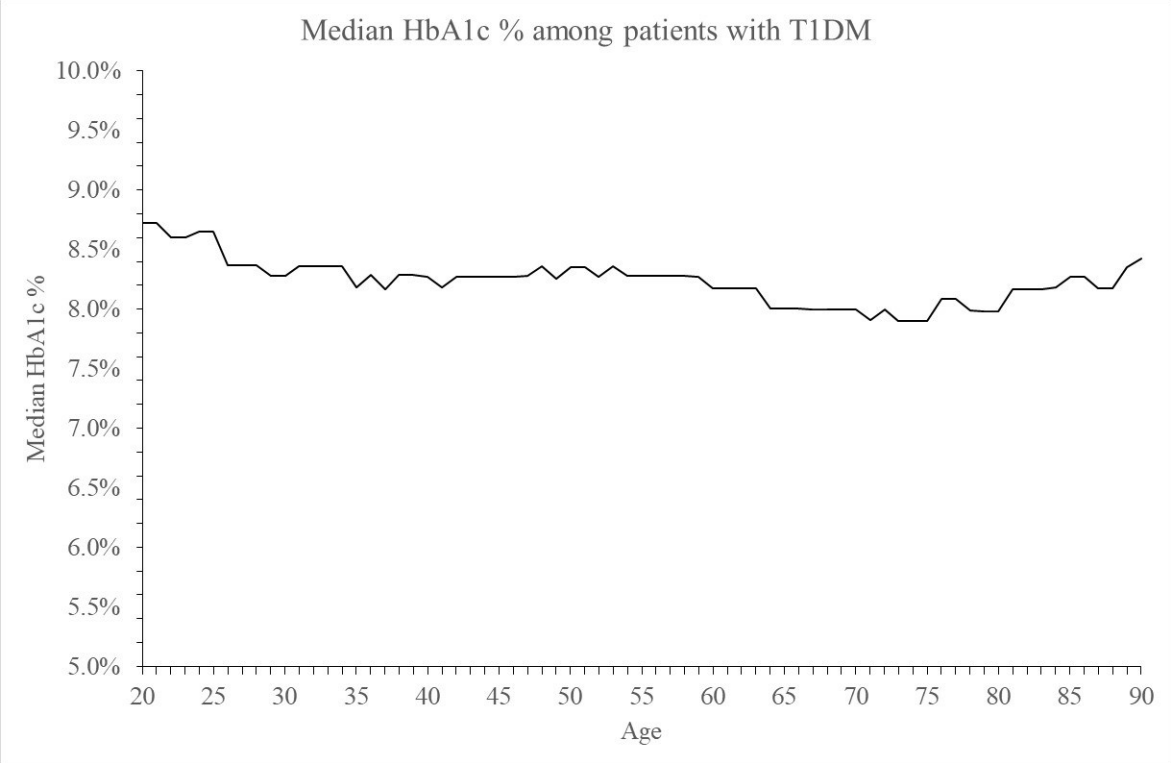


Figure 23: UK Diabetes Audit: Median HbA1c by age

While this does not follow individual patients through time, there is no obvious worsening of the median HbA1c with age. HbA1c appears to become better controlled in early adulthood. This is mirrored in Acharya et al [134] who in a cross sectional study of

255 young Scottish diabetics with T1DM found that those in the youngest age group had statistically significantly higher mean HbA1c than those in the eldest age group, with means of 9.9% for those age 15-18 years, 9.4% for those age 18-22 years and 8.8% for those age 22-25 years. Turning back to the National Audit data, HbA1c remains reasonably constant throughout middle age, possibly showing slight further improvement above the age of 60, though this might be the result of survivor bias, it not rising above the values of middle age until patients are in their 80s.

In the light of the above, for the base case the EAG will assume no annual worsening of HbA1c over time as would be expected in a disease where beta cell capacity is mostly lost by diagnosis. A scenario analyses of an annual worsening of 0.045% will be presented, in part to aid comparison with other modelling efforts.

Modelling of other clinical effects: NSHEs and SHEs

There is some lack of clarity around the iQVIA CDM implementation of the quality of life decrements for NSHEs, as reviewed in greater detail in section 6.2.1.6 below. Coupled with a wish to simplify the implementation of scenario analyses, the EAG uses the iQVIA CDM to model the effects of HbA1c upon survival and the micro and macro vascular complications of diabetes. The iQVIA CDM overall survival curve for each comparator is then coupled with comparator specific treatment costs and in scenario analyses with the comparator specific NSHE rate and SHE rate. With the addition of the events' unit costs and disutilities this enables technologies' other effects to be incorporated into the cost effectiveness analysis.

Note that this assumes that there are no deaths from SHEs, in common with iQVIA CDM defaults and the NG17 model inputs.

6.2.1.5 Perspective, discount rates and time horizon

As per the NICE methods guide, the perspective for costs is the NHS and PSS, the perspective for benefits is that of the patient, and costs and benefits are discounted at 3.5%.

The base case assumes a 50 year time horizon which is effectively a lifetime horizon for all but an insignificant proportion of patients.

Given the uncertainty around the iQVIA CDM outputs for longer time horizons as reviewed in section Modelling of HbA1c effects: iQVIA Core Diabetes Model validation work above time horizons of 8, 12 and 24 years will also be explored. Multiples of 4 years correspond with pumps' lifespans.

6.2.1.6 Health valuation

Quality of life without complications and disutilities of micro and macro vascular complications

The 0.839 values for quality of life without complications for patients with T1DM, based upon Peasgood et al [135], and the disutilities of micro and macro vascular complications are taken from the default values of the iQVIA CDM[***]. This is in line with NG17.

Table 23: Disutilities of micro and macro vascular complications

Complication	Disutility
MI event	-0.055
MI subsequent	-0.055
Angina	-0.090
CHF	-0.108
Stroke event	-0.164
Stroke subsequent	-0.164
PVD	-0.061
Gross proteinuria	-0.048
Haemodialysis	-0.164
Peritoneal dialysis	-0.204
Renal transplant	-0.023

[***] The iQVIA CMD team stated that the default utilities for complications relate to T2DM patients and that to derive utilities for T1DM patients the T2DM disutilities should be calculated and applied to the T1DM quality of life value for no complications.

Background diabetic retinopathy (BDR)	-0.040
BDR wrongly treated	-0.040
Proliferative diabetic retinopathy (PDR)	-0.070
PDR lasered	-0.070
Macular oedema	-0.040
Severe vision loss	-0.074
Cataract	-0.016
Neuropathy	-0.084
Ulcer	-0.170
Amputation	-0.280
Post amputation	-0.280

Disutilities of hypoglycaemia events

Given previous reviews of the effects of hypoglycaemia upon quality of life, the ERG largely relies upon NG17 coupled with the systematic reviews of Chatwin et al [136], Coolen et al [137], Jensen et al [138] and Matlock et al [139] to extract and review papers that may report values compatible with the NICE reference case. The ERG augments this with a systematic literature search from 2020 to find papers that may have been published subsequent to previous reviews' date cut-offs.

The EAG first summarises the papers underlying the iQVIA defaults, with the range of these estimates being subsequently graphed in **Figure 24**, appending the review of Gordon et al [131] to this due to the similarity of its method to that of Currie et al [23]. It then turns to other papers in the literature, these mostly being more recent publications.

If a constant disutility per NSHE is applied the iQVIA CDM default is 0.00335 per event as drawn from the poorly reported US data of Foos & McEwan [140]. But the preference appears to be for non-linear models and diminishing marginal disutilities, in which case the iQVIA CDM defaults for the effect of NSHEs on QoL are to choose either the analyses of Lauridsen et al,[19] based upon the TTO data of Evans et al [141], or the analyses of Currie et al [23].

Foos & McEwan [140] is only available in abstract with minimal information, other than it being a US based survey that collected 6 month data about mild, moderate, severe and very severe hypoglycaemia events. No information about how quality of life was calculated or measured is provided, but this coupled with mean event rates within the categories resulted in annual disutility scores of -0.0011, -0.0062, -0.0148 and -0.0586 for mild, moderate, severe and very severe hypoglycaemia events, the weighted average for mild and moderate events of -0.00340 being essentially the same as the -0.00335 iQVIA CDM default if a linear disutility is selected.

Evans et al [141], sponsored by Novo Nordisk, undertook an internet based time trade-off (TTO) exercise among three samples from the general population, patients with T1DM and patients with T2DM from an existing panel in Canada, the US, Germany, Sweden and the UK. Evans et al did not state how many of those in the existing general population panel chose not to start the questionnaire, but of the 11,196 who did, 90% completed it, among whom a further 17% were excluded leaving 8,286 or 82%.

The central estimates suggested that respondents were willing to sacrifice 3.8% of their future survival to go from one quarterly daytime NSHE to none, and to sacrifice 4.1% to go from one quarterly nocturnal NSHE; i.e. sacrifices of around 2 weeks survival per year. Similarly, to go from none to one annual SHE respondents were willing to sacrifice around 10% of future survival, around 5 weeks per year. The decrements for going from some to no events seem quite high and may not be reasonable. If so, this also carries through to the functions of Lauridsen et al.[19]

Evans et al report mean decrements[†††] per event among the T1DM subgroup of 0.004 for a daytime NSHE, 0.008 for nocturnal NSHE, 0.047 for a daytime SHE and 0.051 for a

[†††] Evans et al imply that their TTO study does not take into account discounting. Given T1DM respondents' mean age of 39 they might reasonably expect to live for at least another 30 years. Time preferences among respondents of the NICE reference case discount rate of 3.5% would reduce e.g. the disutility for one annual SHE from 0.082 to 0.049, a 40% reduction. But it can be noted that Dolan and Gudex 10. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQoL: results from a UK General Population Survey*. University of York; 1995. URL: https://www.york.ac.uk/che/pdf/DP138.pdf (Accessed 9 February 2021). in a study of 39 members of the general public estimated individual discount

nocturnal SHE, the values for severe events being slightly less than those reported for the general population of 0.057 and 0.062. The ERG assumes that these are disutilities per annual event and include the step going from none to some NSHEs.

Lauridsen et al,[19] sponsored by Novo Nordisk, used the TTO values for NSHEs of Evans et al [141] to estimate the quality of life impact of NSHEs recognising the apparent diminishing marginal disutilities as graphed below in **Figure 24**. The non-linearity appears to be mainly driven by the step going from none to some NSHEs. A two stage estimation procedure that modelled this step separately from subsequent increases in the NSHE rate might result in a smaller and more linear effect for the subsequent increases after the initial step.

Currie et al et al [23], sponsored by Novo Nordisk, used the results of postal questionnaires mailed to UK patients, average age 63 years, identified as having either T1DM, 34%, or T2DM, 66%, in two surveys of N=1,500 and N=3,200 with some overlap between the surveys. The overall response rate across the two surveys was 31% which is quite low and may reflect self-selection bias; those responding may tend to have been those whose NSHEs and SHEs had a greater impact upon their quality of life.

They collected data on patient characteristics, comorbidities, the number of NSHEs and the presence of SHEs during a 3-month recall period, the HFS version 1 worry subscale (HFS1-ws) and the EQ-5D. For patients who responded to both surveys their second response was chosen. The effect of this choice was not explored, but it can be noted that the mean HFS score for the first survey of 6.76 was somewhat lower than the 9.39 of the second survey.

Reported rates of SHEs among those experiencing them, 10.3% of T1DM patients, 8.3% of T2DM patients in insulin and 1.8% of T2DM patients on oral antidiabetes drugs

rates scattered around 0%, and it appears standard in TTO to not estimate individuals' time preferences alongside their quality of life estimates.

(OADs) , were quite high[‡‡‡]: annualised rates of 14.3, 22.3 and 7.6 respectively yielding an overall sample mean of 14.9 among those experiencing SHEs. This contrasts with annual rates from the UK hypoglycaemia study group among those experiencing SHEs of 5.1 and 6.9 for T1DM patients of less than 5 years and more than 15 years duration, and 1.5, 1.4 and 2.8 for T2DM patients on OADs, insulin for less than 2 years and insulin for more than 5 years.

Among the 84.7%, 78.0% and 49.5% of patients reporting symptomatic NSHEs the corresponding annual rates are 44.4, 31.2, and 48.7 with an average of 45.5. Nocturnal NSHEs were reported by fewer patients, 30.1%, 25.6% and 4.2% respectively, these patients reporting annual event rates of 21.3, 17.7 and 30.6 yielding an overall average of 21.7. While only a relatively small proportion of patients reported SHEs their average number of SHEs may be a concern, particularly when interpreting their estimated effect upon the HFS1-ws due to this being the presence or absence of SHEs rather than their number.

In a two-stage analysis, the HFS1-ws was modelled as a function of the age, insulin use, the logarithm of the number of NSHEs and the presence or absence of SHEs. Two separate HFS1-ws regressions were undertaken, one for symptomatic NSHEs and one for nocturnal NSHEs. Unfortunately, Currie et al were not explicit about the time period that should be used when calculating the number of NSHEs but it can be noted that the presence or absence of SHEs can only have been calculated based upon the 3-month recall period of the questionnaires[§§§]. The EQ-5D was modelled as a function of the HFS1-ws, age, BMI and the presence or absence of a range of comorbidities.

[‡‡‡] Table 3 is poorly labelled but states the total number of patients, the proportion of patients experiencing SHEs and an annualised SHE rate. For it to be possible for the annualised rate to apply only to those experiencing an SHE during the 3 month recall period the minimum possible annualised rate would be 4. Table 3 gives annualised rates of 1.47, 1.86 and 0.14. The EAG concludes that these annualised rates must be across the entire patient number and not the subgroup who experienced SHEs.

[§§§] The EAG contacted Currie as the corresponding author about this but did not receive a reply. It appears that the iQVIA CDM may input an annual rate of NSHEs to the HFS1-ws function(s) of Currie et al when

Currie et al report disutilities for symptomatic and nocturnal NSHEs of 0.0142 (1.42%) and 0.0084 (0.84%), implicitly suggesting that these are additive. Given the regression analyses and probability of positive covariance between symptomatic and nocturnal NSHEs the EAG thinks that only one of the HFS1-ws regressions should be applied, this also avoiding double counting the effects of SHEs. The stated disutility values also only apply when patients are moving from experiencing no NSHEs to a small number of NSHEs. The functions are non-linear and have a quite rapidly declining marginal disutility for NSHEs.

The more recent paper by Gordon et al [131], sponsored by AstraZeneca, very closely mirrors the analysis of Currie et al, both being co-authored by McEwan. As with Currie et al, Gordon et al used the EQ-5D and did not specify that the UK social tariff was used though this seems likely.

Gordon et al were explicit about the time period that should be used when calculating the NSHE event rate and the presence or absence of SHE events within their functions: a common 4-week period for both. In the light of the common co-authorship and similarity of analyses of Gordon et al and Currie et al, the EAG thinks that the most reasonable assumption about the time period that should be used when calculating the NSHE event rate and the presence or absence of SHE events for the functions of Currie et al should be a common 3-month period in line with the recall period of the questionnaires[****].

calculating their effect. The EAG contacted the iQVIA about this but did not receive a reply. Partly because of the uncertainty about its implementation in the iQVIA CDM, the EAG estimates the effects of NSHEs separately from the modelling that uses the iQVIA CDM through application of the modelled overall survival curve to event rates, disutilities and costs. The EAG adopts a parallel approach for estimating the treatment costs and the costs and quality of life effects of NSHEs and SHEs.

[****] Currie et al noted that the more numerous second questionnaire recall period was 3 months. The EAG assumes that this also applies to the first questionnaire.

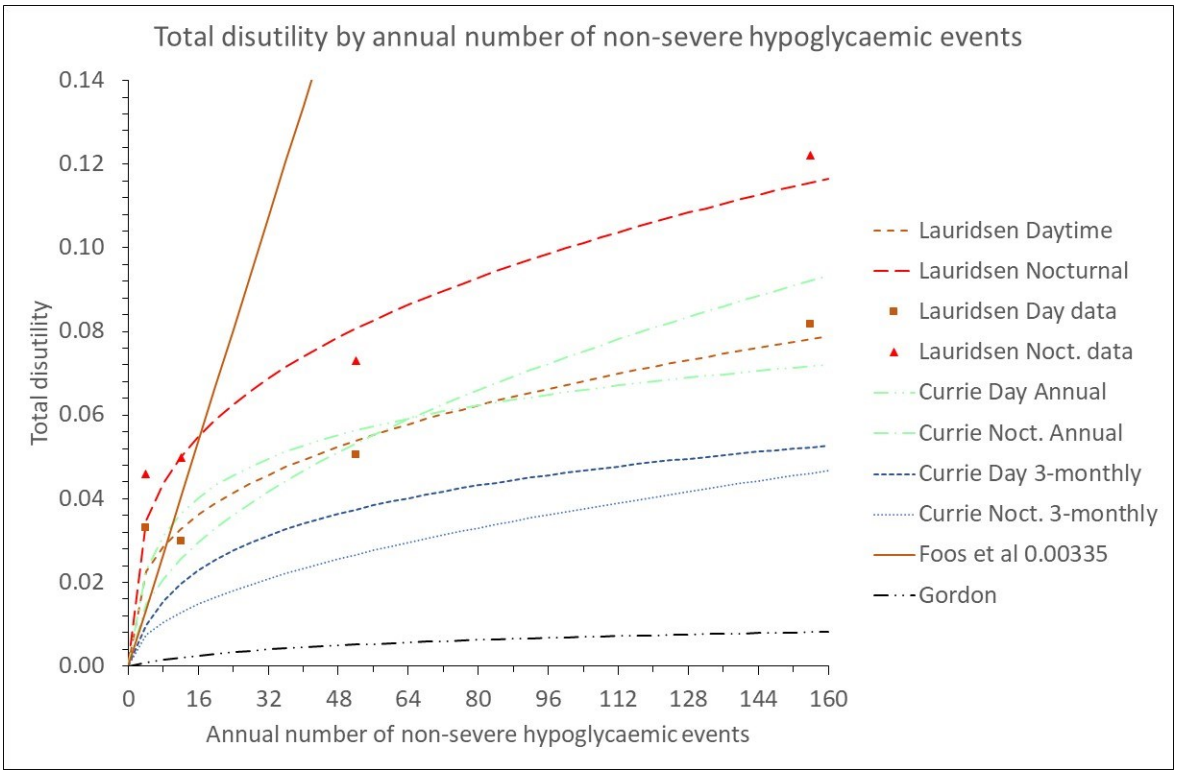


Figure 24: NSHE disutilities for the iQVIA CDM defaults and Gordon et al

Turning to other papers in the literature, Yfantopoulos et al [142] recruited 938 adult subjects with T2DM who were receiving insulin with an average age of 67 years, these being split into an estimation sample of 489 and a validation sample of 449. EQ-5D data was valued using the UK social tariff. Within a multivariate analysis the presence of severe hypoglycaemia was estimated to reduce the EQ-5D by a disutility of -0.050, this being statistically significant. Unfortunately, the period over which SHEs were recorded is not reported.

Zhang et al [143] analysed the records of 7,081 Chinese patients with T2DM receiving oral agents, with an average age of 60 years. EQ-5D data was collected and valued using a Chinese tariff. Unfortunately, the paper does not report the data period or recall period for the hypoglycaemia event rates. An OLS regression that controlled for various patient characteristics and comorbidities estimated that an "additional" NHSE relative to none had a disutility of -0.007 while SHEs has a disutility of -0.008, both being statistically

significant. The similarity of disutilities for NSHEs and SHEs suggests that they relate to the presence or absence of events, rather than a disutility per event.

Nauck et al [144], sponsored by Novo Nordisk, analysed the LEADER cardiovascular outcomes trial among patients with T2DM who had a high risk of cardio-vascular disease, patients being randomised to liraglutide (N=4,668) or placebo (N=4,672). This followed patients for 3.5 to 5.0 years and collected the EQ-5D at baseline, 12 months, 24 months and study completion, it being valued using the UK social tariff. A linear mixed repeated measurements model estimated that severe hypoglycaemia had a disutility of -0.029 but that this did not quite reach statistically significant with a p-value of 0.073 due to the small number of events. The text does not specify whether this related to any severe hypoglycaemia events during follow-up or was e.g. an annualised event rate, but it appears to be the former.

Levy et al [21], sponsored by Novo Nordisk, elicited quality of life values using the TTO for quarterly, monthly and weekly NSHEs from 51 Canadian diabetics, and from 79 and 75 members of the Canadian and UK general population. For those with diabetes the central TTO values reported for annualised NSHE rates of 0, 4, 12 and 52 were 0.92, 0.91, 0.87 and 0.75, which suggests a more linear relationship than the TTO values of Evans et al. An OLS regression estimated that the number of NSHEs had a coefficient of -0.0033 while within a Flogit analysis it was -0.0247, both being statistically significant. They conclude that an NSHE is associated with a -0.0033 disutility for those with diabetes compared to an estimate of -0.0032 from the general public, these estimates being aligned with the -0.00335 that the iQVIA CDM estimates from Foos & McEwan.

Briggs et al [145], sponsored by BMS, analysed the 2 year data from the SAVOR-TIMI 53 trial of saxagliptin against placebo among 16,488 patients with T2DM. Patients were followed for 2 years with the EQ-5D being collected alongside event rates and valued using the UK social tariff. This was focussed upon the impact of cardiovascular events but also included a dichotomous variable for whether the patient had a history of on-trial hypoglycaemic events, which the EAG assumes were SHEs. This estimated a decrement of -0.027 with a p-value of 0.157, this being similar to the -0.029 estimate of Nauck et al.

Pratipanawatr et al [146], sponsored by MSD, analysed EQ-5D data valued using the UK social tariff from a Thai cross-sectional study of sulfonylurea compared to sulfonylurea with metformin among 659 patients with T2DM. Data on hypoglycaemia events was collected using 6 month recall data with patients being classified as to their most severe hypoglycaemia event: none, mild, moderate, severe with 202 (31%) patients having experienced some hypoglycaemia during the preceding 6 months. A multivariate regression that controlled for age, sex, vascular complication, treatment, weight, medication adherence, worry about hypoglycaemia, worry about weight gain and overall satisfaction found that the presence of hypoglycaemia during the preceding 6 months was statistically significantly associated with reduction in quality of life: a worst experienced hypoglycaemia event of mild, moderate or severe reduced quality of life by 0.156, 0.096 or 0.198 respectively.

Peasgood et al [135] analysed data from 2,469 UK patients with T1DM taking part in a DAFNE course who were followed up for 2 years. Quality of life data was collected using the EQ-5D, SF-36 and the EQ-5D VAS. They imply that the EQ-5D was valued using the UK social tariff with a baseline average of 0.839 among a patient group with an average age of 39 years and duration of diabetes of 16 years. Questionnaires were administered at baseline, 1 year and 2 years, with follow-up rates of 58% and 24% respectively, the mean EQ-5D remaining reasonably constant at 0.851 and 0.840 respectively.

Peasgood et al report the distribution of the number of SHEs during the preceding year.

Table 24: Peasgood distribution of the annual number of SHEs

	Baseline	Year 1	Year 2
0	78.4%	89.9%	90.5%
1	9.4%	5.0%	5.4%
2	4.4%	2.0%	1.8%
3	2.2%	1.0%	1.0%
4	1.4%	0.7%	0.8%
5+	4.2%	1.4%	0.6%

While an underestimate, if those experiencing 5+ SHEs are assumed to have experienced 5 SHEs the above suggests annual event rates per patient of 0.51, 0.22 and 0.18 for baseline, year 1 and year 2. It can also be noted that in years 1 and 2 the proportion reporting SHEs is reasonably similar to the 10.3% 3-monthly proportion reported in Currie et al.

Table 25: Peasgood distribution of the annual number of SHEs among those experiencing

	Baseline	Year 1	Year 2
1	43.5%	49.5%	56.5%
2	20.4%	19.8%	18.7%
3	10.2%	9.9%	10.4%
4	6.5%	6.9%	8.3%
5+	19.4%	13.9%	6.3%

Around half of those experiencing SHEs only experienced 1 during the preceding year. The vast majority, over 80% at all time points, experienced at most 4 per year. If it is assumed that those experiencing 5+ experienced only 5 SHEs, among those having had an SHE during the preceding year these correspond to annual rates of 2.38, 2.16 and 1.90 at baseline, year 1 and year 2 respectively. These contrast with the EAG inferred annual rate among the T1DM patients who experienced an SHE of 14.3 for Currie et al.

Peasgood et al undertook linear modelling of the EQ-5D that controlled for a large number of the complications of diabetes. This estimated a -0.0020 fixed effects coefficient and a -0.0022 random effects coefficient for the number of SHEs in the preceding year, though only the random effects coefficient was statistically significant. There may be the possibility of confounding variables or multicollinearity with HbA1c having a statistically significant negative coefficient and the HADS depression score also having a statistically significant coefficient. These might artificially reduce the estimated effect of SHEs upon quality of life.

For the disutility of NSHEs Gordon et al and Currie et al are the papers which provide estimates that conform most closely to the NICE reference case. The key differences between Gordon et al and Currie et al are:

- Gordon et al was specific to T1DM patients receiving insulin while Currie et al had a majority of T2DM patients.
- Gordon et al used data from the RCT of dapagliflozin against placebo within which the trial data definitions, interpretation and collection seem likely to have been more stringently defined and consistently applied than within the postal recall questionnaires of Currie et al.
- The response rate of Gordon et al was high at around 80% of the baseline population and more relevantly at around 90% of those remaining in the trial at the 52 week data analysis point, compared to only 31% for Currie et al.

This leads the EAG to prefer the estimates of Gordon et al over those of Currie et al. The EAG provides a scenario analyse of the estimates of Currie et al assuming that the NSHE rate should be 3-monthly and that the 69% non-responders had the preferences as the 31% responders.

For the disutility of SHEs most papers provide estimates for the presence of SHEs rather than the disutility per annual SHE. If annual SHE rates are of the order reported in Currie et al this is problematic. But if annual SHE rates are more in line with those reported in Peasgood et al this may be less problematic. Subsequent to DAFNE over half of those reporting SHEs only had one SHEs during the preceding year. In this situation any treatment effects upon SHE event rates are more likely to be determining their presence or absence; i.e. going from one to none or none to one SHE.

The EAG adopts the estimates of Gordon et al for SHE disutilities and applies this to the SHE event rate. For relatively rare events like SHEs the short DEPICT-2 4 week window of Gordon et al may be a concern. The EAG supplies a scenario analysis that applies the coefficient of Nauck et al.

Hypoglycaemia events and carer disutilities

Parents are affected by their children having hypoglycaemia events and are fearful of them occurring. Friends and relatives caring for people with T1DM may be similarly affected. The EAG has not identified any research that quantifies these disutilities.

A reasonable upper limit for the effect upon carers might be to assume that they have the same disutility as the patient with T1DM that they are caring for.

The EAG will provide a scenario analysis that simply doubles the disutilities associated with hypoglycaemia events; i.e. that relates to the subset of patients being cared for and that assumes carers experience the same disutility as the patient.

6.2.1.7 Costs

Training costs

The Diabetes Technical Network has provided estimates of the number of OP visits and nursing time required to move from MDI+CGM to CSII+CGM and from MDI+CGM to HCL. There is no difference between these estimates; i.e. going onto a pump using CSII+CGM involves much the same visits and staff time as going onto a pump using HCL. As a consequence, the EAG base case ignores training costs.

This does not cover the situation of moving from CSII+CGM to HCL, with most patients moving from isCGM to rtCGM and with some further training required for changing to HCL pump use. The Diabetes Technical Network indicates that pre-fitment, fitment and additional post fitment vists would total 3 consultant led OP visits, 3 nurse led OP visits, 3 nurse follow up calls or e-mails plus an additional nurse hour for a fitment visit. Costing these at £208 and £144 of the Diabetic Medicine WF01A NHS 2020/21 NHS Schedule of Costs and £51 per hour for Band 5 nursing time spent on patient activities from the 2021 PSSRU Unit costs of Health and Social Care, with an assumption of an average 10 minutes per phone call or e-mail, this results in an additional cost of £1,132.

Treatment costs

To cost the technologies the EAG uses current list prices supplied by the NHS Supply Chain. While the costs of HCL pumps and consumables differ slightly between systems the total 4 year costs are similar, with the exception of one system which is around an annual average of £500 more than the unweighted average. This also applies to the LGS/PLGS systems. The ERG applies the unweighted averages for year1 and years 2, 3 and 4 and provides a scenario analysis which increases these by £500 for both HCL and LGS/PLGS.

In response to EAG clarification questions Dexcom provided data suggesting that the average G6 sensor duration was slightly less than the maximum 10 days, with around 87% lasting for 10 days and a mean duration of 9.5 days or 95% of maximum duration. Medtronic also provided median durations of GS3 of [redacted] days and G4S of [redacted] This is reasonably aligned with the 95% mean of Dexcom. The EAG inflates the cost of all CGM sensors by 5% to account for this.

The EAG assumes that only 10% of Dexcom users require a dedicated receiver due to the near ubiquity of smartphones.

Table 26: Pump and consumable costs

	Year 1	Years 2-4	4 yr Total	Average
HCL	£7,931	£5,015	£22,975	£5,744
LGS/PLGS	£7,135	£4,455	£20,498	£5,125
CSII+CGM	£5,480	£3,751	£16,734	£4,184

The EAG adds an additional annual average £315 insulin cost to all regimes, based upon a daily average of 50IU.

Companies have indicated that prices will change for the next financial year and some products have confidential volume discounts. The EAG addresses these aspects in the cPAS appendix.

Ongoing visits and the costs of micro and macro vascular complications

It is assumed that without complications the average patient once established on treatment is seen in outpatient clinic once per quarter. This is costed at the NHS reference cost for consultant led non-admitted face to face follow-up appointment for diabetic medicine. This cost is reasonably different for 2019-20, £154, compared to 2020-21, £208. The proportion of follow-up visits that were not face to face also differed, 9.6% compared to 49.6%. It seems reasonable to assume that the 2020-21 costs were in part driven by Covid with only the more serious cases being seen in clinic. For this reason the EAG will apply the 2019-20 of £154 uprated by the NHSCII pay and prices index 3.08% to £160 in 2020-21 prices resulting in an annual routine OP cost of £640.

The costs of other routine management for e.g. ACE inhibitors and the proportion in receipt of these and the costs of micro and macro vascular complications are taken from NG17, inflated to 2019-20 prices. All patients are assumed to receive screening.

Table 27: Costs of ongoing management and proportion receiving

		In receipt	
Complication	Cost	Primary prevention	Secondary prevention
Statins	£28.42	47%	84%
Aspirin	£16.96	59%	88%
ACE-I/ARB	£23.71	21%	76%
Stopping ACE-I/ARB due to AEs	£40.72		
Microalbuminuria screening	£4.41		
Gross proteinuria screening	£4.41		
Eye screening	£56.44		

Table 28: Costs of micro and macro vascular complications

Complication	Cost
MI 1st year	£4,231
MI subsequent years	£894
Angina 1st year	£7,265

Angina subsequent years	£327
CHF 1st year	£4,077
CHF subsequent years	£2,945
Stroke 1st year	£4,728
Stroke subsequent years	£175
Stroke death within 30 days	£1,332
PVD 1st year	£1,380
PVD subsequent years	£600
Haemodialysis 1st year	£34,855
Peritoneal dialysis	£31,357
Renal transplant (1st year)	£21,810
Renal transplant (2nd year)	£8,649
Laser treatment	£151
Cataract operation	£962
Following cataract operation	£211
Blindness 1st year	£7,858
Blindness subsequent years	£7,592
Neuropathy 1st year	£39
Neuropathy subsequent years	£39
Active ulcer	£3,654
Amputation event	£8,761
Post amputation	£26,653

NSHE costs

It is assumed that there are no costs to the NHS or PSS from NSHEs.

SHE costs

A number of previous NICE assessments have applied the resource use estimates of Leese et al [4] to estimate the cost per SHE that requires medical attention. Leese et al identified 244 hypoglycaemia events requiring medical attention in Tayside during the year from June 1997, the balance between these being roughly equally split between

T1DM and T2DM[††††]. These were estimated to cost £141,120 when uprated from 2002 prices to 2021 prices, equivalent to an average of £578 per event requiring outside medical assistance.

NG17 used Heller et al [125] to cost severe SHEs, separately for those with T1DM, those with T2DM on insulin and those with T2DM on OADs. They analysed 15 trials, the mean ages being around 42 years for T1DM, 58 years for T2DM on insulin and 57 years for T2DM on OADs. The trials yielded 536 severe glycaemia events for analysis, the proportion of T1DM patients with severe hypoglycaemia being around 11% for the two 26 weeks trials, and 12% and 15% for the two 52 week trials. The majority of events, 78% (N=420) occurred among the T1DM patients. The use of medical services for T1DM patients was slightly lower at 37.9% of events than the 47.4% of T2DM patients but given that most SHEs were among T1DM patients this was little different from the overall average of 39.9%. Across all events 29.3% required an ambulance or emergency room team, 11.9% led to hospital or emergency room assistance and 6.7% required hospital admission for at least 24 hours, these averages being only slightly different for T1DM patients at 31.0%, 9.5% and 5.0% respectively.

NG17 also cited Hammer et al 2009, sponsored by Novo Nordisk, who used resource use questionnaire data from 201 UK T1DM and T2DM patients, all of whom were using insulin and had experienced at least one SHE in the last year. The mean direct costs per SHE, inflated to 2021 prices using the HCHS to 2015 and the NHSCII thereafter, were estimated as £36 for those not requiring external medical assistance, these costs being mostly due to follow-up contacts, £327 for those requiring medical treatment in the community and £1,113 for those requiring hospital treatment. The weighted average of these was £374 which is aligned with the £370 of NG17.

[††††] Even rates of 11% for T1DM and 1.7% for T2DM patients were balanced out by the higher number of T2DM patients.

Applying the weights of Heller et al for T1DM patients results in a lower cost of £260, this being £36 for those with no outside medical assistance and £628 for those requiring outside medical assistance. It is uncertain how accurately subsequent follow-up contacts and visits can be ascribed exclusively to preceding SHEs given that these patients will be receiving ongoing care. Excluding these costs and using the T1DM weights of Heller et al for T1DM patients results in a lower average cost of £206, this being £1.83 for those with no outside medical assistance and £542 for those requiring outside medical assistance. The cost of between £542 and £628 for events requiring outside medical assistance is quite well aligned with the £578 cost of Leese et al, though it should be borne in mind that the latter is a roughly equal mix between events among T1DM patients and T2DM patients.

In the light of the above, for its base case the EAG will apply a cost of £1.83 for SHEs not requiring outside medical attention and of £542 for those requiring medical attention, with it being assumed that 37.9% of SHEs require medical attention. A scenario analysis that applies £36 for SHEs not requiring outside medical attention and of £628 for those requiring medical attention will be supplied. A scenario that costs all SHEs at the 2021 updated £381 of NG17 will also be supplied, somewhat higher than the base case average of £207 despite the same sources being cited.

6.2.2 EAG cost effectiveness modelling results

6.2.2.1 EAG base case

The base case modelling provides the following disaggregate estimates.

Table 29: EAG base case disaggregate results

		PLGS		HCL	
	CSII	Value	net vs CSII	Value	net vs CSII
LYs Undiscounted	32.499	32.685	0.186	32.957	0.458
QALYs					
iQVIA CDM modelled	14.232	14.291	0.059	14.392	0.160
NHSEs	0.000	0.000	0.000	0.000	0.000

SHEs	0.000	0.000	0.000	0.000	0.000
Total QALYs	14.232	14.291	0.059	14.392	0.160
Costs					
Treatment	£86,564	£105,258	£18,694	£117,749	£31,185
Routine OP	£12,182	£12,222	£40	£12,279	£97
SHEs	£0	£0	£0	£0	£0
Other management	£1,700	£1,708	£8	£1,721	£21
CVD	£4,691	£4,649	-£42	£4,531	-£160
Renal	£10,365	£10,367	£3	£9,943	-£421
Ulcer/Amp./Neuropathy	£889	£898	£9	£880	-£9
Eye	£18,270	£17,604	-£666	£16,185	-£2,085
Total Costs	£134,661	£152,706	£18,045	£163,289	£28,628

Undiscounted survival is estimated to increase by 0.458 years through the use of HCL compared to CSII+CGM. But in part due to discounting which reduces the net survival gain to 0.149, the patient gain is only 0.160 QALYs. The net treatment cost of £31,185 is partly offset by renal savings of £421 and eye savings of £3,085, resulting in a net cost of £28,628. This results in the following cost effectiveness estimates.

Table 30: EAG base case cost effectiveness estimates

	CSII	PLGS	HCL
LYs Undiscounted	32.499	32.685	32.957
Total QALYs	14.232	14.291	14.392
Total Costs	£134,661	£152,706	£163,289
ICER vs CSII	..	£305,852	£178,925

The results suggest that PLGS is extendedly dominated by HCL, but that HCL has a poor cost effectiveness estimate of £179k per QALY.

The iQVIA CDM does not permit periodic capital costs to be modelled, so for the deterministic modelling the EAG uses the modelled OS curves to estimate treatment costs. This approach cannot be adapted to the probabilistic modelling so the EAG

approximates these costs within the iQVIA CDM by applying the four yearly annual average costs for CSII+CGM and HCL respectively, the iQVIA CDM only permitting pairwise comparisons. This results in a central cost effectiveness estimate of £186k per QALY for HCL compared to CSII+CGM which is similar to the deterministic estimate, and probabilities of HCL being cost effective at thresholds of £20k, £30k, £50k and £100k per QALY of 21%, 31%, 39% and 47% respectively.

8.2.2.2 EAG scenario analyses

The EAG presents the following scenario analyses.

- SA01: Revising the NMA to [66](a) be restricted to only adult studies and (b) exclude Banhamou [66].
- SA02: Application of the NHSE adult pilot (a) patients baseline characteristics and (b) patients baseline characteristics and HbA1c change of -1.5% for HCL with an assumption of no change for CSII+CGM and (c) SA02b with the costs of complications reduced by their possible overestimation as identified in McEwan et al [123]
- SA03: Time horizons of 8, 12 and 24 years.
- SA04: Durations of HbA1c effect of 5, 10 and 20 years.
- SA05: Inclusion of NSHEs, based upon an HCL annual rate of (a) 20.8, (b) 57.2 and (c) 13.0 with comparator rates based upon the ratio of time below 3 mmol/l, valued using Gordon et al [131]
- SA06: Inclusion of NSHEs as per SA05a and SHEs, valued using Gordon et al
- SA07: Inclusion of NSHEs as per SA05a valued using Currie et al [23] and SHEs valued using (a) Currie et al and (b) Nauck et al [144]
- SA08: SA06 with SHEs costed at (a) £36 for no medical attention and £628 for medical attention, and (b) £381 for all SHEs
- SA09: SA06 with a doubling of the NSHE and SHE quality of life effects to reflect possible carer effects

- SA10: CSII is (a) 85% isCGM and 15% rtCGM and (b) 95% isCGM and 5% rtCGM
- SA11: HCL and PLGS average annual cost being £500 higher
- SA12: Additional £1,132 training cost for transferring from CSII+CGM to either PLGS‡‡‡‡ or HCL
- SA13: Revising non-specific mortality to (a) all-cause mortality and (b) non-specific mortality that also excludes all deaths associated with hypertension.
- SA14: Annual 0.045% HbA1c worsening

Within these results PLGS is extendedly dominated throughout, and for reasons of space the EAG does not consider it further.

Table 31: EAG scenario analyses' ICERs: HCL vs CSII+CGM

	Δ Costs	Δ QALYs	ICER
Base case	£28,628	0.160	£179k
SA01a: Only adult studies	£28,734	0.141	£204k
SA01b: Benhamou excluded	£28,096	0.169	£166k
SA02a: NHS adult pilot baseline characteristics	£25,775	0.205	£126k
SA02b: NHS adult pilot characteristics and effect	£12,447	1.004	£12,398
SA02c: SA02b + reduced complication costs	£21,669	1.004	£21,583
SA03a: 8 year time horizon	£12,740	0.014	£910k
SA03b: 12 year time horizon	£16,601	0.025	£664k
SA03c: 24 year time horizon	£23,975	0.073	£328k
SA04a: 5 year HbA1c effect	£29,571	0.045	£657k
SA04b: 10 year HbA1c effect	£28,887	0.068	£425k
SA04c: 20 year HbA1c effect	£28,369	0.115	£247k

‡‡‡‡ The EAG did not ask the Diabetes Technical Network about transferring from CSII+CGM to PLGS. But since the main issue identified for transferring to HCL was the move from isCGM to rtCGM the EAG assumes that the same costs will be incurred transferring to PLGS.

SA05a: NSHEs with HCL 20.8 annual	£28,628	0.170	£169k
SA05b: NSHEs with HCL 57.2 annual	£28,628	0.173	£166k
SA05c: NSHEs with HCL 13.0 annual	£28,628	0.168	£170k
SA06: HEs: NSHEs and SHEs	£28,325	0.174	£163k
SA07a: SA06 + HEs Currie values	£28,325	0.235	£121k
SA07b: SA06 + HEs Currie and Nauck values	£28,325	0.260	£109k
SA08a: SA06 + £36/£628 SHE cost	£28,246	0.174	£162k
SA08b: SA06 + £381 SHE cost	£28,069	0.174	£161k
SA09: SA06 + HEs double quality of life effect	£28,325	0.188	£151k
SA10a: CSII 85% isCGM 15% rtCGM	£27,117	0.160	£169k
SA10b: CSII 95% isCGM 5% rtCGM	£30,139	0.160	£188k
SA11: HCL/PLGS annual cost £500 more	£38,244	0.160	£239k
SA12: CSII to HCL training cost £1,132	£29,760	0.160	£186k
SA13a: All-cause mortality	£27,846	0.139	£200k
SA13b: Non-specific mortality excl. H.T.	£28,556	0.171	£167k
SA14: Annual 0.045% HbA1c worsening	£27,694	0.181	£153k

7 Discussion

7.1 Summary of key results

The aim of the RCTs was generally to demonstrate improvement of glycaemic control with use of HCL. We identified one study by Stewart of pregnant women included only 16 participants followed for 4 weeks; the population, study design and outcomes in this study were clearly different from other studies so that transitivity in NMA including Stewart is threatened. This was addressed by conducting a sensitivity analysis (see Results of the subgroup and sensitivity analyses compared to the overall NMA results)

There were relatively few studies, they were of small size encompassing a total of ~450 HCL recipients followed for between 4 and 26 weeks accumulating approximately 110 person years of observation. Inclusion criteria applied for the studies were relatively narrow and most participants had reasonably good glycaemic control at entry, as indicated in most of those studies reporting baseline TIR (3.9 to 10 mmol/L) at greater than 50% (range 47% to 62%), and baseline HbA1c at between 7% and 8%. There was considerable heterogeneity across studies regarding the age of participants, some studies presented results stratified by age groups. The relevance of the RCT populations and outcome measure results for the decision problem is debatable and not easy to judge. The quality of studies assessed according to Cochrane criteria was associated with either low risk of bias or some concern.

In the HCL arm of RCTs the intervention achieved a statistically significant improvement in HbA1c % that decreased mean difference 0.28 (-0.34 to -0.21), in TIR between 3.9 to 10 mmol/L significantly increased % TIR (between 3.9 – 10.0 mmol/L) mean difference 8.6 (7.03 to 10.22), and in hyperglycaemic levels (significantly decreased TIR (% above 10.0 mmol/L), with a mean difference of -7.2 (-8.89 to -5.51). Control arms also showed improvement but this was less than that seen with HCL. Irrespective of type of intervention used in the control arms these outcomes were statistically superior in the HCL arm vs. control arm. Available evidence from the RCTs suggests that these gains in

glycaemic control reported for HCL were not accompanied by a greater risk of hypoglycaemia however the power to detect small event sizes was limited because of small size of study groups and relatively short treatment duration. Adverse events were reported in some studies and were mainly low. Patient reported outcomes were assessed using various methods and did not result in clear trends.

The estimated cost effectiveness of PLGS compared to CSII+CGM is consistently worse than that of HCL compared to CSII+CGM, for both the base case and the scenario analyses. PLGS is extendedly dominated by HCL and the EAG does not consider it further

Given the NMA estimated effect upon HbA1c of -0.29% for HCL compared to CSII+CGM the cost effectiveness of HCL is poor. Net treatment costs are estimated to be £31,185, cost offsets from fewer complications and in particular -£2,085 from reduced eye complications, probably mostly severe visual loss, and -£421 from reduced renal complications, probably mostly ESRD, reduce the net total cost to £28,628. The net undiscounted survival gain is 0.458 years, this contributing to a patient gain of 0.160 QALYs. This results in a base case deterministic cost effectiveness estimate of £179k per QALY, a probabilistic central estimate of £186 per QALY and probabilities of HCL being cost effective at £20k per QALY and £30k per QALY thresholds of 21% and 31% respectively.

The NHS adult pilot baseline patient characteristics result in a reasonable improvement to £126k per QALY. Assuming that the pilot's 1.5% improvement in HbA1c is the net effect for HCL over CSII+CGM results in net treatment costs of £35,912. Cost offsets from reduced eye complications of -£16,442 and from reduced renal complications of -£6,731 help reduce the net total cost to £12,447. The net undiscounted survival gain increases to 3.1 years, this contributing to the increased patient gain of 1.004 QALYs. The resulting cost effectiveness estimate of £12,398 per QALY is an order of magnitude better than the EAG base case. The EAG review of the published model validation work highlights that incidences of renal and eye complications may be overestimated.

Adjusting the costs of these roughly doubles the NHS pilot scenario cost effectiveness estimate to £21,583 per QALY. Note that this does not take into account any possible effects upon quality of life or life expectancy.

The EAG review of the published model validation work also highlights that modelling of longer term effects is more uncertain. Time horizons of 8, 12 and 24 years worsen the cost effectiveness estimate to £910k, £664k and £328k per QALY respectively.

The duration of the HbA1c effect is also uncertain. Limiting this to 5, 10 and 20 years while retaining a time horizon of 60 years worsens the cost effectiveness estimate to £657k, £425k and £247 per QALY respectively.

The EAG base case does not include the effects of symptomatic or severe hypoglycaemia events due to the high uncertainty around annual event rates and the lack of direct evidence that HCL has an effect upon these. Incorporating non-severe symptomatic hypoglycaemia event rates, inferred from an annual rate of 20.8 for HCL with an annual rate of 27.1 for CSII+CGM based upon the ratio of times below 3.0 mmol/l, improves the cost effectiveness estimate to £169k per QALY. Annual rates of 57.1 and 13.0 for HCL result in cost effectiveness estimates of £166k and £170k per QALY. Including severe hypoglycaemia events improves the cost effectiveness to £163k per QALY.

If both non-severe and severe hypoglycaemia events are included and are valued using the same source as NG17 the cost effectiveness improves £121k per QALY, while if severe events are valued using another reasonable source within the literature the cost effectiveness improves further to £109k.

Doubling the quality of life effect of hypoglycaemia events to reflect possible carer effects improves the cost effectiveness estimate from £169k to £151k per QALY. Increasing the costs of severe hypoglycaemia events has relatively little effect upon the cost effectiveness estimate.

Reducing the proportion of CSII+CGM that is isCGM from 90% to 85% improves the cost effectiveness to £169k per QALY while increasing it to 95% worsens it to £188k per QALY. Additional annual HCL costs of £500, as may apply to some HCL systems,

worsen the cost effectiveness to £239k per QALY, while training costs for cross over from CSII+CGM to HCL of £1,132 worsen it to £186k per QALY.

The EAG non-specific mortality estimates may be too low if there are competing risks. All-cause mortality is too high but it forms an upper bound. Its application results in a cost effectiveness estimate of £200k per QALY. There may be an argument for removing deaths associated with hypertension from the non-specific mortality. This improves the cost effectiveness estimate to £167k per QALY.

If T1DM is associated with an annual worsening of 0.045% in HbA1c this improves the cost effectiveness estimate by a reasonable amount to £153k per QALY.

The key model inputs are:

- The net effect upon HbA1c.
- The duration of the net effect upon HbA1c.
- The model time horizon.
- Treatment costs.

Other important model inputs are:

- Hypoglycaemia event rates.
- What source is used to value the disutilities of hypoglycaemia event rates.
- What non-specific mortality is applied.
- Whether HbA1c worsens annually among T1DM patients and if so by how much.

The key modelling uncertainties are around:

- Overall survival gains.
- Severe visual loss and its effects upon survival, quality of life and costs.
- ESRD and its effects upon survival, quality of life and cost.

7.2 Generalisability of results

The modelled cost effectiveness of HCL is driven by the change in HbA1c and how long that change persists, the latter depending upon modelling assumptions and the baseline patient age. The larger is the HbA1c effect and the longer it persists, the greater is the difference in the modelled proportions having serious visual loss and ESRD. Assuming an annual worsening of HbA1c compounds this effect. If it is assumed that the HbA1c effect persists for the patient lifetime, the baseline age determines the duration of the HbA1c effect. The EAG base case applies the national diabetes audit mean age of those on pumps, sampling this using the standard deviation.

Exploratory modelling of a paediatric population as presented in appendix 9.5 very broadly mirrors the adult results, but the EAG has reservations about the reliability the iQVIA CDM for modelling a paediatric population. It also raises questions about durations of effects and how the transition from childhood to adulthood may affect these.

The EAG has not considered the cost effectiveness of HCL for pregnant women due to the lack of evidence. It notes the relationship between HbA1c and birth defects. If HCL reduces HbA1c in pregnant women to the same extent as in the adult population the short term additional costs of HCL will have some immediate cost offsets from reduced birth defects, with the potential for additional benefits to the child at no additional cost. It also seems likely that the baseline age of pregnant women is below the national diabetes audit mean age which is likely to further improve cost effectiveness. If after giving birth women remain on HCL into the long term the cost effectiveness estimate of HCL will trend towards that of the adult female T1DM population of the same age, but will remain superior to it.

7.3 Strengths and limitations of analysis

The clinical analysis prioritised randomised controlled evidence that provides superior evidence to other study designs. The clinical evidence also provided additional observational evidence to compare to the NHS audit studies. The analysis was conducted following Cochrane Handbook for Systematic Reviews of Interventions. Forest plots and

network-meta analysis results were presented. Transitivity of the network is threatened because the RCTs were heterogeneous in multiple respects including trial design (parallel groups or cross over design with wash-out phase between different treatments), participants' age, number of participants, and other demographics including run-in times, duration of observation periods, and number and types of previous treatments. Studies screened relatively small numbers of patients. The number of participants randomised ranged from < 20 to 135. However, sensitivity and subgroup analysis were performed and provided some reassurance in our findings. The quality of observational studies is generally poor. Nevertheless, the outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Half of the included studies included UK centres therefore represents some relevance to UK settings. There was very limited evidence on pregnancy and the effectiveness of HCL in pregnant women remains unclear.

A strength and a weakness of the analysis is the availability of published iQVIA CDM validation data against long terms observational studies. This validation data relates at least in part to earlier model iterations of the iQVIA CDM than that used by the EAG. The strength is its availability, it often being absent from other NICE assessments. But it highlights some uncertainty about the reliability of the modelling of the incidence of retinopathy, in one validation exercise this having been overestimated by around 30% for the intervention arm of the EDIC trial, and of the incidence of ESRD, this having been overestimated by around 250% for the intervention arm of the EDIC trial. Modelling of survival appears reasonable in the medium term but the longer term modelling of survival is subject to more uncertainty.

The net HbA1c effect, its duration and the resulting costs offsets from reduced eye and renal complications determine whether HCL is likely to be estimated to be cost effective at conventional thresholds. The trials were of relatively short duration which argues for consideration of shorter effect durations.

There is an argument for reducing the eye and renal cost offsets proportionately to their possible overestimation. Uncertainty around the modelled overall survival argues for consideration of shorter time horizons.

The uncertainty around the modelled long term survival coupled with uncertainty about how much of the clinical data underlying model construction was drawn from a paediatric population causes the EAG to view paediatric modelling using the iQVIA CDM with some caution.

A weakness of the analysis is the lack of data on the effect of HCL upon symptomatic and severe hypoglycaemia events. The EAG has inferred these from the ratio of time below 3.0mmol/l for HCL compared to that of the other comparators, coupled with event rates for HCL. There is considerable uncertainty around these and the EAG only presents the possible effects of hypoglycaemic events within scenario analyses. It should also be noted that the EAG preferred quality of life function for hypoglycaemia events differs from that of NG17 and suggests a somewhat smaller effect.

7.4 Conclusions

RCTs of HCL interventions in comparison CSII+CGM or sensor augmented pump therapy achieved a statistically significant improvement in HbA1c %, in TIR between 3.9 to 10 mmol/L, and in hyperglycaemic levels. The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. Measures of glycaemic performance such as HbA1c%, % time in range (3.9 to 10 mmol/L), and % time above range >10 mmol/L all improved on transfer to HCL.

Well-designed RCTs are needed to explore the effectiveness of hybrid closed loop systems in larger samples of people, with longer follow-ups, and in in pregnant women. Trials that include a wider variety of participants, for example people with poor glycaemic control, or who live in remote or rural areas, would be helpful. Trials that collect data to support economic modelling of hybrid closed loop systems, such as quality of life and adverse events would be very beneficial. Studies are required to clearly describe comparators and should ideally use real time GM+CSII or FGM+CSII as the

control group, as these are the most relevant comparators. There is a lack of evidence on the long term effect of the hybrid closed loop system and especially on clinical outcomes such as cardiovascular disease. Carer outcomes and patient reported outcomes are not systematically captured or reported.

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Diabetes: A Cross-Sectional Study in Thailand. *J Diabetes Res* 2019;**2019**:5903820. http://dx.doi.org/10.1155/2019/5903820

9 APPENDICES

9.1 Appendix 1: Literature Search Strategies

9.1.1 Record of searches – Clinical effectiveness

Overview:

Database / website	**Date searched (date updated)**	**Number of records + update number of records = TOTAL**
MEDLINE ALL (Ovid)	31/03/21 (11/04/22)	1,914 + 789 = 2703
Embase (Ovid)	31/03/21 (11/04/22)	4,267 + 1210 = 5477
Science Citation Index & Conference Proceedings - Science (Web of Science)	31/03/21 (12/04/22)	2,190 + 514 = 2704
Cochrane Library (Wiley)	31/03/21 (12/04/22)	1,327 [all CENTRAL, 0 CDSR] + 159 [all CENTRAL, 0 CDSR] = 1486
Clinicaltrials.gov	12/04/21 (12/04/22)	392 + 57 = 449
HTA database (CRD)	07/04/21	16*
International HTA database (INAHTA)	07/04/21 (06/04/22)	22 + 10 = 32
NIHR Journals Library	12/04/21 (12/04/22)	5 + 1 = 6
AHRQ website	12/04/21 (06/04/22)	1 + 0 + 1
CADTH website	12/04/21 (07/04/22)	14 + 2 = 16
SBU website	12/04/21 (07/04/22)	0 + 0 = 0

* No new records in database so search did not require updating

Note: The WHO International Clinical Trials Registry Platform (ICTRP) was not searched due to being unavailable between 12/4/21 and 22/4/21.

Total results: 10,148 + 2742 from update = 12,890
Total after 4,211 duplicates removed + 1005 duplicates within update results + 382 duplicates with original results removed = 7292

Also searched for background information about hybrid closed loop technologies:

Website	Date searched	Number of records
FDA devices databases	21/04/21	12
MHRA (via www.gov.uk)	22/04/21	7

Search strategies:

Note: See below each database strategy for details of update searches

Medline (via Ovid)

Date searched: 31/03/21
Database: Ovid MEDLINE(R) ALL <1946 to March 30, 2021>
Search Strategy:
---
1 Diabetes Mellitus, Type 1/ (77349)
2 Diabetic Ketoacidosis/ (6613)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kf,ti. (56549)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kf,ti. (28252)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kf,ti. (33812)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kf,ti. (23572)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kf,ti. (11574)
8 Hyperglycemia/ (28751)
9 Hypoglycemia/ (27924)
10 (hyperglyc?em$ or hypoglyc?em$).ab,kf,ti. (116536)
11 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kf,ti. (151415)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 [population: T1DM] (365002)
13 Pancreas, Artificial/ (816)
14 closed loop.ab,kf,ti. (10516)
15 (artificial adj2 (pancreas or beta cell$)).ab,kf,ti. (1729)
16 (bionic adj2 pancreas).ab,kf,ti. (25)
17 (Automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kf,ti. (285)
18 ((minimed or medtronic) and (670G or 780G)).ab,kf,ti. (57)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,kf,ti. (175)
20 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (12163)

21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kf,ti. (7798)
22 SAPT.ab,kf,ti. (533)
23 predictive low glucose.ab,kf,ti. (95)
24 basal iq.ab,kf,ti. (9)
25 ((minimed or medtronic) and 640G).ab,kf,ti. (33)
26 (paradigm$ adj3 (veo or pump$)).ab,kf,ti. (57)
27 (veo adj3 pump$).ab,kf,ti. (9)
28 (g4 adj3 platinum).ab,kf,ti. (58)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,kf,ti. (14)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (8467)
31 Insulin Infusion Systems/ (5477)
32 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kf,ti. (14806)
33 (pump$ adj2 (therap$ or treatment$)).ab,kf,ti. (3223)
34 ((subcutaneous adj2 insulin$) or CSII).ab,kf,ti. (3863)
35 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,kf,ti. (376)
36 (medtronic adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (719)
37 (tandem adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (925)
38 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,kf,ti. (34)
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 [insulin pumps/CSII] (20952)
40 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kf,ti. (5859)
41 (glucose adj (sensor$ or sensing)).ab,kf,ti. (4186)
42 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kf,ti. (4526)
43 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,kf,ti. (2410)
44 40 or 41 or 42 or 43 [continuous or flash glucose monitors] (13031)
45 (2014082* or 2014083* or 201409* or 201410* or 201411* or 201412* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).dt,ez,da. [added to database since search for previous DAR in 2014] (8960844)
46 12 and 20 and 45 [T1DM and closed loop + date limit] (1134)
47 12 and 30 and 45 [T1DM and SAPT + date limit] (498)
48 12 and 39 and 44 and 45 [T1DM and pumps and GMs + date limit] (1090)
49 46 or 47 or 48 (1951)
50 limit 49 to english language (1903)
51 exp Pregnancy/ (912957)
52 exp Pregnancy Complications/ (435723)
53 Perinatal Care/ or Preconception Care/ or Prenatal Care/ (35143)
54 exp Cesarean Section/ (46694)
55 Pregnant Women/ (9180)
56 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kf,ti. (1208728)

57 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kf,ti. (352238)
58 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kf,ti. (364876)
59 apgar.ab,kf,ti. (12586)
60 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 [pregnancy, planning pregnancy, pregnancy complications; broad] (1735176)
61 exp Insulin/ and Injections, Subcutaneous/ (2455)
62 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (1309)
63 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (563)
64 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (10207)
65 MDI.ti,ab,kf. (3832)
66 (injection adj3 therapy).ti,ab,kf. (4196)
67 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,kf. (1376)
68 (short acting adj3 insulin).ti,ab,kf. (576)
69 (rapid acting adj3 insulin).ti,ab,kf. (799)
70 or/61-69 [insulin injections] (21919)
71 Blood Glucose Self-Monitoring/ (7126)
72 Blood Glucose/ (167907)
73 (blood glucos$ or blood sugar$).ab,kf,ti. (87354)
74 72 or 73 (210595)
75 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kf,ti. (43222)
76 (capillary adj4 (test$ or measur$)).ab,kf,ti. (5082)
77 75 or 76 (47993)
78 74 and 77 (5789)
79 SMBG.ab,kf,ti. (1195)
80 glucometer$.ab,kf,ti. (1146)
81 71 or 78 or 79 or 80 [self monitoring of blood glucose] (11381)
82 44 and 70 [continuous or flash GMs AND MDI] (488)
83 81 and 39 [SMBG AND CSII] (1709)
84 82 or 83 (2022)
85 12 and 60 and 84 and 45 [T1DM and pregnancy and any of the comparator groups specific to this population + date limit] (55)
86 limit 85 to english language (54)
87 50 or 86 (1914)

Update
Date searched: 11/04/22
Re-ran above search with search line 45 altered to:
45 ("20210331" or 202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022*).dt,ez,da. [added to database since original MTA search in March 2021]
Total:
87 50 or 86 (789)

Search strings used in the previous technology assessment on integrated sensor-augmented pump therapy systems were used as the basis for developing selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections:

Appendix 1: Literature search strategies. In: Riemsma R, Corro Ramos I, Birnie R, Büyükkaramikli N, Armstrong N, Ryder S, et al. Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation. Health Technol Assess 2016;20(17):v-xxxi, 1-251. http://dx.doi.org/10.3310/hta20170

The following were used as sources of search terms for pregnancy and related concepts:

Tessier V. Périnatalité: Perinatality: Rappel favorisé sur la précision. Canadian Health Libraries Association - Association des bibliothèques de la santé du Canada; 2017. URL: https://extranet.santecom.qc.ca/wiki/!biblio3s/doku.php?id=concepts:perinatalite (Accessed 26 April 2021).

Kyrgiou M, Mitra A, Arbyn M, Paraskevaidi M, Athanasiou A, Martin-Hirsch PPL, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2015. http://dx.doi.org/10.1002/14651858.CD008478.pub2

Cochrane Pregnancy and Childbirth's Trials Register: Detailed search methods used to maintain and update the Specialised Register. 2018. URL: https://pregnancy.cochrane.org/sites/pregnancy.cochrane.org/files/public/uploads/cochrane_pregnancy_and_childbirth_search_methods_2018_1.docx (Accessed 26 April 2021).

Embase (via Ovid)

Date searched: 31/03/21
Database: Embase <1974 to 2021 March 30>
Search Strategy:
---
1 insulin dependent diabetes mellitus/ (120636)
2 diabetic ketoacidosis/ (13211)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kw,ti. (89362)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kw,ti. (39641)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kw,ti. (42438)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kw,ti. (41350)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kw,ti. (17665)
8 hypoglycemia/ or insulin hypoglycemia/ or nocturnal hypoglycemia/ or hyperglycemia/ (169981)
9 (hyperglyc?em$ or hypoglyc?em$).ab,kw,ti. (171413)
10 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kw,ti. (219463)

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 [population: T1DM] (552812)
12 exp artificial pancreas/ (2518)
13 "glucose monitoring/insulin pump system"/ (19)
14 closed loop.ab,kw,ti. (13542)
15 (artificial adj2 (pancreas or beta cell$)).ab,kw,ti. (2728)
16 (bionic adj2 pancreas).ab,kw,ti. (84)
17 (automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kw,ti. (501)
18 ((minimed or medtronic) and (670G or 780G)).ab,dm,dv,kw,ti. (204)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,dm,dv,kw,ti. (452)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (16556)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kw,ti. (9751)
22 SAPT.ab,kw,ti. (498)
23 predictive low glucose.ab,kw,ti. (216)
24 basal iq.ab,dm,dv,kw,ti. (35)
25 ((minimed or medtronic) and 640G).ab,dm,dv,kw,ti. (162)
26 (paradigm$ adj3 (veo or pump$)).ab,dm,dv,kw,ti. (251)
27 (veo adj3 pump$).ab,dm,dv,kw,ti. (63)
28 (g4 adj3 platinum).ab,dm,dv,kw,ti. (215)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,dm,dv,kw,ti. (56)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (10819)
31 insulin infusion/ (8355)
32 insulin pump/ or implantable insulin pump/ (7934)
33 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kw,ti. (23686)
34 (pump$ adj2 (therap$ or treatment$)).ab,kw,ti. (6128)
35 ((subcutaneous adj2 insulin$) or CSII).ab,kw,ti. (7275)
36 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,dm,dv,kw,ti. (1653)
37 (medtronic adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (3028)
38 (tandem adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (1170)
39 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,dm,dv,kw,ti. (174)
40 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 [insulin pumps/CSII] (36787)
41 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kw,ti. (10566)
42 (glucose adj (sensor$ or sensing)).ab,kw,ti. (5539)
43 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kw,ti. (8864)
44 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,dm,dv,kw,ti. (4605)
45 41 or 42 or 43 or 44 [continuous or flash glucose monitors] (20571)
46 11 and 20 [T1DM and closed loop] (4001)
47 11 and 30 [T1DM and SAPT] (1703)
48 11 and 40 and 45 [T1DM and pumps and GMs] (4215)
49 46 or 47 or 48 (7448)

50 limit 49 to dc=20140825-20210331 (4300)
51 limit 50 to english language (4177)
52 exp pregnancy/ (688558)
53 exp pregnancy disorder/ (555248)
54 exp cesarean section/ (101840)
55 pregnant woman/ (87032)
56 pregnancy outcome/ (63986)
57 perinatal care/ or prepregnancy care/ or prenatal care/ (57151)
58 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kw,ti. (1447977)
59 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kw,ti. (455281)
60 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kw,ti. (465863)
61 apgar.ab,kw,ti. (19929)
62 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 [pregnancy, planning pregnancy, pregnancy complications; broad] (1956753)
63 blood glucose monitoring/ (28256)
64 glucose blood level/ (263683)
65 (blood glucos$ or blood sugar$).ab,kw,ti. (130425)
66 64 or 65 (300041)
67 self monitoring/ (8173)
68 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kw,ti. (67932)
69 (capillary adj4 (test$ or measur$)).ab,kw,ti. (6773)
70 67 or 68 or 69 (76712)
71 66 and 70 (9965)
72 SMBG.ab,kw,ti. (2497)
73 glucometer$.ab,kw,ti. (2300)
74 63 or 71 or 72 or 73 [self monitoring of blood glucose] (35552)
75 insulin/ and exp injection/ (5679)
76 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (2612)
77 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (783)
78 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (15088)
79 MDI.ab,kw,ti. (6716)
80 (injection adj3 therapy).ab,kw,ti. (6291)
81 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ab,kw,ti. (2369)
82 (short acting adj3 insulin).ab,kw,ti. (969)
83 (rapid acting adj3 insulin).ab,kw,ti. (1412)
84 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 [insulin injections / MDI] (34854)
85 45 and 84 [continuous or flash GMs AND MDI] (1390)
86 74 and 40 [SMBG AND CSII] (5410)
87 85 or 86 (6238)

88 11 and 62 and 87 [T1DM and pregnancy and any comparator group specific to the pregnancy population] (443)
89 limit 88 to dc=20140825-20210331 (240)
90 limit 89 to english language (233)
91 51 or 90 (4267)

Update
Date searched: 11/04/22
Re-ran above search with search lines 50 and 89 altered to:
50 limit 49 to dc=20210331-20220411
89 limit 88 to dc=20210331-20220411
Total:
91 51 or 90 (1210)

Science Citation Index – Expanded & Conference Proceedings Citation Index - Science (via Web of Science)

Date searched: 31/03/21

# 69	2,190	#68 OR #43 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 68	43	(#66 AND #48 AND #8) *AND* **LANGUAGE:** (English) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 67	47	#66 AND #48 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 66	605	#65 OR #64 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 65	248	#55 AND #33 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 64	400	#63 AND #38 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 63	6,208	#62 OR #61 OR #60 OR #59 OR #58 OR #57 OR #56 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 62	1,189	TS=(insulin* NEAR/0 inject*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 61	338	TS=("rapid acting" NEAR/3 insulin) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 60	137	TS=("short acting" NEAR/3 insulin) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 59	1,994	TS=(injection NEAR/3 therapy) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 58	2,420	TS=MDI *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

# 57	109	TS=("multiple dose" NEAR/3 (inject* OR insulin* OR regime* OR routine*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 56	737	TS=("multiple daily" NEAR/3 (inject* OR insulin* OR regime* OR routine*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 55	2,407	#54 OR #53 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 54	1,088	TS=(SMBG OR glucometer*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 53	1,823	#52 AND #49 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 52	57,400	#51 OR #50 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 51	2,658	TS=(capillary NEAR/4 (test* OR measur*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 50	54,859	TS=("self monitor*" OR "test* strip*" OR "finger prick*" OR fingerprick* OR "finger stick*" OR fingerstick* OR lancet* OR meter*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 49	32,964	TS=("blood glucos*" OR "blood sugar*") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 48	450,041	#47 OR #46 OR #45 OR #44 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 47	3,630	TS=apgar *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 46	103,621	TS=(perinatal OR "peri natal" OR fetal OR foetal OR intrauterine OR "intra uterine") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 45	124,549	TS=(miscarr* OR abort* OR cesarean OR caesarean OR "c section*" OR (prematur* AND (birth* OR rupture* OR infant*)) OR preterm OR "pre term" OR prematurity OR prom OR macrosomia* OR "birth weight*" OR birthweight* OR eclamp* OR preeclamp* OR stillbirth* OR "still birth*" OR stillborn* OR "still born*") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 44	379,961	TS=(pregnan* OR "ante natal*" OR antenatal* OR "pre natal*" OR prenatal* OR (expectant* NEAR/2 mother*) OR "mother* to be" OR matern* OR conception* OR preconception* OR "trying to conceive" OR prepregnan* OR periconception* OR "giving birth" OR childbirth* OR labo*r OR newborn* OR "new born*" OR neonat* OR "neo nat*" OR baby OR babies) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 43	2,175	(#41 OR #40 OR #39) *AND* **LANGUAGE:** (English) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 42	2,255	#41 OR #40 OR #39

		Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021
# 41	983	#38 AND #33 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 40	593	#25 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 39	1,445	#15 AND #8 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 38	14,694	#37 OR #36 OR #35 OR #34 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 37	1,701	TS=(dexcom OR freestyle OR libre OR enlite OR (guardian AND (medtronic OR sensor)) OR eversense OR "glucomen day") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 36	7,203	TS=(CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 35	4,043	TS=(glucose NEAR/0 (sensor* OR sensing)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 34	4,292	TS=((continu* OR flash OR intermittent* OR sensor OR sensors or "real time") NEAR/4 glucose NEAR/4 (monitor* OR measurement*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 33	9,131	#32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 32	26	TS=((accu-chek OR accuchek) NEAR/3 (pump* OR system* OR deliver* OR combo OR insight OR solo)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 31	1,121	TS=(tandem NEAR/3 (pump* OR system* OR deliver*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 30	310	TS=(medtronic NEAR/3 (pump* OR system* OR deliver*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 29	232	TS=(minimed OR "dana diabecare" OR "dana R" OR "dana RS" OR kaleido OR omnipod OR medtrum OR touchcare OR ypsopump OR cellnovo) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 28	1,748	TS=((subcutaneous NEAR/2 insulin*) OR CSII) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 27	2,715	TS=(pump* NEAR/2 (therap* OR treatment*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 26	5,555	TS=(insulin* NEAR/3 (pump* OR infus* OR deliver* OR catheter*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 25	14,388	#24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 24	12	TS=((animas OR vibe) NEAR/3 (pump* OR infus* OR system*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 23	53	TS=(g4 NEAR/3 platinum)

		Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021
# 22	7	TS=(veo NEAR/3 pump*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 21	40	TS=(paradigm* NEAR/3 (veo OR pump*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 20	45	TS=((minimed OR medtronic) AND 640G) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 19	12	TS="basal iq" *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 18	115	TS="predictive low glucose" *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 17	440	TS=SAPT *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 16	13,776	TS=(sensor$ NEAR/3 (augment* OR integrat* OR pump$ OR insulin)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 15	42,226	#14 OR #13 OR #12 OR #11 OR #10 OR #9 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 14	177	TS=(tslim OR "t slim" OR "control iq" OR camAPS OR camdiab OR "dexc om G6" OR "dexcom G7" OR smartguard OR "smart guard" OR diabeloop OR dblg1 OR ilet OR "beta bionics" OR (omnipod AND horizon) OR (mylife AND loop) OR (tidepool AND loop) OR bigfoot OR "anydana loop") *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 13	88	TS=((minimed OR medtronic) AND (670G OR 780G)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 12	258	TS=(automat* NEAR/2 ("insulin deliver*" OR "insulin dosing" OR "glucose control*" OR "glyc$emic control*")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 11	124	TS=(bionic NEAR/2 pancreas) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 10	1,299	TS=(artificial NEAR/2 (pancreas OR "beta cell*")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 9	41,216	TS="closed loop" *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 8	146,413	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 7	78,894	TS=((high OR higher OR low OR lower OR increas* OR decreas* OR defic ien* OR sufficien* OR insufficien* OR reduce* OR reduction* OR fluctuat * OR fallen OR falling OR threshold OR safe) NEAR/3 (glucose* OR sugar* OR hba1c OR "hb a1" OR hba1 OR a1c OR h$emoglob* OR glycoh$emoglob*)) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 6	47,313	TS=(hyperglyc$em* OR hypoglyc$em*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

# 5	4,801	TS=(ketoacidosis OR acidoketosis OR "keto acidosis" OR ketoacidemia OR ketosis OR dka) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 4	11,210	TS=(dm1 OR "dm 1" OR dmt1 OR "dm t1" OR t1dm OR "t1 dm" OR t1d OR iddm) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 3	3,716	TS=((insulin* NEAR/2 depend*) OR insulindepend*) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 2	11,031	TS=(diabet* NEAR/3 (britt* OR juvenil* OR pediatric OR paediatric OR early OR keto* OR labil* OR acidos* OR autoimmun* OR "auto immun*" OR "sudden onset")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*
# 1	27,913	TS=(diabet* NEAR/3 ("typ* 1" OR "typ* i" OR type1 OR typei OR "typ* one")) *Indexes=SCI-EXPANDED, CPCI-S Timespan=2014-2021*

Update
Date searched: 12/04/22
Original search above not fully saved in WoS because it is over 40 lines so strategy re-entered using fewer lines (one line for each concept), combined as above and run with Timespan altered to:
Timespan: 2021-03-31 to 2022-04-12 (Index Date)
Total: 514

The Ovid Medline search strategy was translated for use in Web of Science with the aid of the Polyglot Search Translator:
Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc 2020;108(2):195-207. http://dx.doi.org/10.5195/jmla.2020.834

Cochrane Database of Systematic Reviews (CDSR) & Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Cochrane Library)

Date searched: 31/03/21
Search interface: https://www.cochranelibrary.com/advanced-search/search-manager

#1	[mh ^"Diabetes Mellitus, Type 1"]	5614
#2	[mh ^"Diabetic Ketoacidosis"]	139
#3	(diabet* NEAR/3 ((typ* NEXT 1) OR (typ* NEXT i) OR type1 OR typei OR (typ* NEXT one))):ti,ab,kw	10200
#4	(diabet* NEAR/3 (britt* OR juvenil* OR pediatric OR paediatric OR early OR keto* OR labil* OR acidos* OR autoimmun* OR (auto NEXT immun*) OR "sudden onset")):ti,ab,kw	3429

#5	((insulin* NEAR/2 depend*) OR insulindepend*):ti,ab,kw	22663
#6	(dm1 OR (dm NEXT 1) OR dmt1 OR (dm NEXT t1) OR t1dm OR "t1 dm" OR t1d OR iddm):ti,ab,kw	3481
#7	(ketoacidosis OR acidoketosis OR "keto acidosis" OR ketoacidemia OR ketosis OR dka):ti,ab,kw	1174
#8	[mh ^Hyperglycemia]	1952
#9	[mh ^Hypoglycemia]	2258
#10	(hyperglyc?em* OR hypoglyc?em*):ti,ab,kw	24948
#11	((high OR higher OR low OR lower OR increase* OR decreas* OR deficien* OR sufficien* OR insufficien* OR reduce* OR reduction* OR fluctuat* OR fallen OR falling OR threshold OR safe) NEAR/3 (glucose* OR sugar* OR hba1c OR (hb NEXT a1) OR hba1 OR a1c OR h?emoglob* OR glycoh?emoglob*)):ti,ab,kw	23784
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	59772
#13	[mh ^"Pancreas, Artificial"]	73
#14	"closed loop":ti,ab,kw	1264
#15	(artificial NEAR/2 (pancreas OR (beta NEXT cell*))):ti,ab,kw	365
#16	(bionic NEAR/2 pancreas):ti,ab,kw	47
#17	(automat* NEAR/2 ((insulin NEXT deliver*) OR "insulin dosing" OR (glucose NEXT control*) OR (glyc?emic NEXT control*))):ti,ab,kw	117
#18	((minimed OR medtronic) AND (670G OR 780G)):ti,ab,kw	32
#19	(tslim OR "t slim" OR "control iq" OR camAPS OR camdiab OR "dexcom G6" OR “dexcom G7” OR smartguard OR "smart guard" OR diabeloop OR dblg1 OR ilet OR "beta bionics" OR (omnipod AND horizon) OR (mylife AND loop) OR (tidepool AND loop) OR bigfoot OR "anydana loop"):ti,ab,kw	152
#20	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	1564
#21	(sensor? NEAR/3 (augment* OR integrat* OR pump? OR insulin)):ti,ab,kw	838
#22	SAPT:ti,ab,kw	48
#23	"predictive low glucose":ti,ab,kw	63
#24	"basal iq":ti,ab,kw	11
#25	((minimed OR medtronic) AND 640G):ti,ab,kw	30
#26	(paradigm* NEAR/3 (veo OR pump*)):ti,ab,kw	42
#27	(veo NEAR/3 pump*):ti,ab,kw	24
#28	(g4 NEAR/3 platinum):ti,ab,kw	39
#29	((animas OR vibe) NEAR/3 (pump* OR infus* OR system*)):ti,ab,kw	17
#30	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	984
#31	[mh ^"Insulin Infusion Systems"]	669
#32	(insulin* NEAR/3 (pump* OR infus* OR deliver* OR catheter*)):ti,ab,kw	4129
#33	(pump* NEAR/2 (therap* OR treatment*)):ti,ab,kw	1666
#34	((subcutaneous NEAR/2 insulin*) OR CSII):ti,ab,kw	1528

#35	(minimed OR "dana diabecare" OR "dana R" OR "dana RS" OR kaleido OR omnipod OR medtrum OR touchcare OR ypsopump OR cellnovo):ti,ab,kw	203
#36	(medtronic NEAR/3 (pump* OR system* OR deliver*)):ti,ab,kw	214
#37	(tandem NEAR/3 (pump* OR system* OR deliver*)):ti,ab,kw	57
#38	((accu-chek OR accuchek) NEAR/3 (pump* OR system* OR deliver* OR combo OR insight OR solo)):ti,ab,kw	17
#39	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	5680
#40	((continu$ or flash or intermittent$ or sensor or sensors or real time) NEAR/4 glucose NEAR/4 (monitor* OR measurement*)):ti,ab,kw	625
#41	(glucose NEXT (sensor? OR sensing)):ti,ab,kw	348
#42	(CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS):ti,ab,kw	2033
#43	(dexcom OR freestyle OR libre OR enlite OR (guardian AND (medtronic OR sensor)) OR eversense OR "glucomen day"):ti,ab,kw	1563
#44	#40 OR #41 OR #42 OR #43	3621
#45	#12 AND #20	861
#46	#12 AND #30	556
#47	#12 AND #39 AND #44	853
#48	#45 OR #46 OR #47	1520
#49	#45 OR #46 OR #47 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021*	1319
#50	[mh Pregnancy]	22393
#51	[mh "Pregnancy Complications"]	12074
#52	[mh ^"Perinatal Care"] OR [mh ^"Preconception Care"] OR [mh ^"Prenatal Care"]	1792
#53	[mh "Cesarean Section"]	3153
#54	[mh ^"Pregnant Women"]	297
#55	(pregnan* OR (ante NEXT natal*) OR antenatal* OR (pre NEXT natal*) OR prenatal* OR (expectant* NEAR/2 mother*) OR (mother? NEAR/2 "to be") OR matern* OR conception* OR preconception* OR "trying to conceive" OR prepregnan* OR periconception* OR "giving birth" OR childbirth* OR labo?r OR newborn* OR (new NEXT born*) OR neonat* OR (neo NEXT nat*) OR baby OR babies):ti,ab,kw	107835
#56	(miscarr* OR abort* OR cesarean OR caesarean OR (c NEXT section*) OR (prematur* AND (birth* OR rupture* OR infant*)) OR preterm OR "pre term" OR prematurity OR prom OR macrosomia* OR (birth NEXT weight*) OR birthweight* OR eclamp* OR preeclamp* OR stillbirth* OR (still NEXT birth*) OR stillborn* OR (still NEXT born*)):ti,ab,kw	46780
#57	(perinatal OR "peri natal" OR fetal OR foetal OR intrauterine OR "intra uterine"):ti,ab,kw	21877
#58	apgar:ti,ab,kw	4463

#59	#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	122190
#60	[mh Insulin] AND [mh ^"Injections, Subcutaneous"]	454
#61	("multiple daily" NEAR/3 (inject* OR insulin* OR regime* OR routine*)):ti,ab,kw	714
#62	("multiple dose" NEAR/3 (inject* OR insulin* OR regime* OR routine*)):ti,ab,kw	249
#63	(multiple NEAR/3 (inject* OR insulin* OR regime* OR routine*)):ti,ab,kw	2186
#64	MDI:ti,ab,kw	2986
#65	(injection NEAR/3 therapy):ti,ab,kw	2610
#66	((basal* AND bolus) NEAR/3 (injection* OR regime* OR routine* OR system*)):ti,ab,kw	3745
#67	("short acting" NEAR/3 insulin):ti,ab,kw	363
#68	("rapid acting" NEAR/3 insulin):ti,ab,kw	417
#69	#60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68	11689
#70	[mh ^"Blood Glucose Self-Monitoring"]	805
#71	[mh ^"Blood Glucose"]	16258
#72	((blood NEXT glucose*) OR (blood NEXT sugar*)):ti,ab,kw	34151
#73	#71 OR #72	34151
#74	((self NEXT monitor*) OR (test* NEXT strip*) OR (finger NEXT prick*) OR fingerprick* OR (finger NEXT stick*) OR fingerstick* OR lancet? OR meter?):ti,ab,kw	14651
#75	(capillary NEAR/4 (test* OR measur*)):ti,ab,kw	600
#76	#74 OR #75	15159
#77	#73 AND #76	2965
#78	SMBG:ti,ab,kw	797
#79	glucometer*:ti,ab,kw	401
#80	#70 OR #77 OR #78 OR #79	3438
#81	#44 AND #69	400
#82	#39 AND #80	513
#83	#81 OR #82	822
#84	#12 AND #59 AND #83	52
#85	#12 AND #59 AND #83 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021*	44
#86	#49 OR #85	1327
#87	#49 OR #85 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021, in Cochrane Reviews and Cochrane Protocols*	0
#88	#49 OR #85 *with Limits: Cochrane Library publication date from Sep 2014 to Apr 2021, in Trials*	1327

Update
Date searched: 12/04/22
Re-ran above search with limit for search lines 49, 85, 87 and 88 altered to:
Cochrane Library publication date from Apr 2021 to Apr 2022
Results:

#87	#49 OR #85 *with Limits: Cochrane Library publication date from* Apr 2021 to Apr 2022*, in Cochrane Reviews and Cochrane Protocols*	0
#88	#49 OR #85 *with Limits: Cochrane Library publication date from* Apr 2021 to Apr 2022*, in Trials*	159

The Ovid Medline search strategy was translated for use in the Cochrane Library with the aid of the Polyglot Search Translator:
Clark JM, Sanders S, Carter M, Honeyman D, Cleo G, Auld Y, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. J Med Libr Assoc 2020;108(2):195-207. http://dx.doi.org/10.5195/jmla.2020.834

clinicaltrials.gov

Date searched: 12/04/21
Search interface: 'Advanced search' https://clinicaltrials.gov/ct2/search/advanced

Original search	Results	Update	Results
"closed loop" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021	190	"closed loop" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	29
"artificial pancreas" OR "artificial endocrine pancreas" OR "bionic pancreas" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021	158	"artificial pancreas" OR "artificial endocrine pancreas" OR "bionic pancreas" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	15
"minimed 670G" OR "minimed 780G" OR "control iq" OR camaps OR camdiab OR "dexcom G6" OR "dexcom G7" [other terms] | (diabetes AND "type 1") OR	83	"minimed 670G" OR "minimed 780G" OR "control iq" OR camaps OR camdiab OR "dexcom G6" OR "dexcom G7" [other terms] | (diabetes AND "type 1")	30

hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021		OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	
"sensor augmented" OR SAPT OR "predictive low glucose" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 01/01/2014 to 04/12/2021	79	"sensor augmented" OR SAPT OR "predictive low glucose" [other terms] | (diabetes AND "type 1") OR hypoglycemia OR hyperglycemia [condition or disease] | First posted from 04/12/2021 to 04/12/2022	1
insulin AND infusion AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	95	insulin AND infusion AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	11
insulin AND infusion AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	107	insulin AND infusion AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	11
("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	197	("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	27
("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	210	("insulin pump" OR "insulin pumps" OR "subcutaneous insulin") AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	27

CSII AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	39	CSII AND ("glucose monitor" OR "glucose monitors" OR "glucose monitoring") [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	6
CSII AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	42	CSII AND (CGM OR CGMs OR FGM OR FGMs OR iCGM OR iCGMs OR rtCGM OR rtCGMS) [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	5
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	6	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	0
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	4	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND injection AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	1
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	5	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND SMBG [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	0
(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 01/01/2014 to 04/12/2021	5	(pregnancy OR pregnant OR conception OR preconception OR childbirth OR fetus) AND MDI AND "self monitoring" [other terms] | diabetes AND "type 1" [condition or disease] | First posted from 04/12/2021 to 04/12/2022	0

Total:	1220		163
Total after duplicate removal (using EndNote):	392		57

Update

Date searched: 12/04/22. For update search and numbers see right-hand columns in original strategy table above. 57 new.

Health Technology Assessment (HTA) database (via CRD website)

Date searched: 07/04/21
Search interface: https://www.crd.york.ac.uk/CRDWeb/

((closed loop) OR (artificial NEAR2 pancreas) OR (bionic NEAR2 pancreas)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	2
((minimed or control iq or camAPS or camdiab or dexcom)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((sensor augmented) OR (SAPT)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((automat* NEAR2 (insulin OR glucose OR glycemic OR glycaemic))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	0
((insulin NEAR2 (pump* OR infus*)) OR (subcutaneous NEAR2 insulin*) OR (CSII)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	10
((continu* or flash or intermittent* or sensor or sensors or real time) AND (glucose) AND (monitor* or measurement*)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	6
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	3
((diabet* or insulin*) AND (pregn*) AND (injection* or MDI or self monitoring or SMBG)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
Total unique records:	16

No new records so update search not needed.

International HTA database (via INAHTA website)

Date searched: 07/04/21
Search interface: Advanced search builder https://database.inahta.org/search/advanced

(closed loop) FROM 2014 TO 2021	0
(artificial pancreas) FROM 2014 TO 2021	2
(bionic pancreas) FROM 2014 TO 2021	0
(minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2021	2
("Pancreas, Artificial"[mh]) FROM 2014 TO 2021	2
("sensor augmented") FROM 2014 TO 2021	1
(SAPT) FROM 2014 TO 2021	0
("Insulin Infusion Systems"[mh]) FROM 2014 TO 2021	7
(insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2021	8
(CSII) FROM 2014 TO 2021	2
((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2021	15
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2021	7
((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2021	4
Total:	50
Total after duplicate removal (using EndNote):	22

Update

Date searched: 06/04/22
Re-ran search above search in one line with end date altered to 2022:

(((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2022) OR (((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2022) OR (((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2022) OR ((CSII) FROM 2014 TO 2022) OR ((insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2022) OR (("Insulin Infusion Systems"[mh]) FROM 2014 TO 2022) OR ((SAPT) FROM 2014 TO 2022) OR (("sensor

augmented") FROM 2014 TO 2022) OR (("Pancreas, Artificial"[mh]) FROM 2014 TO 2022) OR ((minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2022) OR ((bionic pancreas) FROM 2014 TO 2022) OR ((artificial pancreas) FROM 2014 TO 2022) OR ((closed loop) FROM 2014 TO 2022)

Total: 32

Notes: After checking several lines from the original search above and finding some of the new records were for HTAs were published before 2021, it was decided that all 32 should be exported and de-duplicated with the previous results in EndNote.

Total after de-duplication in EndNote: 10

NIHR Journals Library

Date searched: 12/04/21
Search interface: Basic search https://www.journalslibrary.nihr.ac.uk/#/

Search terms	**Total results**	**Total at update**	**Number of new (not in previous results or sets), possibly relevant results**
“closed loop”	3	3	0
"closed-loop"	2	3	1
"artificial pancreas"	2	1	0
"bionic pancreas"	0	0	0
Minimed	5	5	0
"Control IQ"	0	0	0
"Control-IQ"	0	0	0
camAPS	0	1	0
Camdiab	0	0	0
dexcom	0	1	0
"automated insulin delivery"	0	0	0
Total unique results, added since 2014:	*5*		*1*

Update

Date searched: 12/04/22. For numbers see right-hand column in original strategy table above. 1 new, 1 potentially relevant.

Agency for Healthcare Research and Quality (AHRQ) website

Agency for Healthcare Research and Quality (AHRQ) website

Date searched: 12/04/21

Search Publications: https://www.ahrq.gov/research/publications/search.html

Search terms	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	0		0	
diabetes	6	0 relevant	6 (0 new)	
insulin	0		0	

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 0 new.

Search Evidence Based Reports: https://www.ahrq.gov/research/findings/evidence-based-reports/search.html

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	0 relevant; about pancreatic adeno-carcinoma	1 (0 new)	
Browsed Topic: Endocrine conditions	25 reports, of which 10 published 2014-present	0 relevant	26 reports, of which 11 published 2014-present (1 new)	0 relevant

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 1 new, 0 relevant.

Full Research Reports: https://www.ahrq.gov/research/findings/final-reports/index.html
Checked 10 reports listed; none relevant.

Update. Checked again 06/04/22. 0 new reports listed.

Technology Assessment Program: https://www.ahrq.gov/research/findings/ta/index.html
Checked all reports and projects listed; none relevant

Update. Checked again 06/04/22. 0 new published reports listed. 1 new revised report listed, but not relevant.

Technology Assessment Archive (up to 2016): https://archive.ahrq.gov/clinic/techarch.htm
Used ctrl + F to search webpage for:

diabet
closed
pancreas
insulin
glucose

- nothing relevant found

AHRQ Research Studies: https://www.ahrq.gov/research/findings/studies/index.html

Search term	**Total results**	**Comments**	**Total at update 04/22**	**Comments at update 04/22**
Closed loop	4	0 relevant (all about closed loop communi-cation systems; not diabetes)	5 (1 new)	0 relevant (all about closed loop communi-cation systems; not diabetes)
Artificial pancreas	0		0	
Bionic pancreas	0		0	
insulin delivery	3	0 relevant	0	
minimed	0		0	
control iq	0		527 (technical	See new search in row below

			changes to search likely)	
control iq AND diabetes	-	-	58	Checked 2021 and 2022. None relevant
camAPS	0		0	
camdiab	0		0	
dexcom	0		0	
insulin pump	0		0	
insulin pumps	0		0	
insulin infusion	1	0 relevant	1 (0 new)	
insulin infusions	0		0	
CSII	0		0	
glucose monitoring	3	0 relevant (2 x type 2 diabetes, 1 about behaviour change)	6 (3 new)	0 relevant
glucose monitors	0		0	
glucose monitor	1	1 possibly relevant	1 (0 new)	
flash	0		0	
insulin AND injections	0		0	
daily injections	0		0	
blood glucose	13	0 relevant; either type 2 diabetes, or not about self-monitoring	15 (2 new)	0 relevant
smbg	0		0	
Total possibly relevant studies:		*1*		*0*

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 6 new, 0 relevant.

Canadian Agency for Drugs and Technologies in Health (CADTH) website

Date searched: 12/04/21
Search box on homepage https://www.cadth.ca/

Limit results by 'Result Type: Reports; Projects in Progress'.
Sort by Newest to Oldest (to enable easy exclusion of pre-2014 records)

Search terms	**Total results**	**Number of new (not in previous sets), possibly relevant results**	**Total at update 04/22**	**Number of new (not in previous results or sets), possibly relevant results**
"closed loop"	34	5	19	1
artificial pancreas	22	2	9	0
bionic pancreas	5	0	2	0
automated insulin delivery	18	0	10	0
minimed	16	1	5	0
"control IQ"	2	0	1	0
camAPS	0	0	0	0
camdiab	0	0	0	0
Dexcom	10	1	2	0
"insulin pump"	41	1	12	0
"insulin infusion"	51	0	5	0
CSII	23	0	3	0
"glucose monitor"	25	0	10	0
"glucose monitoring"	80	4	29	1
"insulin injections"	41	0	3	0
"daily injections"	43	0	8	0
"self monitoring" AND glucose	124	0	0	0
SMBG	31	0	5	0
Total unique, possibly relevant results:		*14*		*2*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 2 new, 2 potentially relevant.

Note: Assume website has been restructured or search interface / system changed since original search. Searched for words without quotation marks in 'Contains all the words' and terms in quotation marks in 'Advanced Search'. Sorted by Last updated and checked records for 2021 and 2022.

Swedish Agency For Health Technology Assessment And Assessment Of Social Services (SBU) website

Date searched: 12/04/21
Search box on home page: https://www.sbu.se/en/

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	not relevant; 'dialysis for acute hepatic failure'	1 (0 new)	
bionic pancreas	0		0	
diabetes > Filter on subject and publication type > Publication year From 2014 to 2021	30	0 relevant	5 new	0 relevant
insulin > Filter on subject and publication type > Publication year From 2014 to 2021	5	0 relevant	1 new	0 relevant
Total possibly relevant studies, published since 2014:		*0*		*0*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 0 relevant.

U.S. Food & Drug Administration (FDA) Premarket Notification, Premarket Approval & De novo databases (via FDA website)

Date searched: 21/4/21
Search interfaces:

- devices@FDA (searches PMN-510(k) Premarket Notification and PMA-Premarket Approval databases) https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm
- De novo database, 'device name' field https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm

Search terms	devices@FDA results	De novo database results	**Documents downloaded** (judged to contain potentially useful/relevant information not already identified in previous sets)

dexcom	13	2	3 decision summaries, 1 classification order
control-IQ	4	1	2 decision summaries, 1 classification order
control iq	Same results as control-IQ		0
t:slim	0	1	1 decision summary, 1 classification order
t slim	3	1	0
tslim	1	0	0
camaps	0	0	0
camdiab	0	0	0
minimed 670G	7	0	2 summaries of safety & effectiveness data
minimed 780G	0	0	0
minimed		0	0
smartguard	8	0	0
smart guard	2	0	0
ilet	0	0	0
beta bionics	0	0 (also tried 'Requester name' field)	0
closed loop	13		1 summary of safety & effectiveness data
artificial pancreas	1		0
bionic pancreas	0		0

Medicines & Healthcare Products Regulatory Agency (MHRA) (via gov.uk website)

Date searched: 22/04/21
Search interface: https://www.gov.uk/

Filters selected:
About (Topic): Health and social care and Medicines, medical devices
Updated after: 1 January 2014

Search term	**Results**	**Documents downloaded** (judged to contain potentially useful/relevant information not already identified in previous sets)
dexcom	6	2 Field Safety Notices (FSNs), 1 gov.uk web page
"control-iq"	0	0
"control iq"	0	0
"t:slim"	2	1 FSN, 1 gov.uk web page

"t slim"	1	0
tslim	0	0
camaps	0	0
camdiab	0	0
“minimed 670G”	2	2 FSNs
minimed 780G	1	0
smartguard	0	0
“smart guard”	0	0
ilet	0	0
"beta bionics"	0	0
“closed loop”	3	0
“artificial pancreas”	0	0
“bionic pancreas”	0	0

9.1.2 Record of searches – Cost effectiveness

Overview:

Database / website	**Date searched (date updated)**	**Number of records + update = TOTAL**
MEDLINE ALL (Ovid)	07/04/21 (05/04/22)	162 + 56 = 218
Embase (Ovid)	07/04/21 (05/04/22)	312 + 91 = 403
EconLit (Ebsco)	07/04/21 (05/04/22)	7 + 1 = 8
HTA database (CRD)	07/04/21 *	16
International HTA database (INAHTA)	07/04/21 (06/04/22)	22 + 10 = 32
EconPapers (RePEc)	07/04/21 (06/04/22)	16 + 6 = 22
AHRQ website	12/04/21 (06/04/22)	1 + 0 = 1
CADTH website	12/04/21 (07/04/22)	14 + 2 = 16
SBU website	12/04/21 (07/04/22)	0 + 0 = 0
CEA registry	14/04/21 (07/04/22)	27 + 2 = 29
ScHARRHUD	14/04/21 *	0

* No new records in database so search did not require updating

Total results: 577 + 168 from update = 745
Total after 158 duplicates + 43 duplicates within update results + 28 duplicates with original results removed = 516

Additional targeted searches were made for other parameters later (see end)

Search strategies:

Note: See below each database strategy for details of update searches

MEDLINE (via Ovid)

Date searched: 07/04/21
Database: Ovid MEDLINE(R) ALL <1946 to April 06, 2021>

Search Strategy:
---
1 Diabetes Mellitus, Type 1/ (77411)
2 Diabetic Ketoacidosis/ (6618)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kf,ti. (56642)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kf,ti. (28281)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kf,ti. (33825)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kf,ti. (23617)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kf,ti. (11593)
8 Hyperglycemia/ (28779)
9 Hypoglycemia/ (27948)
10 (hyperglyc?em$ or hypoglyc?em$).ab,kf,ti. (116710)
11 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kf,ti. (151670)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 [population: T1DM] (365496)
13 Pancreas, Artificial/ (816)
14 closed loop.ab,kf,ti. (10542)
15 (artificial adj2 (pancreas or beta cell$)).ab,kf,ti. (1730)
16 (bionic adj2 pancreas).ab,kf,ti. (25)
17 (Automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kf,ti. (287)
18 ((minimed or medtronic) and (670G or 780G)).ab,kf,ti. (58)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,kf,ti. (176)
20 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (12190)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kf,ti. (7831)
22 SAPT.ab,kf,ti. (536)
23 predictive low glucose.ab,kf,ti. (97)
24 basal iq.ab,kf,ti. (9)
25 ((minimed or medtronic) and 640G).ab,kf,ti. (33)
26 (paradigm$ adj3 (veo or pump$)).ab,kf,ti. (58)
27 (veo adj3 pump$).ab,kf,ti. (9)
28 (g4 adj3 platinum).ab,kf,ti. (58)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,kf,ti. (14)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (8503)
31 Insulin Infusion Systems/ (5481)

32 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kf,ti. (14832)
33 (pump$ adj2 (therap$ or treatment$)).ab,kf,ti. (3232)
34 ((subcutaneous adj2 insulin$) or CSII).ab,kf,ti. (3868)
35 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,kf,ti. (380)
36 (medtronic adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (720)
37 (tandem adj3 (pump$ or system$ or deliver$)).ab,kf,ti. (926)
38 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,kf,ti. (34)
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 [insulin pumps/CSII] (20986)
40 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kf,ti. (5882)
41 (glucose adj (sensor$ or sensing)).ab,kf,ti. (4191)
42 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kf,ti. (4544)
43 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,kf,ti. (2422)
44 40 or 41 or 42 or 43 [continuous or flash glucose monitors] (13072)
45 (2014082* or 2014083* or 201409* or 201410* or 201411* or 201412* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).dt,ez,da. [added to database since search for previous DAR in 2014] (8999414)
46 12 and 20 and 45 [T1DM and closed loop + date limit] (1143)
47 12 and 30 and 45 [T1DM and SAPT + date limit] (505)
48 12 and 39 and 44 and 45 [T1DM and pumps and GMs + date limit] (1100)
49 46 or 47 or 48 (1967)
50 limit 49 to english language (1919)
51 exp Pregnancy/ (913489)
52 exp Pregnancy Complications/ (435971)
53 Perinatal Care/ or Preconception Care/ or Prenatal Care/ (35179)
54 exp Cesarean Section/ (46725)
55 Pregnant Women/ (9210)
56 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kf,ti. (1210177)
57 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kf,ti. (352725)
58 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kf,ti. (365250)
59 apgar.ab,kf,ti. (12609)
60 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 [pregnancy, planning pregnancy, pregnancy complications; broad] (1736892)
61 exp Insulin/ and Injections, Subcutaneous/ (2457)
62 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (1309)
63 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (564)
64 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ti,ab,kf. (10216)

65 MDI.ti,ab,kf. (3837)
66 (injection adj3 therapy).ti,ab,kf. (4204)
67 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ti,ab,kf. (1376)
68 (short acting adj3 insulin).ti,ab,kf. (576)
69 (rapid acting adj3 insulin).ti,ab,kf. (799)
70 or/61-69 [insulin injections] (21941)
71 Blood Glucose Self-Monitoring/ (7144)
72 Blood Glucose/ (168038)
73 (blood glucos$ or blood sugar$).ab,kf,ti. (87483)
74 72 or 73 (210806)
75 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kf,ti. (43311)
76 (capillary adj4 (test$ or measur$)).ab,kf,ti. (5095)
77 75 or 76 (48093)
78 74 and 77 (5795)
79 SMBG.ab,kf,ti. (1197)
80 glucometer$.ab,kf,ti. (1147)
81 71 or 78 or 79 or 80 [self monitoring of blood glucose] (11403)
82 44 and 70 [continuous or flash GMs AND MDI] (488)
83 81 and 39 [SMBG AND CSII] (1715)
84 82 or 83 (2028)
85 12 and 60 and 84 and 45 [T1DM and pregnancy and any of the comparator groups specific to this population + date limit] (56)
86 limit 85 to english language (55)
87 50 or 86 (1930)
88 Economics/ (27310)
89 exp "costs and cost analysis"/ (243824)
90 Economics, Dental/ (1915)
91 exp economics, hospital/ (25035)
92 Economics, Medical/ (9127)
93 Economics, Nursing/ (4002)
94 Economics, Pharmaceutical/ (2977)
95 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (852480)
96 (expenditure$ not energy).ti,ab. (31555)
97 value for money.ti,ab. (1740)
98 budget$.ti,ab. (30786)
99 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 (1007726)
100 ((energy or oxygen) adj cost).ti,ab. (4248)
101 (metabolic adj cost).ti,ab. (1480)
102 ((energy or oxygen) adj expenditure).ti,ab. (26059)
103 100 or 101 or 102 (30788)
104 99 not 103 (1000667)
105 letter.pt. (1129857)
106 editorial.pt. (563250)
107 historical article.pt. (362940)
108 105 or 106 or 107 (2035927)

109 104 not 108 (963183)
110 exp animals/ not humans/ (4809908)
111 109 not 110 [economic studies filter] (901889)
112 87 and 111 (162)

Update
Date searched: 05/04/22
Re-ran above search with search line 45 altered to:
45 (202104* or 202105* or 202106* or 202107* or 202108* or 202109* or 202110* or 202111* or 202112* or 2022*).dt,ez,da. [added to database since original search for this MTA]
Total: 112 87 and 111 (56)

The economics terms (lines 88-111) are based on the CRD NHS EED filter:

Centre for Reviews and Dissemination. *Search strategies: NHS EED MEDLINE using OvidSP*. York: Centre for Reviews and Dissemination; 2014. URL: https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (Accessed 27 April 2021).

Search strings used in the previous technology assessment on integrated sensor-augmented pump therapy systems were used as the basis for developing selected lines relating to type 1 diabetes, insulin pumps, sensor augmented pumps and multiple daily injections:

Appendix 1: Literature search strategies. In: Riemsma R, Corro Ramos I, Birnie R, Büyükkaramikli N, Armstrong N, Ryder S, et al. Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic review and economic evaluation. Health Technol Assess 2016;20(17):v-xxxi, 1-251. http://dx.doi.org/10.3310/hta20170

The following were used as sources of search terms for pregnancy and related concepts:

Tessier V. Périnatalité: Perinatality: Rappel favorisé sur la précision. Canadian Health Libraries Association - Association des bibliothèques de la santé du Canada; 2017. URL: https://extranet.santecom.qc.ca/wiki/!biblio3s/doku.php?id=concepts:perinatalite (Accessed 26 April 2021).

Kyrgiou M, Mitra A, Arbyn M, Paraskevaidi M, Athanasiou A, Martin-Hirsch PPL, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database of Systematic Reviews 2015. http://dx.doi.org/10.1002/14651858.CD008478.pub2

Cochrane Pregnancy and Childbirth's Trials Register: Detailed search methods used to maintain and update the Specialised Register. 2018. URL: https://pregnancy.cochrane.org/sites/pregnancy.cochrane.org/files/public/uploads/cochrane_pregnancy_and_childbirth_search_methods_2018_1.docx (Accessed 26 April 2021).

Embase (via Ovid)

Date searched: 07/04/21
Database: Embase <1974 to 2021 April 06>

Search Strategy:

---
1 insulin dependent diabetes mellitus/ (120816)
2 diabetic ketoacidosis/ (13238)
3 (diabet$ adj3 (typ$ 1 or typ$ i or type1 or typei or typ$ one)).ab,kw,ti. (89502)
4 (diabet$ adj3 (britt$ or juvenil$ or pediatric or paediatric or early or keto$ or labil$ or acidos$ or autoimmun$ or auto immun$ or sudden onset)).ab,kw,ti. (39710)
5 ((insulin$ adj2 depend$) or insulindepend$).ab,kw,ti. (42510)
6 (dm1 or dm 1 or dmt1 or dm t1 or t1dm or t1 dm or t1d or iddm).ab,kw,ti. (41428)
7 (ketoacidosis or acidoketosis or keto acidosis or ketoacidemia or ketosis or dka).ab,kw,ti. (17695)
8 hypoglycemia/ or insulin hypoglycemia/ or nocturnal hypoglycemia/ or hyperglycemia/ (170292)
9 (hyperglyc?em$ or hypoglyc?em$).ab,kw,ti. (171683)
10 ((high or higher or low or lower or increas$ or decreas$ or deficien$ or sufficien$ or insufficien$ or reduce$ or reduction$ or fluctuat$ or fallen or falling or threshold or safe) adj3 (glucose$ or sugar$ or hba1c or hb a1 or hba1 or a1c or h?emoglob$ or glycoh?emoglob$)).ab,kw,ti. (219849)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 [population: T1DM] (553786)
12 exp artificial pancreas/ (2523)
13 "glucose monitoring/insulin pump system"/ (22)
14 closed loop.ab,kw,ti. (13576)
15 (artificial adj2 (pancreas or beta cell$)).ab,kw,ti. (2733)
16 (bionic adj2 pancreas).ab,kw,ti. (84)
17 (automat$ adj2 (insulin deliver$ or insulin dosing or glucose control$ or glyc?emic control$)).ab,kw,ti. (501)
18 ((minimed or medtronic) and (670G or 780G)).ab,dm,dv,kw,ti. (204)
19 (tslim or t slim or control iq or camAPS or camdiab or dexcom G6 or dexcom G7 or smartguard or smart guard or diabeloop or dblg1 or ilet or beta bionics or (omnipod and horizon) or (mylife and loop) or (tidepool and loop) or bigfoot or anydana loop).ab,dm,dv,kw,ti. (452)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [Intervention: closed loop systems] (16596)
21 (sensor? adj3 (augment$ or integrat$ or pump? or insulin)).ab,kw,ti. (9770)
22 SAPT.ab,kw,ti. (499)
23 predictive low glucose.ab,kw,ti. (216)
24 basal iq.ab,dm,dv,kw,ti. (35)
25 ((minimed or medtronic) and 640G).ab,dm,dv,kw,ti. (162)
26 (paradigm$ adj3 (veo or pump$)).ab,dm,dv,kw,ti. (251)
27 (veo adj3 pump$).ab,dm,dv,kw,ti. (63)
28 (g4 adj3 platinum).ab,dm,dv,kw,ti. (215)
29 ((animas or vibe) adj3 (pump$ or infus$ or system$)).ab,dm,dv,kw,ti. (56)
30 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 [sensor augmented pumps] (10839)
31 insulin infusion/ (8362)
32 insulin pump/ or implantable insulin pump/ (7947)
33 (insulin$ adj3 (pump$ or infus$ or deliver$ or catheter$)).ab,kw,ti. (23717)
34 (pump$ adj2 (therap$ or treatment$)).ab,kw,ti. (6135)
35 ((subcutaneous adj2 insulin$) or CSII).ab,kw,ti. (7277)
36 (minimed or dana diabecare or dana R or dana RS or kaleido or omnipod or medtrum or touchcare or ypsopump or cellnovo).ab,dm,dv,kw,ti. (1656)

37 (medtronic adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (3033)
38 (tandem adj3 (pump$ or system$ or deliver$)).ab,dm,dv,kw,ti. (1171)
39 ((accu-chek or accuchek) adj3 (pump$ or system$ or deliver$ or combo or insight or solo)).ab,dm,dv,kw,ti. (174)
40 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 [insulin pumps/CSII] (36842)
41 ((continu$ or flash or intermittent$ or sensor or sensors or real time) adj4 glucose adj4 (monitor$ or measurement$)).ab,kw,ti. (10589)
42 (glucose adj (sensor$ or sensing)).ab,kw,ti. (5548)
43 (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ab,kw,ti. (8880)
44 (dexcom or freestyle or libre or enlite or (guardian and (medtronic or sensor)) or eversense or glucomen day).ab,dm,dv,kw,ti. (4614)
45 41 or 42 or 43 or 44 [continuous or flash glucose monitors] (20610)
46 11 and 20 [T1DM and closed loop] (4008)
47 11 and 30 [T1DM and SAPT] (1705)
48 11 and 40 and 45 [T1DM and pumps and GMs] (4222)
49 46 or 47 or 48 (7461)
50 limit 49 to dc=20140825-20210331 (4304)
51 limit 50 to english language (4181)
52 exp pregnancy/ (689502)
53 exp pregnancy disorder/ (556137)
54 exp cesarean section/ (102040)
55 pregnant woman/ (87246)
56 pregnancy outcome/ (64095)
57 perinatal care/ or prepregnancy care/ or prenatal care/ (57272)
58 (pregnan$ or ante natal$ or antenatal$ or pre natal$ or prenatal$ or (expectant$ adj2 mother$) or "mother? to be" or matern$ or conception$ or preconception$ or "trying to conceive" or prepregnan$ or periconception$ or giving birth or childbirth$ or labo?r or newborn$ or new born$ or neonat$ or neo nat$ or baby or babies).ab,kw,ti. (1450554)
59 (miscarr$ or abort$ or cesarean or caesarean or c section$ or (prematur$ and (birth$ or rupture$ or infant$)) or preterm or pre term or prematurity or prom or macrosomia$ or birth weight$ or birthweight$ or eclamp$ or preeclamp$ or stillbirth$ or still birth$ or stillborn$ or still born$).ab,kw,ti. (456116)
60 (perinatal or peri natal or fetal or foetal or intrauterine or intra uterine).ab,kw,ti. (466666)
61 apgar.ab,kw,ti. (19962)
62 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 [pregnancy, planning pregnancy, pregnancy complications; broad] (1960053)
63 blood glucose monitoring/ (28324)
64 glucose blood level/ (264217)
65 (blood glucos$ or blood sugar$).ab,kw,ti. (130659)
66 64 or 65 (300664)
67 self monitoring/ (8184)
68 (self monitor$ or test$ strip$ or finger prick$ or fingerprick$ or finger stick$ or fingerstick$ or lancet? or meter?).ab,kw,ti. (68060)
69 (capillary adj4 (test$ or measur$)).ab,kw,ti. (6781)
70 67 or 68 or 69 (76851)
71 66 and 70 (9977)

72 SMBG.ab,kw,ti. (2499)
73 glucometer$.ab,kw,ti. (2303)
74 63 or 71 or 72 or 73 [self monitoring of blood glucose] (35625)
75 insulin/ and exp injection/ (5682)
76 (multiple daily adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (2615)
77 (multiple dose adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (783)
78 (multiple adj3 (inject$ or insulin$ or regime$ or routine$)).ab,kw,ti. (15107)
79 MDI.ab,kw,ti. (6724)
80 (injection adj3 therapy).ab,kw,ti. (6301)
81 ((basal$ and bolus) adj3 (injection$ or regime$ or routine$ or system$)).ab,kw,ti. (2372)
82 (short acting adj3 insulin).ab,kw,ti. (969)
83 (rapid acting adj3 insulin).ab,kw,ti. (1412)
84 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 [insulin injections / MDI] (34894)
85 45 and 84 [continuous or flash GMs AND MDI] (1390)
86 74 and 40 [SMBG AND CSII] (5427)
87 85 or 86 (6255)
88 11 and 62 and 87 [T1DM and pregnancy and any comparator group specific to the pregnancy population] (446)
89 limit 88 to dc=20140825-20210331 (242)
90 limit 89 to english language (235)
91 51 or 90 (4272)
92 Health Economics/ (33568)
93 exp Economic Evaluation/ (318503)
94 exp Health Care Cost/ (302491)
95 pharmacoeconomics/ (7520)
96 92 or 93 or 94 or 95 (558862)
97 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1149601)
98 (expenditure$ not energy).ti,ab. (43069)
99 (value adj2 money).ti,ab. (2579)
100 budget$.ti,ab. (40898)
101 97 or 98 or 99 or 100 (1188152)
102 96 or 101 (1417777)
103 letter.pt. (1175320)
104 editorial.pt. (692507)
105 note.pt. (850530)
106 103 or 104 or 105 (2718357)
107 102 not 106 (1310667)
108 (metabolic adj cost).ti,ab. (1614)
109 ((energy or oxygen) adj cost).ti,ab. (4538)
110 ((energy or oxygen) adj expenditure).ti,ab. (33372)
111 108 or 109 or 110 (38389)
112 107 not 111 [economic studies filter] (1302843)
113 91 and 112 (312)

Update
Date searched: 05/04/22

Re-ran above search with search lines 50 and 89 altered to:
50 limit 49 to dc=20210405-20220405
89 limit 88 to dc=20210405-20220405
Total: 113 91 and 112 (91)

The economics terms (lines 92-112) are based on the CRD NHS EED filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED Embase using OvidSP. York: Centre for Reviews and Dissemination; 2014. URL: https://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase (Accessed 27 April 2021).

EconLit with Full Text (via EBSCOhost)

Date searched: 07/04/21
Search screen: Advanced Search

#	Query	Limiters/Expanders	Results
S27	S4 AND S26	Limiters - Published Date: 20140101-20210431 Search modes - Boolean/Phrase	7
S26	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	Search modes - Boolean/Phrase	11,027
S25	TI (minimed or medtronic or tslim or "t slim" or "control iq" or "basal iq" or camAPS or camdiab or dexcom or smartguard or "smart guard" or diabeloop or dblg1 or ilet or "beta bionics" or omnipod or mylife or tidepool or bigfoot or anydana or paradigm* or veo or platinum or animas or vibe or dana or kaleido or medtrum or touchcare or ypsopump or cellnovo or tandem or "accu chek" or accuchek or freestyle or libre or enlite or (guardian and sensor) or eversense or glucomen) OR AB (minimed or medtronic or tslim or "t slim" or "control iq" or "basal iq" or camAPS or camdiab or dexcom or smartguard or "smart guard" or diabeloop or dblg1 or ilet or "beta bionics" or omnipod or mylife or tidepool or bigfoot or anydana or paradigm* or veo or platinum or animas or vibe or dana or kaleido or medtrum or touchcare	Search modes - Boolean/Phrase	10,312

	or ypsopump or cellnovo or tandem or "accu chek" or accuchek or freestyle or libre or enlite or (guardian and sensor) or eversense or glucomen)		
S24	TI (SMBG or glucometer*) OR AB (SMBG or glucometer*)	Search modes - Boolean/Phrase	1
S23	TI (("blood glucos*" or "blood sugar*") AND ("self monitor*" or "test* strip*" or "finger prick*" or fingerprick* or "finger stick*"or fingerstick* or lancet* or meter* or (capillary N4 (test* or measur*)))) OR AB (("blood glucos*" or "blood sugar*") AND ("self monitor*" or "test* strip*" or "finger prick*" or fingerprick* or "finger stick*"or fingerstick* or lancet* or meter* or (capillary N4 (test* or measur*))))	Search modes - Boolean/Phrase	4
S22	TI (("short acting" or "rapid acting") N3 insulin*) OR AB (("short acting" or "rapid acting") N3 insulin*)	Search modes - Boolean/Phrase	1
S21	TI ((basal* and bolus) N3 (injection* or regime* or routine* or system*)) OR AB ((basal* and bolus) N3 (injection* or regime* or routine* or system*))	Search modes - Boolean/Phrase	0
S20	TI injection N3 therapy OR AB injection N3 therapy	Search modes - Boolean/Phrase	1
S19	TI MDI OR AB MDI	Search modes - Boolean/Phrase	21
S18	TI (multiple N4 (inject* or insulin* or regime* or routine*)) OR AB (multiple N4 (inject* or insulin* or regime* or routine*))	Search modes - Boolean/Phrase	275
S17	TI (insulin* N3 (inject* or therapy*)) OR AB (insulin* N3 (inject* or therapy*))	Search modes - Boolean/Phrase	9
S16	TI (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS) OR AB (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)	Search modes - Boolean/Phrase	45
S15	TI ("glucose sensor*" or "glucose sensing") OR AB ("glucose sensor*" or "glucose sensing")	Search modes - Boolean/Phrase	0
S14	TI ((continu* or flash or intermittent* or sensor or sensors or "real time") N4 glucose N4 (monitor* or measurement*)) OR AB ((continu* or flash or	Search modes - Boolean/Phrase	1

	intermittent* or sensor or sensors or "real time") N4 glucose N4 (monitor* or measurement*))		
S13	TI ((subcutaneous N2 insulin*) or CSII) OR AB ((subcutaneous N2 insulin*) or CSII)	Search modes - Boolean/Phrase	2
S12	TI ((pump* N2 (therap* or treatment*)) OR AB ((pump* N2 (therap* or treatment*))	Search modes - Boolean/Phrase	2
S11	TI ((insulin* N3 (pump* or infus* or deliver* or catheter*)) OR AB ((insulin* N3 (pump* or infus* or deliver* or catheter*))	Search modes - Boolean/Phrase	2
S10	TI (SAPT or "predictive low glucose") OR AB (SAPT or "predictive low glucose")	Search modes - Boolean/Phrase	0
S9	TI (sensor* N3 (augment* or integrat* or pump* or insulin)) OR AB (sensor* N3 (augment* or integrat* or pump* or insulin))	Search modes - Boolean/Phrase	12
S8	TI (automat* N2 ("insulin deliver*" or "insulin dosing" or "glucose control*" or "glyc#emic control*")) OR AB (automat* N2 ("insulin deliver*" or "insulin dosing" or "glucose control*" or "glyc#emic control*"))	Search modes - Boolean/Phrase	0
S7	TI bionic N2 pancreas OR AB bionic N2 pancreas	Search modes - Boolean/Phrase	0
S6	TI (artificial N2 (pancreas or "beta cell*")) OR AB (artificial N2 (pancreas or "beta cell*"))	Search modes - Boolean/Phrase	0
S5	TI "closed loop" OR AB "closed loop"	Search modes - Boolean/Phrase	354
S4	S1 OR S2 OR S3	Search modes - Boolean/Phrase	688
S3	TI (hyperglyc#em* OR hypoglyc#em*) OR AB (hyperglyc#em* OR hypoglyc#em*)	Search modes - Boolean/Phrase	19
S2	TI (ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis or dka) OR AB (ketoacidosis or acidoketosis or "keto acidosis" or ketoacidemia or ketosis or dka)	Search modes - Boolean/Phrase	0
S1	TI (diabet* or insulin* or insulindepend* or dm1 or dmt1 or t1dm or t1d or iddm or "dm 1" or "dm t1" or "t1 dm") OR AB (diabet* or insulin* or insulindepend* or dm1 or dmt1 or t1dm or t1d or iddm or "dm 1" or "dm t1" or "t1 dm")	Search modes - Boolean/Phrase	683

Update
Date searched: 06/04/22
Re-ran above search with line 27 changed to: Published Date: 20210101-20220431
Total: 1

Health Technology Assessment (HTA) database (via CRD website)

Date searched: 07/04/21
Search interface: https://www.crd.york.ac.uk/CRDWeb/

((closed loop) OR (artificial NEAR2 pancreas) OR (bionic NEAR2 pancreas)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	2
((minimed or control iq or camAPS or camdiab or dexcom)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((sensor augmented) OR (SAPT)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
((automat* NEAR2 (insulin OR glucose OR glycemic OR glycaemic))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	0
((insulin NEAR2 (pump* OR infus*)) OR (subcutaneous NEAR2 insulin*) OR (CSII)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	10
((continu* or flash or intermittent* or sensor or sensors or real time) AND (glucose) AND (monitor* or measurement*)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	6
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	3
((diabet* or insulin*) AND (pregn*) AND (injection* or MDI or self monitoring or SMBG)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 2014 TO 2021	1
Total unique records:	16

No new records so update search not needed.

International HTA database (via INAHTA website)

Date searched: 07/04/21
Search interface: Advanced search builder https://database.inahta.org/search/advanced

(closed loop) FROM 2014 TO 2021	0
(artificial pancreas) FROM 2014 TO 2021	2
(bionic pancreas) FROM 2014 TO 2021	0
(minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2021	2
("Pancreas, Artificial"[mh]) FROM 2014 TO 2021	2
("sensor augmented") FROM 2014 TO 2021	1
(SAPT) FROM 2014 TO 2021	0
("Insulin Infusion Systems"[mh]) FROM 2014 TO 2021	7
(insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2021	8
(CSII) FROM 2014 TO 2021	2
((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2021	15
((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2021	7
((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2021	4
Total:	50
Total after duplicate removal (using EndNote):	22

Update

Date searched: 06/04/22
Re-ran search above search in one line with end date altered to 2022:

(((diabet* or insulin*) AND pregn* AND (injection* or MDI or "self monitoring" or SMBG)) FROM 2014 TO 2022) OR (((diabet* or insulin*) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)) FROM 2014 TO 2022) OR (((continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)) FROM 2014 TO 2022) OR ((CSII) FROM 2014 TO 2022) OR ((insulin AND (pump* OR infusion* OR subcutaneous)) FROM 2014 TO 2022) OR (("Insulin Infusion Systems"[mh]) FROM 2014 TO 2022) OR ((SAPT) FROM 2014 TO 2022) OR (("sensor augmented") FROM 2014 TO 2022) OR (("Pancreas, Artificial"[mh]) FROM 2014 TO 2022) OR ((minimed OR "control iq" OR camAPS OR camdiab OR dexcom) FROM 2014 TO 2022) OR

((bionic pancreas) FROM 2014 TO 2022) OR ((artificial pancreas) FROM 2014 TO 2022) OR ((closed loop) FROM 2014 TO 2022)

Total: 32

Notes: After checking several lines from the original search above and finding some of the new records were for HTAs were published before 2021, it was decided that all 32 should be exported and de-duplicated with the previous results in EndNote.

Total after de-duplication in EndNote: 10

EconPapers (via Research Papers in Economics (RePEc))

Date searched: 07/04/21
Search interface: Advanced search https://econpapers.repec.org/scripts/search.pf
Filters selected: Working Papers, Journal Articles, Books & Chapters.
Sort by Date modified (to enable easy exclusion of pre-2014 records)

Search terms (entered in 'Free text search')		Update
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND ("closed loop" OR "artificial pancreas" OR "artificial endocrine pancreas" OR "bionic pancreas")	13	5
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND (minimed OR "control iq" OR camAPS OR camdiab OR 277excom)	0	0
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND ("sensor augmented" OR SAPT)	0	0
insulin AND (pump* OR infusion* OR subcutaneous) AND (continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)	3	2
insulin AND (pump* OR infusion* OR subcutaneous) AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)	2	1
CSII AND (continu* OR flash OR intermittent* OR sensor OR sensors OR "real time") AND (glucose) AND (monitor* or measurement*)	2	1
CSII AND (CGM or CGMs or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS)	1	0
(diabet* OR insulin* OR hyperglyc* OR hypoglyc* OR dm1 OR dmt1 OR t1dm OR t1d OR iddm OR "dm 1" OR "dm t1" OR "t1 dm") AND pregn* AND (injection* OR MDI OR "self-monitoring" OR SMBG)	2	0
Total:	23	9

Total after duplicate removal (using EndNote):	16	6

Update

Date searched: 06/04/22
Re-ran search above searches with box ticked for added to EconPapers in the last 1 year (New or updated items, selected Modified last 1 year and Date is Creation/revision of Metadata). For numbers see right-hand column in original strategy table above.

Agency for Healthcare Research and Quality (AHRQ) website

Date searched: 12/04/21

Search Publications: https://www.ahrq.gov/research/publications/search.html

Search terms	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	0		0	
diabetes	6	0 relevant	6 (0 new)	
insulin	0		0	

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 0 new.

Search Evidence Based Reports: https://www.ahrq.gov/research/findings/evidence-based-reports/search.html

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	0 relevant; about pancreatic adeno-carcinoma	1 (0 new)	
Browsed Topic: Endocrine conditions	25 reports, of which 10	0 relevant	26 reports, of which 11 published	0 relevant

	published 2014-present		2014-present (1 new)	

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 1 new, 0 relevant.

Full Research Reports: https://www.ahrq.gov/research/findings/final-reports/index.html
Checked 10 reports listed; none relevant.

Update. Checked again 06/04/22. 0 new reports listed.

Technology Assessment Program: https://www.ahrq.gov/research/findings/ta/index.html
Checked all reports and projects listed; none relevant

Update. Checked again 06/04/22. 0 new published reports listed. 1 new revised report listed, but not relevant.

Technology Assessment Archive (up to 2016): https://archive.ahrq.gov/clinic/techarch.htm
Used ctrl + F to search webpage for:

diabet
closed
pancreas
insulin
glucose

- nothing relevant found

AHRQ Research Studies: https://www.ahrq.gov/research/findings/studies/index.html

Search term	**Total results**	**Comments**	**Total at update 04/22**	**Comments at update 04/22**
Closed loop	4	0 relevant (all about closed loop communi-cation systems; not diabetes)	5 (1 new)	0 relevant (all about closed loop communi-cation systems; not diabetes)
Artificial pancreas	0		0	

Bionic pancreas	0		0	
insulin delivery	3	0 relevant	0	
minimed	0		0	
control iq	0		527 (technical changes to search likely)	See new search in row below
control iq AND diabetes	-	-	58	Checked 2021 and 2022. None relevant
camAPS	0		0	
camdiab	0		0	
dexcom	0		0	
insulin pump	0		0	
insulin pumps	0		0	
insulin infusion	1	0 relevant	1 (0 new)	
insulin infusions	0		0	
CSII	0		0	
glucose monitoring	3	0 relevant (2 x type 2 diabetes, 1 about behaviour change)	6 (3 new)	0 relevant
glucose monitors	0		0	
glucose monitor	1	1 possibly relevant	1 (0 new)	
flash	0		0	
insulin AND injections	0		0	
daily injections	0		0	
blood glucose	13	0 relevant; either type 2 diabetes, or not about self-monitoring	15 (2 new)	0 relevant
smbg	0		0	
Total possibly relevant studies:		*1*		*0*

Update

Date searched: 06/04/22. For numbers see right-hand column in original strategy table above. 6 new, 0 relevant.

Canadian Agency for Drugs and Technologies in Health (CADTH) website

Date searched: 12/04/21
Search box on homepage https://www.cadth.ca/

Limit results by 'Result Type: Reports; Projects in Progress'.
Sort by Newest to Oldest (to enable easy exclusion of pre-2014 records)

Search terms	**Total results**	**Number of new (not in previous sets), possibly relevant results**	**Total at update 04/22**	**Number of new (not in previous results or sets), possibly relevant results**
"closed loop"	34	5	19	1
artificial pancreas	22	2	9	0
bionic pancreas	5	0	2	0
automated insulin delivery	18	0	10	0
minimed	16	1	5	0
"control IQ"	2	0	1	0
camAPS	0	0	0	0
camdiab	0	0	0	0
Dexcom	10	1	2	0
"insulin pump"	41	1	12	0
"insulin infusion"	51	0	5	0
CSII	23	0	3	0
"glucose monitor"	25	0	10	0
"glucose monitoring"	80	4	29	1
"insulin injections"	41	0	3	0
"daily injections"	43	0	8	0
"self monitoring" AND glucose	124	0	0	0
SMBG	31	0	5	0
Total unique, possibly relevant results:		*14*		*2*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 2 new, 2 potentially relevant.

Note: Assume website has been restructured or search interface / system changed since original search. Searched for words without quotation marks in 'Contains all the words' and terms in quotation marks in 'Advanced Search'. Sorted by Last updated and checked records for 2021 and 2022.

Swedish Agency For Health Technology Assessment And Assessment Of Social Services (SBU) website

Date searched: 12/04/21
Search box on home page: https://www.sbu.se/en/

Search terms / method	Total results	Comments	Total at update 04/22	Comments at update 04/22
closed loop	0		0	
artificial pancreas	1	not relevant; 'dialysis for acute hepatic failure'	1 (0 new)	
bionic pancreas	0		0	
diabetes > Filter on subject and publication type > Publication year From 2014 to 2021	30	0 relevant	5 new	0 relevant
insulin > Filter on subject and publication type > Publication year From 2014 to 2021	5	0 relevant	1 new	0 relevant
Total possibly relevant studies, published since 2014:		*0*		*0*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 0 relevant.

Cost-Effectiveness Analysis (CEA) Registry (via Tufts Medical Center)

Date searched: 14/04/21
Search interface: Basic search, Search for: Methods
http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx

Search terms	Total results	Results published since 2014	Number of new (not in previous sets), possibly relevant results	Results added since 2021	Number of new (not in previous CEA search or sets), possibly relevant results
closed loop	0	0	0	0	
artificial pancreas	0	0	0	0	

bionic pancreas	0	0	0	0	
insulin delivery	4	4	4	0	
minimed	2	2	1	0	
control IQ	0	0	0	0	
camAPS	0	0	0	0	
camdiab	0	0	0	0	
dexcom	1	1	1	1	1
insulin pump	10	9	7	0	
insulin pumps	3	2	0	0	
insulin infusion	20	15	5	0	
insulin infusions	0	0	0	0	
CSII	19	14	0	0	
glucose monitoring	16	14	6	2	0
glucose monitors	0	0	0	0	
glucose monitor	16	14	0	2	0
flash	6	2	0	0	
insulin injections	5	5	0	1	1
daily injections	17	11	1	1	0
blood glucose	47	22	2	3	0
smbg	17	10	0	1	0
Total unique, possibly relevant results:			*27*		*2*

Update

Date searched: 07/04/22. For numbers see right-hand column in original strategy table above. 2 potentially relevant, but duplicates of those found in MEDLINE in original search.

ScHARRHUD

Date searched: 14/04/21
Search interface: https://www.scharrhud.org/index.php?recordsN1&m=search

closed loop OR artificial pancreas OR bionic pancreas AND 2014 > 2021:YR	0
(minimed OR control iq OR camAPS OR camdiab OR dexcom) AND 2014 > 2021:YR	0
sensor augmented OR sapt AND 2014 > 2021:YR	0
automated insulin OR insulin delivery AND 2014 > 2021:YR	0
insulin pump* OR insulin infusion* OR CSII AND 2014 > 2021:YR	1 (not relevant; type 2 diabetes)
glucose monitor* AND 2014 > 2021:YR	0
flash AND 2014 > 2021:YR	0
insulin inject* AND 2014 > 2021:YR	0
insulin injections AND 2014 > 2021:YR	0
daily injections AND 2014 > 2021:YR	0

MDI AND 2014 > 2021:YR	0
blood glucose AND 2014 > 2021:YR	0
smbg AND 2014 > 2021:YR	0

Update

*Note (07/04/22): Searching * in any field limited to 2021 to 2022 in Date in ScHARRHUD retrieved 0 results. Searching * in any field limited to 2020 to 2022 in Date in ScHARRHUD retrieved 302 results so no new records have been added since 2020. Therefore, the searches were not re-run.*

Additional targeted searches for individual parameters

Hypoglycaemia and Quality of Life

Date: 10/06/2022

Ovid MEDLINE(R) ALL <1946 to June 09, 2022>

1 hypoglycemia/ or insulin coma/ 29970
2 (hypoglycemi* or hypoglycaemi*).ti,ab,kf. 63398
3 1 or 2 70791
4 Quality-Adjusted Life Years/ 14835
5 (quality adjusted or adjusted life year$).tw,kf. 20920
6 (qaly$ or qald$ or qale$ or qtime$).tw,kf. 13223
7 (illness state$1 or health state$1).tw,kf. 7688
8 (hui or hui1 or hui2 or hui3).tw,kf. 1807
9 (multiattribute$ or multi attribute$).tw,kf. 1133
10 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).tw,kf. 18324
11 utilities.tw,kf. 8545
12 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).tw,kf. 15107
13 (euro$ adj3 (d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).tw,kf. 5797
14 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).tw,kf. 25017
15 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw,kf. 2184
16 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).tw,kf. 14297
17 quality of life/ and ec.fs.10868
18 quality of life/ and (health adj3 status).tw,kf. 10904
19 (quality of life or qol).tw,kf. and Cost-Benefit Analysis/ 7271
20 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or

effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. 47789
21 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).tw,kf. 4707
22 *quality of life/ and (quality of life or qol).ti. 61866
23 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).tw,kf. 36382
24 quality of life/ and health-related quality of life.tw,kf. 40638
25 models,economic/ 11001
26 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 202159
27 3 and 26 907
28 limit 27 to yr="2020 -Current" 177
29 (hypoglycemi* or hypoglycaemi*).ti. 21153
30 1 or 29 36314
31 26 and 30 358
32 limit 31 to yr="2020 -Current" 55 [Hypos and QoL 2020 onwards hypo terms in title or MeSH indexing]
33 28 not 32 122 [Hypos and QoL 2020 onwards hypo terms only in abstract or keywords]

Total: 177 exported in two batches (55 (line 32) and 122 (line 33)

Website searches

Date: 10/06/2022

Checked:

https://hypo-resolve.eu/publications

Quantitative papers sent by team members and noted in original sifting for economic evaluations.

9.2 Appendix 2: Additional characteristics of included RCTs

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
Tauschmann 2018 NCT02523131	UK, US	Modified 640G insulin pump (investigational use only; Medtronic, Northridge, CA, USA), Enlite 3 glucose sensor (Medtronic), and Contour Next Link 2.4 glucometer (Ascensia Diabetes Care, Basel, Switzerland).	a run-in period of at least 4 weeks. Participants were trained to perform a glucose sensor calibration check before breakfast and evening meals.	12 week		Next generation sensor-augmented Medtronic insulin pump 640G (Medtronic Minimed, CA, USA) incorporating the Medtronic Enlite 3 family real time CGM. Glucose suspend features will be turned off.	training on the effective use of real-time continuous glucose monitoring for optimisation of insulin therapy.	12 weeks	Similar to intervention
Bergenstal2021 NCT03040414	7 endocrinology practices, 4 in the USA, 1 Germany, 1 Israel, 1Slovenia	MiniMed 670G, Mean total daily insulin dose was 50 units (SD 21) in the 670G group, with an average of 25 units (SD 11; 51%)	a run-in phase, each participant was trained to use the study pump (without automated insulin delivery) and the	26 weeks two x 12 week periods.	12 weeks of 670G followed by 12 weeks of AHCL or vice versa	advanced hybrid closed loop systems consisted of the same Medtronic 670G insulin pump and Guardian Sensor 3 continuous glucose	The AHCL system was started with an auto mode target glucose setpoint of 120 mg/dL (6·7 mmol/L).	12 weeks, 2–4 weeks of start-up/run-in for device naive participants	12-week periods of closed-loop use (119 unscheduled visits occurred when using the advanced hybrid closed-loop system (1·1 per participant

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		of the insulin delivery as basal and 25 units (SD 12; 49%) as bolus	continuous glucose monitor. participants and a parent or guardian when applicable were trained on use of their assigned closed-loop system.			monitor, with only the software differing between systems			
Benhamou 2021 NCT04042207	France	DBLHU system: Dexcom G6 CGM system, Kaleido insulin pump, DBLHU handset software (Sony XZ1 all in one pump and CGM controller) v2019.5.9.2779, Diabeloop	2 week run-in, where patients used Medtronic 640g with smartguard	two consecutive crossover cycles of 4 week treatment periods	Hospital visits at weeks 4, 8, 12, 16 (i.e. at end of each DBLHU or PLGS treatment period in order to switch treatment sequences 24/7 helpline available to all patients	Standard Open Loop-PLGS system: consists of sensor-augmented pump therapy (SAP) / Low Glucose Predictive Suspend system (with predictive low glucose management technology). An open-loop insulin delivery system, coupling an Enlite® CGM sensor with a Medtronic 640G insulin pump through Smartguard® safety system (Medtronic,	Same as intervention (crossover trial)	Same as intervention (crossover trial)	Same as intervention (crossover trial)

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
						Northridge, USA). *			
Thabit2015 NCT01961622 and NCT01778348	UK,Germany, Austria	The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, UK)	run-in period lasting 4 to 6 weeks, training regarding the use of the insulin pump and the CGM device	**12 weeks**	During the first 2 days of closed-loop use, participants were contacted by telephone or email. Washout period lasting 4 to 6 weeks between intervention 1 and intervention 2.	SAP (Identical insulin pumps and continuous glucose-monitoring devices were used during the	me as for HCL but HCL training was replaced by "Likewise on the first day of the control period, participants attended the clinical research facility for a similar duration." Participants were not contacted within the first two days.	12 weeks,	Participants were not contacted within the first two days.
Ware20222925299	UK, USA (paediatric diabetes centres, 7 UK & USA)	Cambridge model predictive control algorithm (version 0.371) in two hardware configurations: FlorenceM and CamAPS FX	14 days run-in period, Masked CGM (Freestyle Libre Pro FGM system) whilst wearing their own insulin pump. After run-in, intervention participants and parents trained to use study insulin pump and study CGM, used in open loop mode for 3-4 weeks.	24 weeks	Follow up at 3 months and 6 months Participants contacted monthly to record adverse events	Insulin pump therapy, with or without sensor (usual care)	14 day run-in wearing masked CGM (Freestyle Libre Pro FGM system alongside their own insulin pump, with or without senso.**	24 weeks	Follow up at 3 months and 6 months Participants contacted monthly to record adverse events

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
Ware 2022 NCT03784027	Austria (Graz, Innsbruck, and Vienna), Germany (Leipzig), Luxembourg (Luxembourg), and the United Kingdom (Cambridge and Leeds)	The hybrid closed-loop system comprised an unlocked smartphone (Galaxy S8, Samsung) hosting the proprietary CamAPS FX application (CamDiab), which ran the Cambridge proprietary model predictive control algorithm (version 0.3.71). The smartphone communicated wirelessly with both the Dana Diabecare RS insulin pump (Sooil) and the Dexcom G6 transmitter (Dexcom)	caregivers were trained in the use of the trial glucose sensor, the trial insulin pump, and the CamAPS FX application. The application was used in open-loop mode for 2 to 4 weeks during the run-in period.	initial treatment for 16 weeks and then crossed over to the second trial treatment after a washout period of 1 to 4 weeks	After two initial contacts by telephone or email in the first week of each treatment period, caregivers were contacted monthly to allow staff to record adverse events, device deficiencies, and other relevant information. All the participants and caregivers had access to a 24-hour telephone helpline to the local research team.	The CamAPS FX application was used during each trial period. During the sensor-augmented pump therapy period, closed-loop functionality was disabled.	Same as intervention group-crossover trial	initial treatment for 16 weeks and then crossed over to the second trial treatment after a washout period of 1 to 4 weeks	Crossover trial
Boughton 2022 NCT04025762	UK (n=3 centres), Austria (n=1 centre) (diabetes outpatient clinics)	CamAPS FX hybrid closed loop system. CamAPS FX app (CamDiab, Cambridge UK), Cambridge adaptive model predictive control	Baseline measurements and questionnaires. Study device training in SAP mode (auto mode disabled) for 3-4 week run-in	16 weeks	3 telephone or email contacts in the first 2 weeks of treatment period. Then monthly contact from study team to	Same devices as for closed loop intervention, but with auto mode function disabled	Baseline measurements and questionnaires. Study device training in SAP mode (auto mode disabled) for 3-4 week run-in	16 weeks	As for intervention (crossover trial)

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		algorithm (v. 0.3.71); Dexcom G6 continuous glucose monitor, Dana Diabecare RS insulin pump	period. If assigned to HCL first, this was used at home over 16 weeks		record adverse events, device deficiencies and other relevant information 24hr helpline available		period. If assigned to HCL first, this was used at home over 16 weeks		
Collyns, Wheeler 2022 NCT04073576	New Zealand (two centres)	MiniMed 670G with the addition of: a choice of target set points of 5.6 mmol/L (100 mg/dL) or 6.7 mmol/L (120 mg/dL); and an automated correction bolus feature delivered up to every 5 min, correcting to 6.7 mmol/L (120 mg/dl).	Two to 4 week run-in phase	4 weeks	None reported	Traditional sensor augmented pump therapy with predictive low glucose management (SAP+PLGM)	Two to 4 week run-in phase	4 weeks	None reported
Kariyawasam 2022 NCT03671915	France (2 centres), Belgium (1 centre), paediatric endocrinology departments	DexCom G6 CGM and Diabeloop device (Diabeloop for Kids DBL4K HCL system), and Kaleido insulin pump (ViCentra,	Training session from investigators and clinical staff on how to insert and calibrate subcutaneous CGM, interpret	6 weeks	Email or telephone contacts during the closed loop home phase, for assessments of safety and adherence, and	DexCom G6 CGM, combined with the participant's usual insulin pump, programmed with the usual	As for intervention	6 weeks	As for intervention (crossover trial)

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
		Netherlands), managed by DBLG1 application on an Android smartphone	data on the DexCom, and adjust insulin dose. Run-in period of 72 hours in hospital		for review of technical aspects of treatment	basal settings. No additional functions activated.			
Stewart 2018 ISRCTN83316328	England (3 antenatal clinics)	Florence D2A closed loop system, University of Cambridge. Readings transmitted by Bluetooth to an android mobile phone Florence D2A control algorithm, version 0.3.41p DANA pump	30-60 minute training session on device for closed loop group	4 weeks	24 hour phone line staffed by research team	As intervention, but with auto mode disabled (SAP)	As for intervention	4 weeks	As for intervention (crossover trial)
von dem Berge 2022 NCT03815487	Germany (single centre)	Minimed 670G insulin pump, with a Guardian 3 glucose sensor connected to a Guardian Link 3 Transmitter (all Medtronic, Inc.	System briefing by diabetes educators for participants and parents	8 weeks	Not reported	As intervention, but without closed loop functionality (PLGM)	As for intervention	8 weeks	As for intervention (crossover trial)

Author	Country of recruitment	Description of intervention (HCL)	Pre-intervention details	Duration of intervention	Intervention follow-ups	Description of comparator	Pre-intervention details	Duration of comparator?	Comparator follow ups
			2 week run-in period with SAP functionality						
McAuley 2022 ACTRN12619000515190	Australia (two centres)	Guardian Sensor3 glucose sensor, MiniMed 670g insulin pump, Guardian Link3 transmitter and algorithm	Multidisciplinary education from diabetes nurse educators, dietitians, endocrinologists 3 to 6 week run-in period with standard SAP therapy	16 weeks	Clinical review visits, with device upload and review of pump settings in the first month and at mid point of each treatment period	As intervention with equipment used exclusively in manual mode (SAP)	As for intervention (crossover trial)	16 weeks	As for intervention (crossover trial)

9.3 Appendix 3: RCTs additional outcomes

Outcomes	FLAIR 2022	Benhamou 2021	Tauschmann 2018	Thabit 2015	Ware 2022	Ware 2022	Boughton 2022	Collyns, [illegible] 2022	Kariyawasa [illegible] 2022	Stewart 2018	von dem [illegible] 2022	McAuley 2022
Intermediate measures												
· Fear of hypoglycaemia	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	YES
· Rate of severe hypoglycaemic events	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES
· Rate of severe hyperglycaemic events	YES	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO
· Episodes of diabetic ketoacidosis	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO
· Rate of ambulance call outs	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Rate of hospital out-patient visits	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Clinical outcomes												
· Retinopathy	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Neuropathy	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Cognitive impairment	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· End-stage renal disease	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Cardiovascular disease	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Additional clinical outcomes in women who are pregnant/have recently given birth:												
· Premature birth	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Miscarriage related to fetal abnormality	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Increased proportion of babies delivered by caesarean section	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Macrosomia (excessive birth weight)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Respiratory distress syndrome in the new-born	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Device related outcomes												
· Adverse events related to the use of devices	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
Patient-reported outcomes												
· Heath-related quality of life	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
· Psychological well being	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
· Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep)	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

9.4 Appendix 4: Properties of RCTs not included for NMA but used for comparing HCL recipients in observational studies

	HbA1c% mean sd	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe *mean sd **Median IQR*	*N hypo severe *mean sd*	*DKA Event *mean sd*
Abraham et al., 2021 HCL MiniMed™ 670G- Guardian™ 3 sensor, Guardian™ Link 3 transmitter) vs. CSII or 10% on multiple injections/day +/- CGM vs. ; 5yr (3.1); N = 135 ; Tx 26 wks.											
Inter Base	7.8 (1.0)	41.8(15.4)	53.1(13.0)	*2.9(1.7,6.4)	NR	*1.1(0.6,3.2)	*0.6(0.2,1.8)	0.4(0.1,1.0)	*NR*	*3 (3.0)*	*3(4.5)*
Inter end	7.5 (1.1)	34.4 (13.0)	62.5 (12.0)	*2.2(1.7,6.4)	NR	*0.8(0.4,2.0)	*0.4(0.2,1.8)	0.3(0.1,0.5)			
DIFF	-0.3	-7.4	9.4	*-0.7	NR	*-0.3	*-0.2	-0.1	*7*		
Comp base	7.7 (0.8)	39.4(14.5)	54.6(12.5)	*4.8(2.6,9.0)	NR	*2.2(0.8,4.60)	*1.3(0.3,2.8)	0.7(0.2,1.7)	*NR*	*3(4.4)	*3(4.4)
Comp end	7.6	37.9 (13.8)	56.1 (12.2)	*4.1 (2.6,8.7)	NR	*1.8(0.7,4.1)	*1.0(0.4,2.3)	0.6(0.2,1.6)			
DIFF	-0.1	-1.5	1.5	*-0.7	NR	*-0.4	*-0.3	-0.1	*13*		
Rep.Net effect 95%CI	*-0.3 (-0.5,0.0)*	*-4.3 (-8.8,0.2)*	*6.7 (2.7,10.8)*	*-1.9 (-2.5,-1.3)*	*NR*	* *-1.0 (-1.2,-0.50)*	*-0.5 (-0.7,-0.3)*	*-0.3 (-0.4,-0.2)*	*- 6*	*0	*0
Breton 2020 : HCL vs. SAP ; 11.3 yr vs.-10.8 yr ; N 78 vs N 23 : Tx 16 weeks											
Inter Base *N78*	7.6 (1.0)	45 (18)	53 (17)	*1.2 (0.5,2.4)	NR	NR	*0.1 (0.0,0.4)	NR	NR	NR	NR

	HbA1c% mean sd	*% TIR >10 mmol/L mean sd *median IQR*	*% TIR 3.9-10.0 mmol/L mean sd *median IQR*	*% TIR <3.9 mmol/L [70mg/dl] mean sd *median IQR*	*% TIR <3.5 mmol/L [63mg/dl] mean sd *median IQR*	*% TIR<3.3 mmol/L [60mg/dl] mean sd *median IQR*	*% TIR<3.0 mmol/L [54mg/dl] mean sd *median IQR*	*% TIR <2.8 mmol/L [50mg/dl] mean sd *median IQR*	*N hypo non-severe *mean sd **Median IQR*	*N hypo severe *mean sd*	*DKA Event *mean sd*
Inter end	7.0 (0.8)	31 (10)	67 (10)	*1.6 (0.8,2.4)	NR	NR	*0.2 (0.1,0.4)	NR	NR	NR	NR
DIFF	-0.6	-14	14	0.4	NR	NR	0.1	NR	*0.5/week (0.1,0.8)	0	0
Comp base *N23*	7.9 (0.9)	47 (17)	51 (16)	*1.0 (0.2,2.1)	NR	NR	*0.1 (0.0,0.3)	NR	NR	NR	NR
Comp end	7.6 (0.9)	43 (14)	55 (13)	*1.8 (1.1,3.0)	NR	NR	*0.3 (0.1.0.6)	NR	NR	NR	NR
DIFF	-0.3	-4	4	0.8	NR	NR	0.2	NR	*0.6 / week (0.1,1.0)	0	0
Net effect 95%CI	*-0.4 (-0.9,0.1)*	*-10 (-14,-6)*	*-10 (-14,-6)*	*-0.4 (-0.83,-0.02)*	NR	NR	*-0.07 (-0.19,0.02)*	NR	*P 0.16*	*0*	*0*
Brown et al., 2021 : HCL vs SAP ; 33 yr;; N = 112 vs. N = 56 ; Tx 6 months											
Inter Base *N112*	7.40 (9.6)	36 (19)	61 (17)	3.58 (3.39)	NR	NR	0.90 (1.36)	NR	NR	NR	NR
Inter end	7.06 (0.79)	27 (12)	71 (12)	1.58 (1.15)	NR	NR	0.29 (0.29)	NR	NR	NR	NR
DIFF	-0.34	-9	10	-2	NR	NR	-0.61	NR	*0.4/week (0.1,0.9)	0	1*(dev rel)*
Comp base *N56*	7.4 (0.76)	38 (15)	59 (14)	2.84 (2.54)	NR	NR	0.56 (0.79)	NR		NR	NR
Comp end	7.39 (0.92)	38 (15)	59 (14)	2.25 (1.46)	NR	NR	0.35 (0.32)	NR		NR	NR
DIFF	0.01	0	0	-0.59	NR	NR	-0.21	NR	*0.5/week (0.2,0.9)	0	0
Net effect 95%CI	*-0.3 (-0.53,-0.13)*	*-10 (-13,-8)*	*11 (9,14)*	*-0.88 (-1.19,-0.57)*	NR	NR	*-0.01 (-0.19,-0.02)*	NR	*P 0.06*	0	*1(dev rel)*

9.5 Appendix 5: Exploratory paediatric modelling

As reviewed in section 6.2.1.4 above the EAG has concerns about the reliability of using the iQVIA CDM to model a paediatric population. Exploratory analysis using the EAG NMA results for the subset of paediatric studies and a scenario analysis that applies the NSHE paediatric pilot results are presented. Given the mean baseline age the time horizon is extended to the iQVIA CDM maximum of 80 years.

Table 32: Exploratory paediatric modelling: HbA1c (s.e.) changes

	NMA	NMA paed.	NHSE pilot paed.
HCL	-0.28% (0.033%)	-0.31% (0.059%)	-0.70% (0.019%)
PLGS	-0.06% (0.079%)	-0.11% (0.125%)	..
CSII+CGM	0.00%	0.00%	..

Patient baseline characteristics are revised to reflect the NHSE paediatric pilot baseline data.

Table 33: Exploratory paediatric modelling: baseline characteristics

	NHSE pilot paed.	
	Mean	s.d.
Age	12	3.5
Duration diabetes	6.6	3.7
HbA1c	7.9%	1.1%
Male	58%	n.a.
Race		
White	94%	n.a.
Black	3%	n.a.
Asian	3%	n.a.

It is further assumed that paediatric patients have not developed any of the complications associated with diabetes and modelled by the iQVIA CDM. As reviewed in section

6.2.1.4 the ERG presents a scenario using the Pittsburg CVD modelling. For the EAG NMA results a scenario assuming CSII is 75% isCGM and 25% rtCGM is presented.

Note that the NHSE paediatric pilot reported time in hypoglycaemia of 3.6% prior to HCL and 2.4% with HCL, a ratio of 150% which is similar to the 130% of the EAG base case for CSII+CGM to HCL.

The paediatric pilot also reports the means of the HFS2-ws at baseline and at 6 months for the subset of children of at least 12 years of age, 33.7 and 29.1 respectively, and means of an amended HFS for parents with young children of 29.6 and 23.1 respectively. This suggests child quality of life decrements for the comparator of -0.081 and for HCL of -0.070. The EAG presents a scenario that applies the child disutilities for the time horizon of the model. It also provides a scenario analysis that trebles this for 15 years to allow for parental quality of life changes.

Table 34: Exploratory paediatric modelling: base case disaggregate results

		PLGS		HCL	
	CSII	Value	net vs CSII	Value	net vs CSII
LYs Undiscounted	60.123	60.291	0.168	60.942	0.819
QALYs					
iQVIA CDM modelled	19.252	19.301	0.049	19.448	0.196
NHSEs	0.000	0.000	0.000	0.000	0.000
SHEs	0.000	0.000	0.000	0.000	0.000
Total QALYs	19.252	19.301	0.049	19.448	0.196
Costs					
Treatment	£114,157	£138,421	£24,264	£154,762	£40,606
Routine OP	£16,129	£16,146	£17	£16,212	£83
SHEs	£0	£0	£0	£0	£0
Other management	£2,182	£2,192	£10	£2,214	£32
CVD	£2,088	£2,067	-£21	£2,000	-£88
Renal	£13,468	£12,774	-£693	£11,008	-£2,459
Ulcer/Amp./Neuropathy	£1,754	£1,707	-£47	£1,691	-£63
Eye	£26,850	£25,264	-£1,586	£21,707	-£5,143
Total Costs	£176,628	£198,572	£21,944	£209,595	£32,966

Table 35: Exploratory paediatric modelling: base case results summary

	CSII	PLGS	HCL
LYs Undiscounted	60.123	60.291	60.942
Total QALYs	19.252	19.301	19.448
Total Costs	£176,628	£198,572	£209,595
ICER vs CSII	..	£447,834	£168,196

As with the adult modelling, PLGS is extendedly dominated by HCL and the EAG does not consider it further.

HCL is estimated to increase overall discounted survival compared to CSII+CGM by 0.819 years, though it should be noted that this will be a slight underestimate due to around 10% of patients remaining alive at the end of the 80 year time horizon. The additional treatment costs of £40,606 are partially offset by savings in renal complications of £2,459 and in eye diseases of £5,143 resulting in total net costs of £32,966. Coupled with the gain of 0.196 QALYs yields a cost effectiveness estimate of £168,196 per QALY.

Table 36: Exploratory paediatric modelling: scenario analyses

	Δ Costs	Δ QALYs	ICER
Base case	£32,966	0.196	£168k
SA01a: Only paediatric studies	£30,924	0.266	£116k
SA02a: NHSE paediatric pilot	£25,448	0.465	£54,727
SA02b: SA2a + HFS2-ws QoL	£25,448	0.722	£35,259
SA02c: SA2a + triple HFS2-ws QoL	£25,448	0.984	£25,868
SA02d: SA02a + reduced complications costs	£32,091	0.465	£69,013
SA03: Pittsburgh CVD modelling	£32,245	0.169	£191k
SA04: CSII 75% isCGM and 25% rtCGM	£26,961	0.196	£138k

The base case cost effectiveness estimate of £168k per QALY improves quite markedly to £116k per QALY if only paediatric studies are included.

If the 0.7% HbA1c improvement of the NHS paediatric pilot is applied the undiscounted survival gain increases from 0.819 to 2.025 years. Net treatment costs of £41,684 also have larger cost offsets from reduced renal complications, £5,458, and reduced eye complications £10,646. Total net costs of £25,448 and gains of 0.465 QALYs result in a cost effectiveness estimate of £54,727 per QALY. Including the quality of life effects of the improvements reported in the HFS2-ws during the pilot improves the cost effectiveness to £35,259 per QALY, while if both parents also have a similar quality of life improvement for 15 years it improves further to £25,868 per QALY. Reducing the cost of complications to account for their possible overestimation worsens the cost effectiveness to £69,013 per QALY.

In all of the above, the HbA1c effect, the HFS2-ws effect and the composition of CSII+CGM may change as the patient moves from childhood into adulthood.

9.6 Appendix 6: Non-specific mortality

The iQVIA CDM explicitly models deaths from MI, CHF, stroke and renal disease. These causes of death need to be removed from the England and Wales life tables to yield "non-specific mortality" estimates. Due to Covid-19 the EAG uses the 2015-2017 England and Wales life table. An adjustment factor is applied to the annual probabilities of death, being the fraction of all deaths among those of a given age that are not caused by the following ICD-10 codes.

Table 37: ICD-10 codes for deaths modelled within iQVIA CDM

ICD10	Cause of death
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I50	Heart failure
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
N17	Acute renal failure
N18	Chronic kidney disease
N19	Unspecified kidney failure

The iQVIA modellers suggest that hypertension may also be reasonable to exclude, codes I10-I13 and I15, this resulting in a slightly different set of estimates. But there may be competing risks in that those who died of, say, myocardial infarction had they not died of it been at greater risk of dying from other comorbidities than the average. As a consequence, the adjustment may be too large which may argue for a sensitivity analysis of simply applying the unadjusted all-cause mortality while recognising that the best estimate may lie somewhere between this and those of the base case.

Table 38: All cause and non-specific mortality that excludes that modelled by iQVIA CDM

	All cause mortality		Non-specific base case		Non-specific inc. hyper.	
Age	Male	Female	Male	Female	Male	Female
0	0.00431	0.00356	0.00430	0.00356	0.00430	0.00356
1	0.00024	0.00022	0.00024	0.00021	0.00024	0.00021
5	0.00009	0.00009	0.00009	0.00008	0.00009	0.00008
10	0.00008	0.00006	0.00007	0.00006	0.00007	0.00006
15	0.00017	0.00010	0.00017	0.00010	0.00017	0.00010
20	0.00050	0.00018	0.00049	0.00018	0.00049	0.00018
25	0.00055	0.00025	0.00053	0.00025	0.00053	0.00025
30	0.00072	0.00036	0.00069	0.00035	0.00069	0.00035
35	0.00099	0.00056	0.00094	0.00053	0.00093	0.00053
40	0.00146	0.00085	0.00136	0.00080	0.00134	0.00079
45	0.00225	0.00138	0.00203	0.00130	0.00201	0.00129
50	0.00326	0.00210	0.00291	0.00195	0.00287	0.00194
55	0.00468	0.00312	0.00417	0.00290	0.00412	0.00288
60	0.00744	0.00491	0.00666	0.00455	0.00658	0.00451
65	0.01181	0.00775	0.01061	0.00715	0.01050	0.00709
70	0.01796	0.01210	0.01609	0.01100	0.01592	0.01089
75	0.03064	0.02079	0.02725	0.01853	0.02697	0.01831
80	0.05310	0.03779	0.04689	0.03333	0.04632	0.03284
85	0.09361	0.07158	0.08259	0.06288	0.08149	0.06171
90	0.15812	0.13211	0.13999	0.11701	0.13762	0.11421
95	0.26151	0.22718	0.23152	0.20122	0.22761	0.19641
100	0.38711	0.35129	0.34272	0.31115	0.33693	0.30370
105	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000

9.7 Appendix 7: Baseline characteristics

NG17 provides the following additional patient baseline characteristics.

Table 39: NG17 additional patient baseline characteristics

	Mean	s.d.	Source
Systolic blood pressure (mmHg)	131.3	16.3	Repose trial
Diastolic blood pressure (mmHg)	80	0	IQVIA CDM default
Total Cholesterol (mg/dL)	90	16.2	Repose trial
High density cholesterol (mg/dL)	28.8	7.2	Repose trial
Low density cholesterol (mg/dL)	50.4	16.2	Repose trial
Triglyceride (mg/dL)	25.2	18	Repose trial
Body mass index (kg/m2)	27.2	5	Repose trial
Estimated GFR (ml/min/1.72m)	78.58	13.24	REPOSE6
Haemoglobin (gr/dl)	14.5	0	IQVIA CDM default
White blood cell count (10	6.8	0	IQVIA CDM default
Heart rate (bpm)	72	0	IQVIA CDM default
Waist to hip ratio	0.93	0	IQVIA CDM default
Waist circumference	87.84	n/a	IQVIA CDM default
Urinary Alb. creatinine (mg.mmol)	4.78	10.19	Repose trial
Serum Creatinine (mg/dL)	1.1	0	IQVIA CDM default
Serum Albumin (g/dl)	3.9	0	IQVIA CDM default
Prop. Smoker	0.192	n/a	Repose trial
Cigarettes/ day	15	n/a	HSE 2017/18 DM subset
Alcohol consumption (Oz/week)	7.7	n/a	WHO
Prop. Physical activity	62%	n/a	HSE 2017/18 T1DM subset
Fasting glucose	180.72	n/a	IQVIA CDM default
Prop. Family history stroke	0.0436	n/a	IQVIA CDM default
Prop. Family history CHD	0.1474	n/a	IQVIA CDM default

NG17 provides the following patient baseline complication rates.

Table 40: NG17 patient baseline complication rates

	Mean	s.d.	Source
MI	2.2%	n/a	Repose trial
Angina	1.2%	n/a	Repose trial
Peripheral vascular disease	0.0%	n/a	Assumption
Stroke	0.3%	n/a	Repose trial
Heart failure	0.6%	n/a	Repose trial
Atrial Fibrillation	0.0%	n/a	Assumption
Left ventricular hypertrophy	0.0%	n/a	Assumption
Microalbuminuria	12.0%	n/a	Repose trial
Gross proteinuria	4.5%	n/a	Repose trial
End stage renal disease	0.0%	n/a	Assumption
Background retinopathy	34.8%	n/a	Repose trial
Proliferative diabetic retinopathy	9.3%	n/a	Repose trial
Severe vision loss	0.0%	n/a	Assumption
Macular Oedema	0.0%	n/a	Assumption
Cataract	0.0%	n/a	Assumption
History of foot ulcer	0.0%	n/a	Assumption
History of amputation	0.0%	n/a	Assumption
Neuropathy	7.1%	n/a	Repose trial