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Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes [ID3957]

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

Produced by: Warwick Evidence

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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).

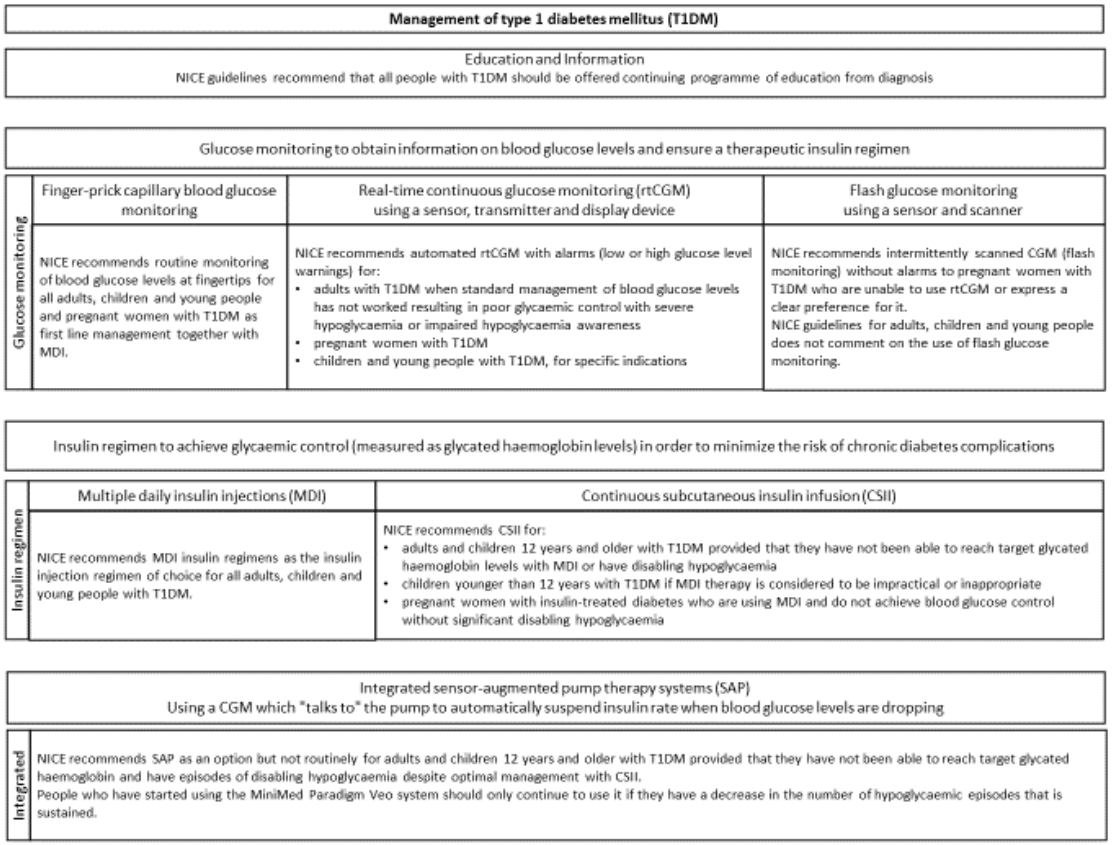


Figure 1. Management of type 1 diabetes mellitus (www.nice.org.uk/guidance/ng17)

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 <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] 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

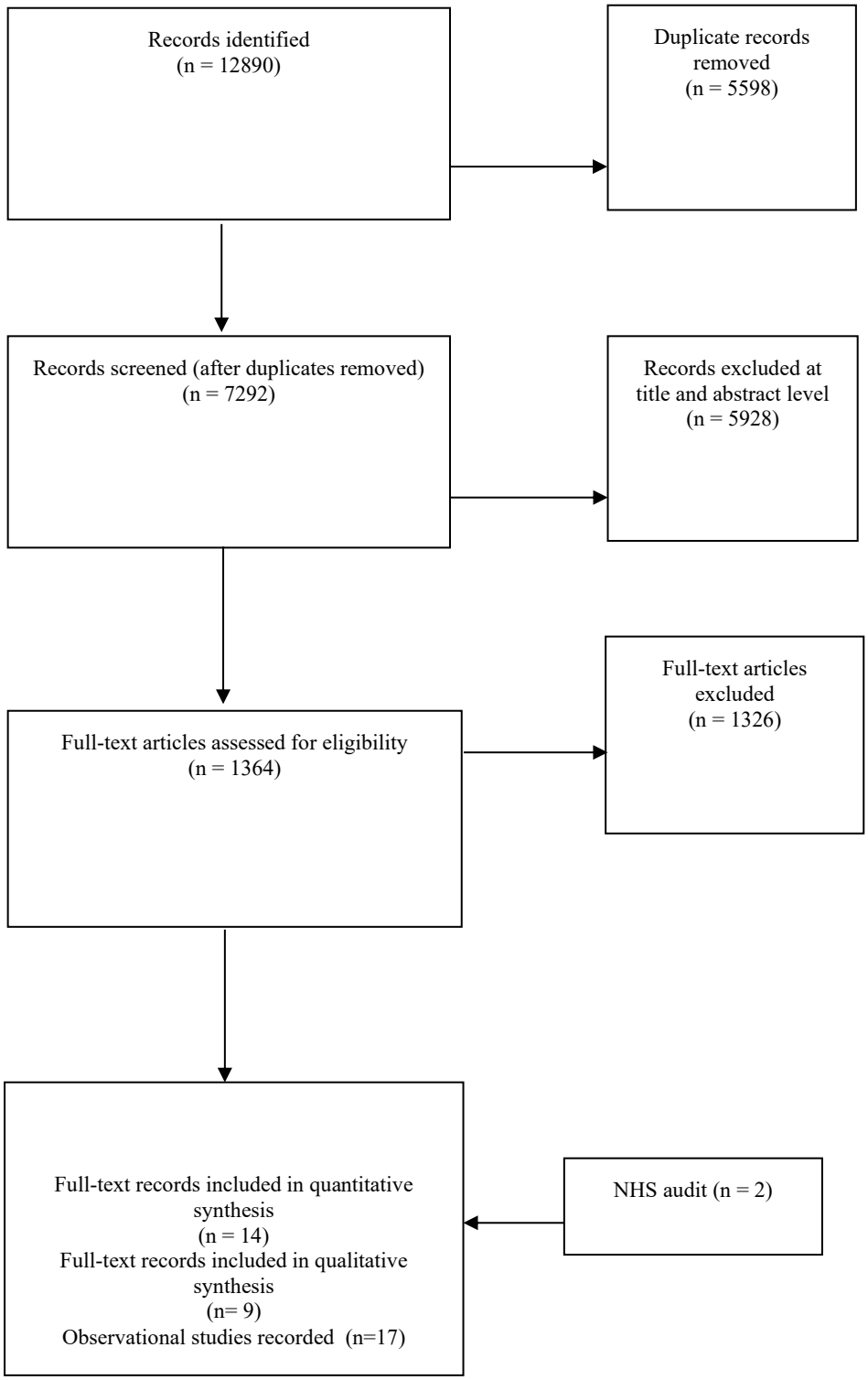
We conducted the review according to the registered protocol.

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.

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.									

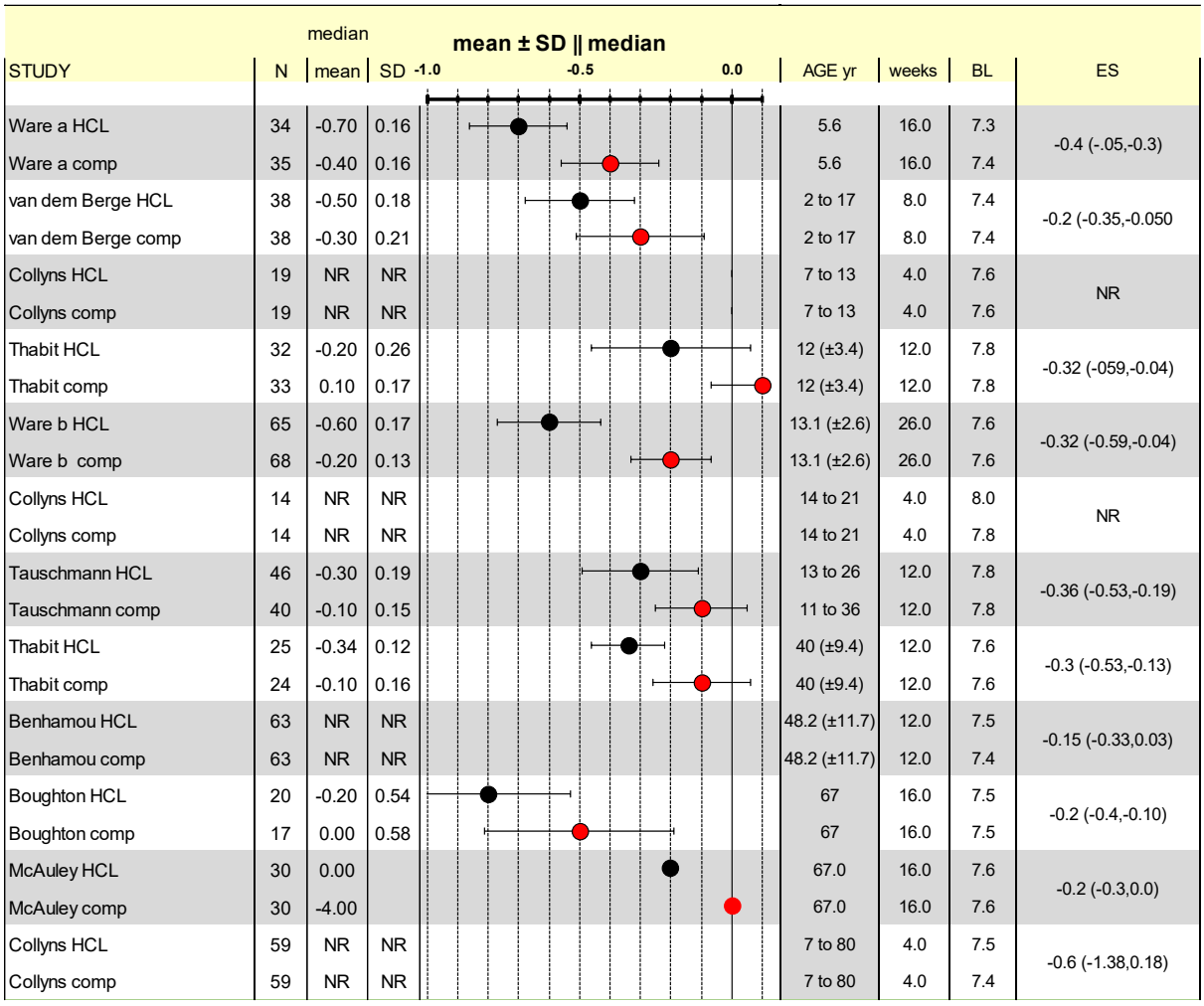
	HbA1c% mean sd *median IQR	*% TIR >10 mmol/L mean sd* *median IQR	*% TIR 3.9-10.0 mmol/L mean sd* *median IQR	*% TIR <3.9 mmol/L [70mg/dl] mean sd* *median IQR	*% TIR <3.5 mmol/L [63mg/dl] mean sd* *median IQR	*% TIR<3.3 mmol/L [60mg/dl] mean sd* *median IQR	*% TIR<3.0 mmol/L [54mg/dl] mean sd* *median 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.

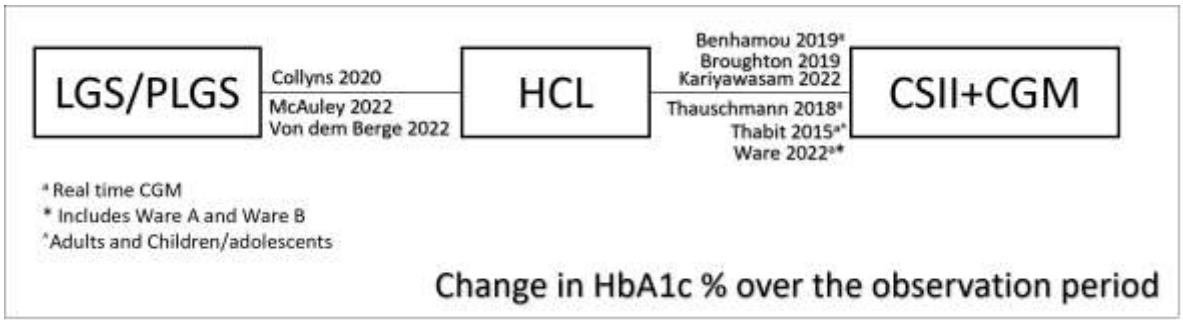


Figure 2. Network map of the outcome Change in HbA1c % over observation period

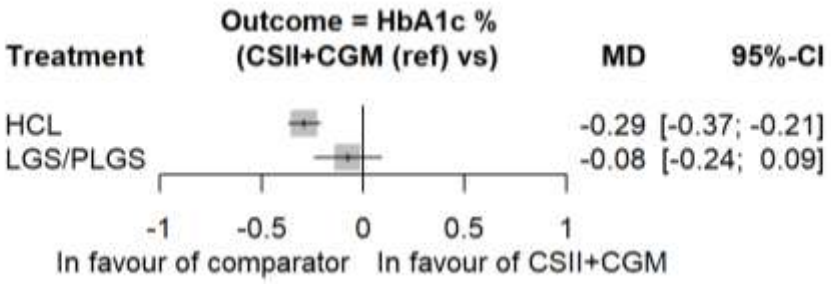


Figure 3. Results of the NMA of the outcome Change in HbA1c % over observation period

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	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.

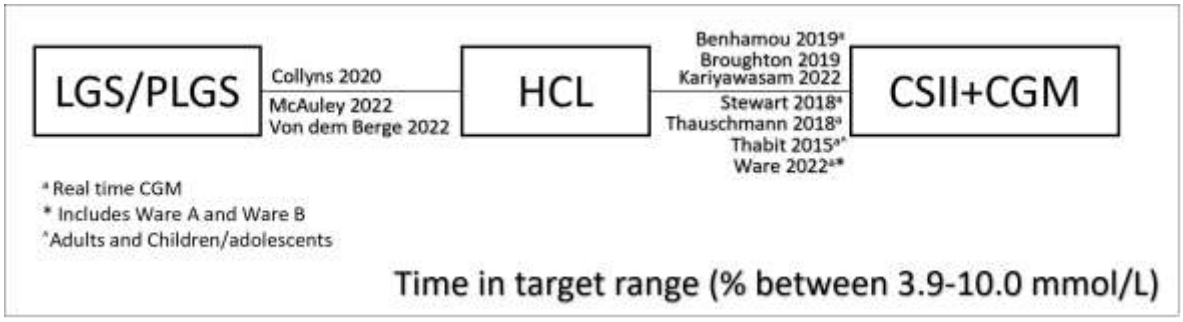
4.2.5 % time within range (between 3.9-10.0 mmol/L) – NMA

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)



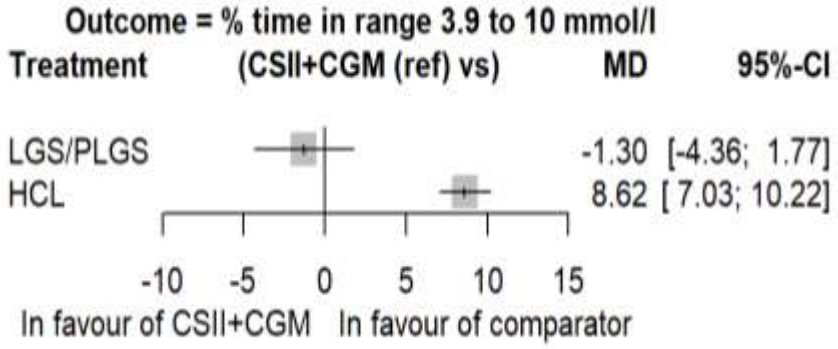


Figure 6. Results of the NMA of the outcome Time in target range (% between 3.9 and 10.0 mmol/l)

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	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)

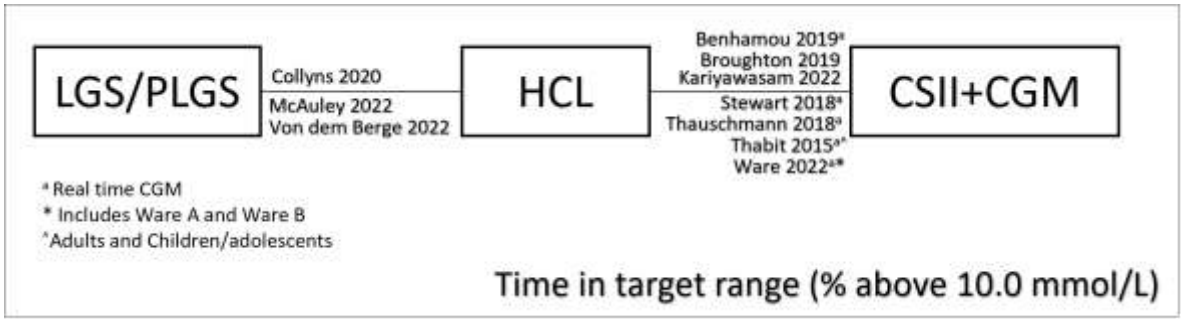
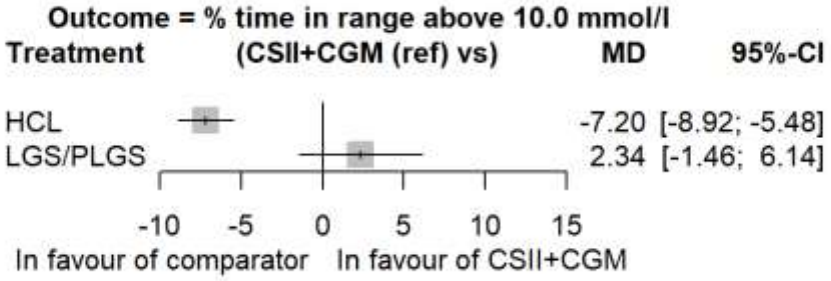


Figure 9. Results of the NMA of the outcome Time in target range (% above 10.0 mmol/l)



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	mean ± SD ‖ median -5 -4 -3 -2 -1 0 1 2 3 4 5	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)

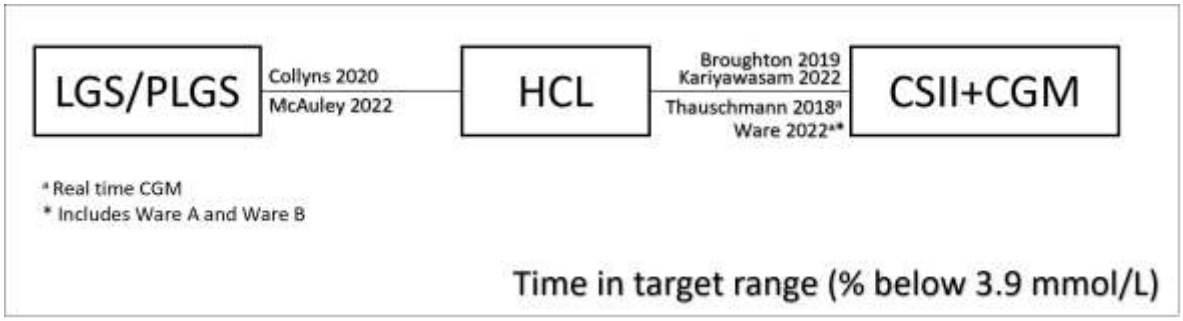
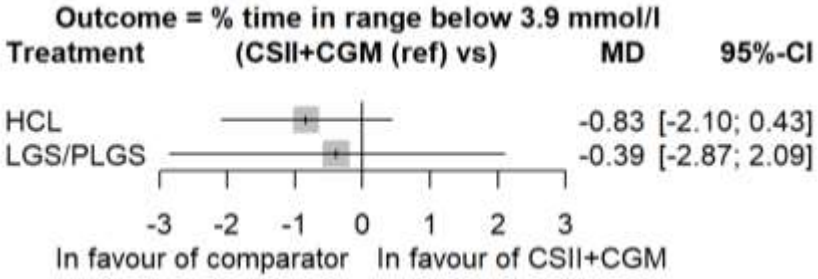


Figure 13. Results of the NMA of the outcome Time in target range (% below 3.9 mmol/l)



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

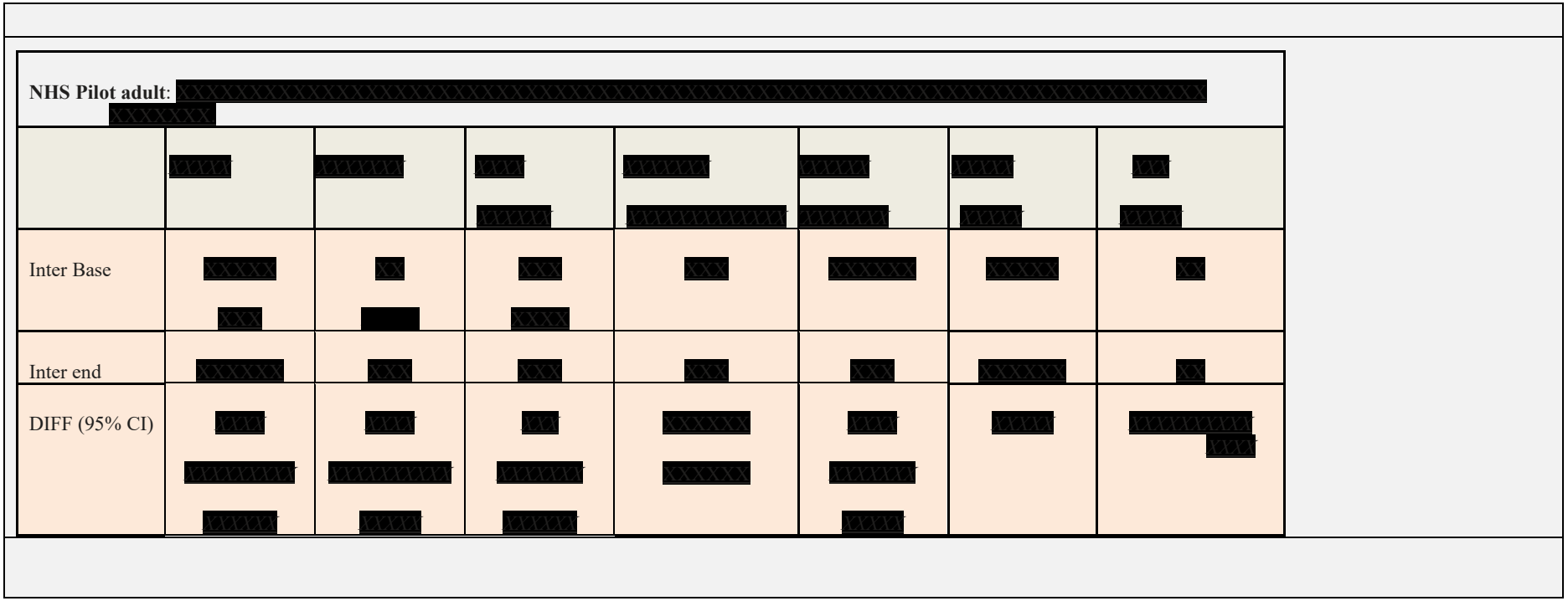
Study	Population at recruitment / randomisation	Age description	N
NHS Pilot study adults. HCL (Report provided to EAG by NICE, 17 June 2022)	[redacted]	[redacted]	[redacted]
Forlenza 2022 HCL [65]	Diag: ≥ 0.25 yr; Pump ≥ 3 months; HbA1c < 10%; total insulin ≥ 8 U/day; no severe hypo in last 3 months.	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 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*	*% TIR <2.8 mmol/L 50mg/dl] mean sd*	*po 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)

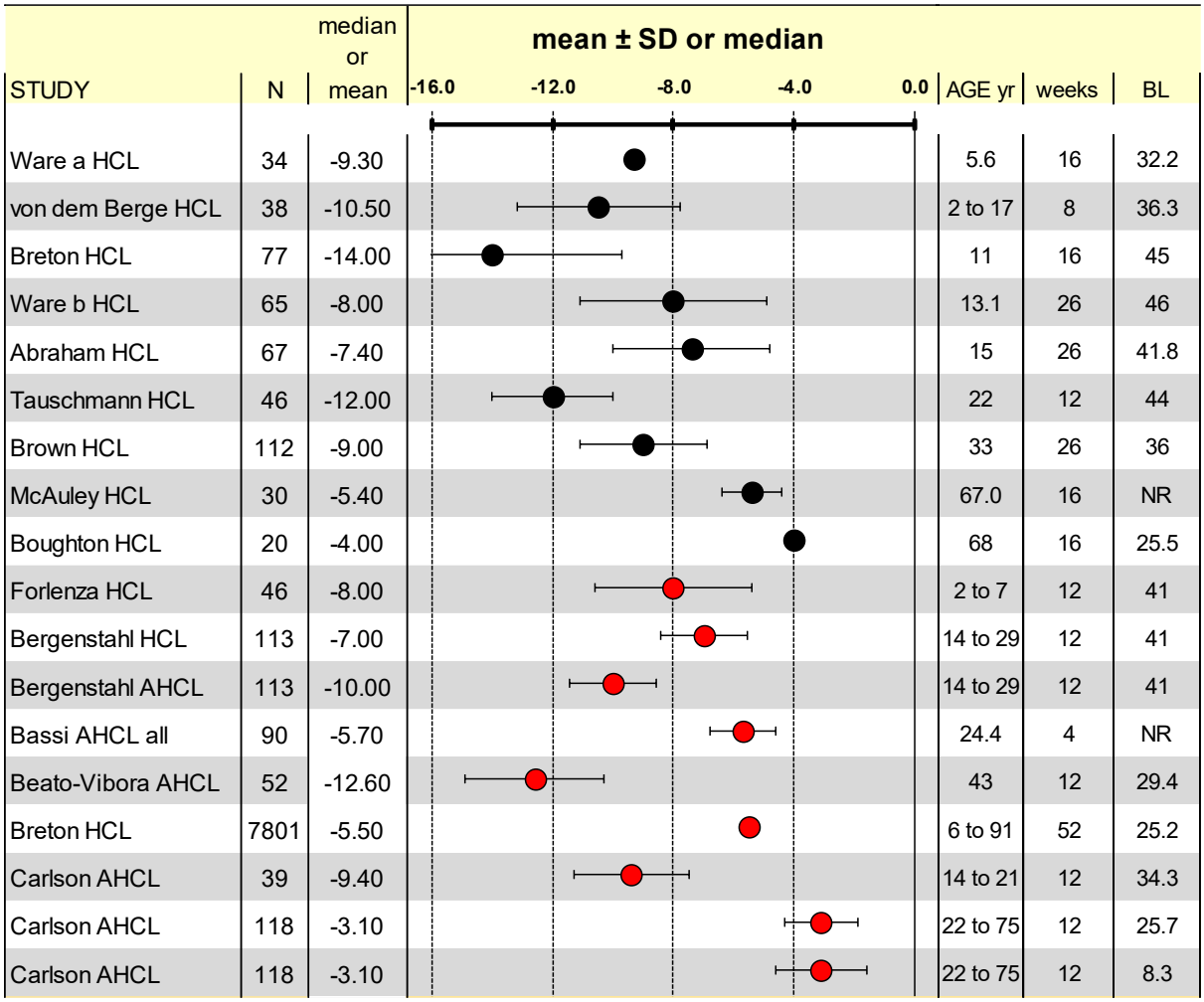
Median values have no error bars. RCTs shown include Abraham 2021[67] Brown 2019[68] Breton 2020 [69] details of these studies available in 10.4.

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

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].

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]

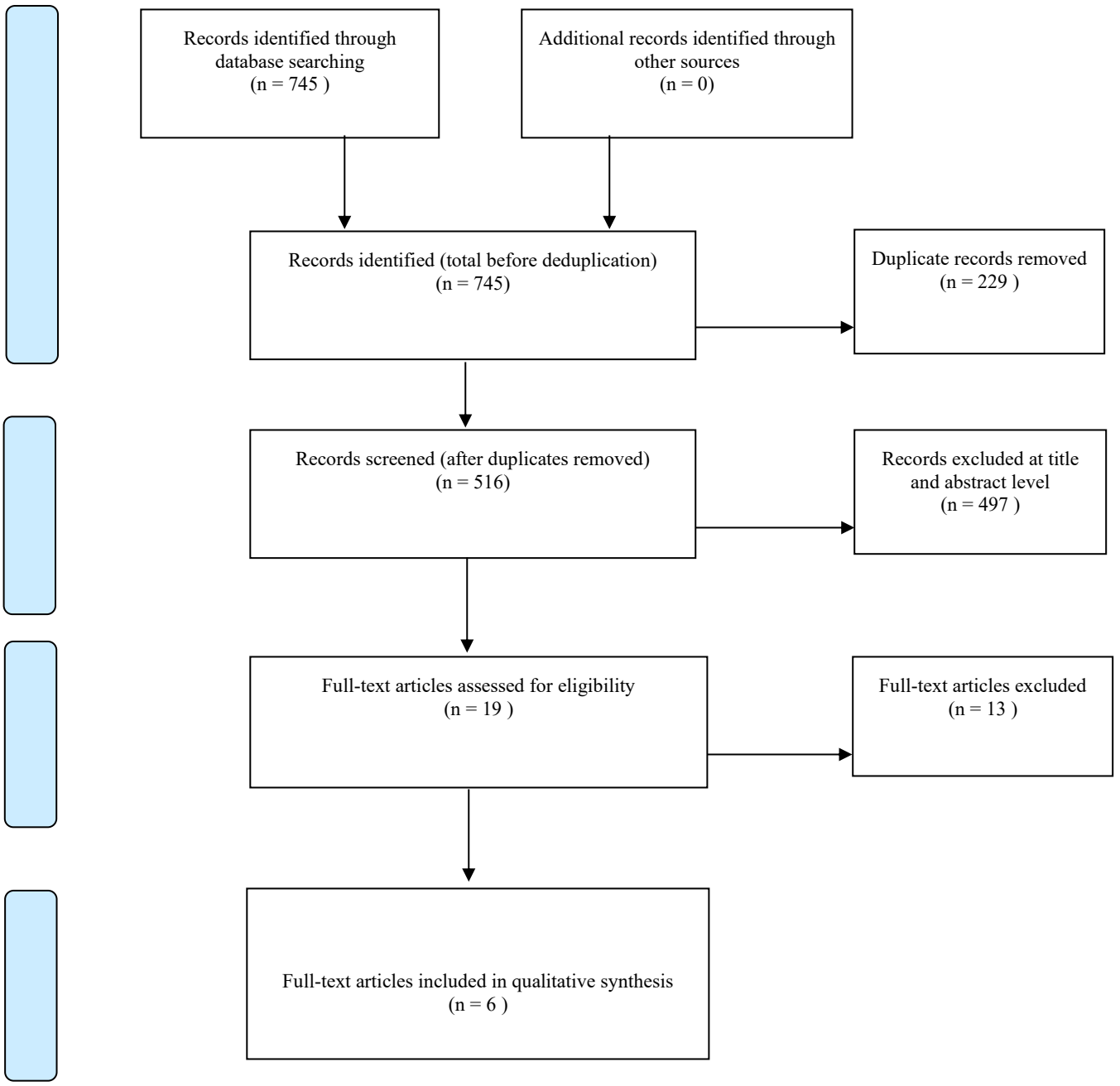


Figure 19. Search strategy flow diagram

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 £5,420 for A/HCL 780G, £5,342 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 and the other based upon the KidsAP02 study among patients aged 1 to 7 years using

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%.

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]

[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]

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

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 1248519680.546.1248519680.546 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 1248519680.546.1248519680.546 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.

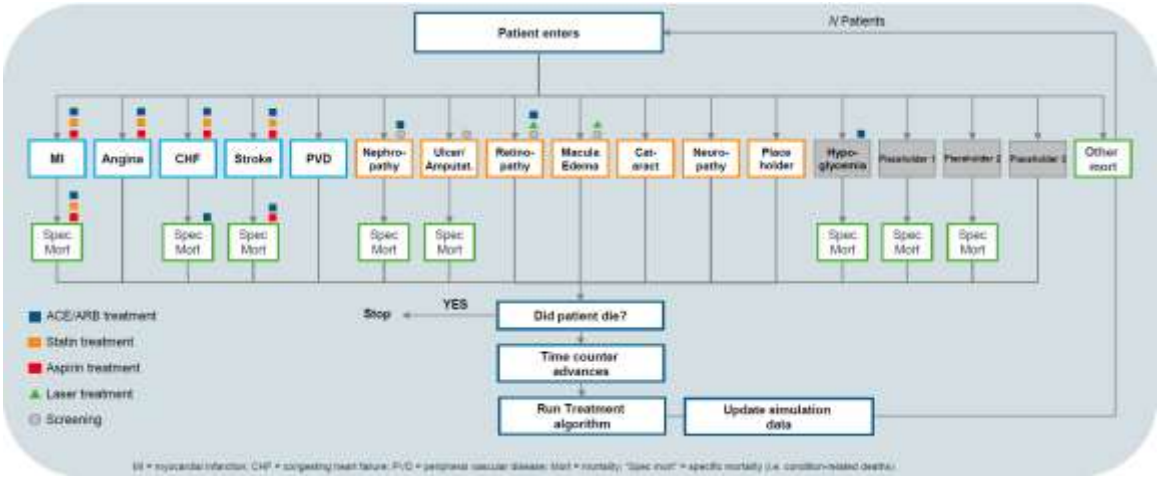


Figure 20: iQVIA CDM structure[§§]

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.

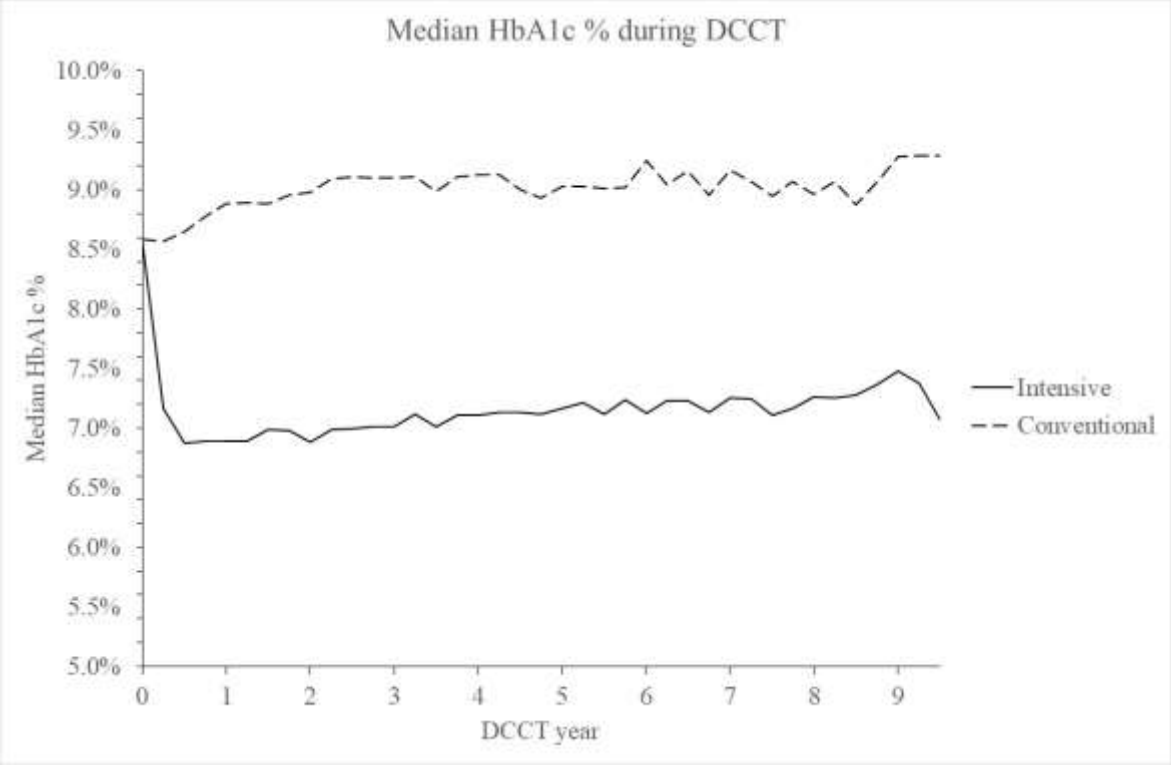


Figure 21: Median HbA1c during the DCCT trial

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.

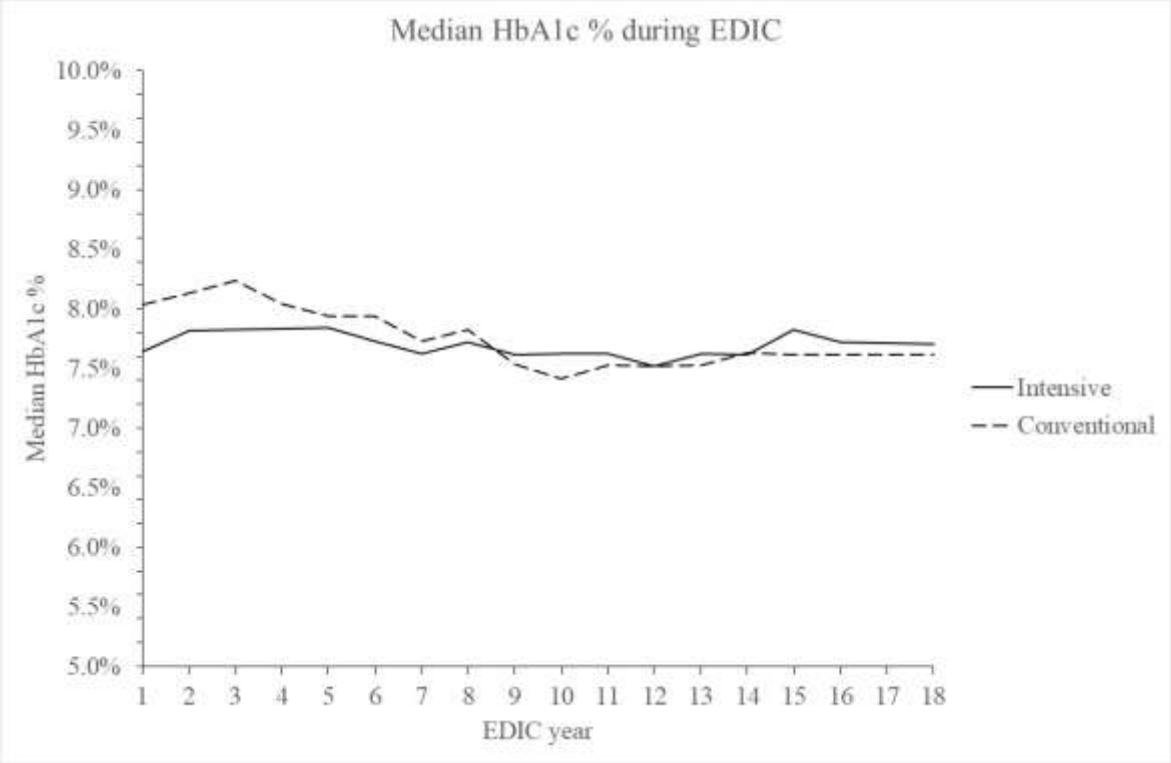


Figure 22: Median HbA1c during the EDIC extension trial

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.

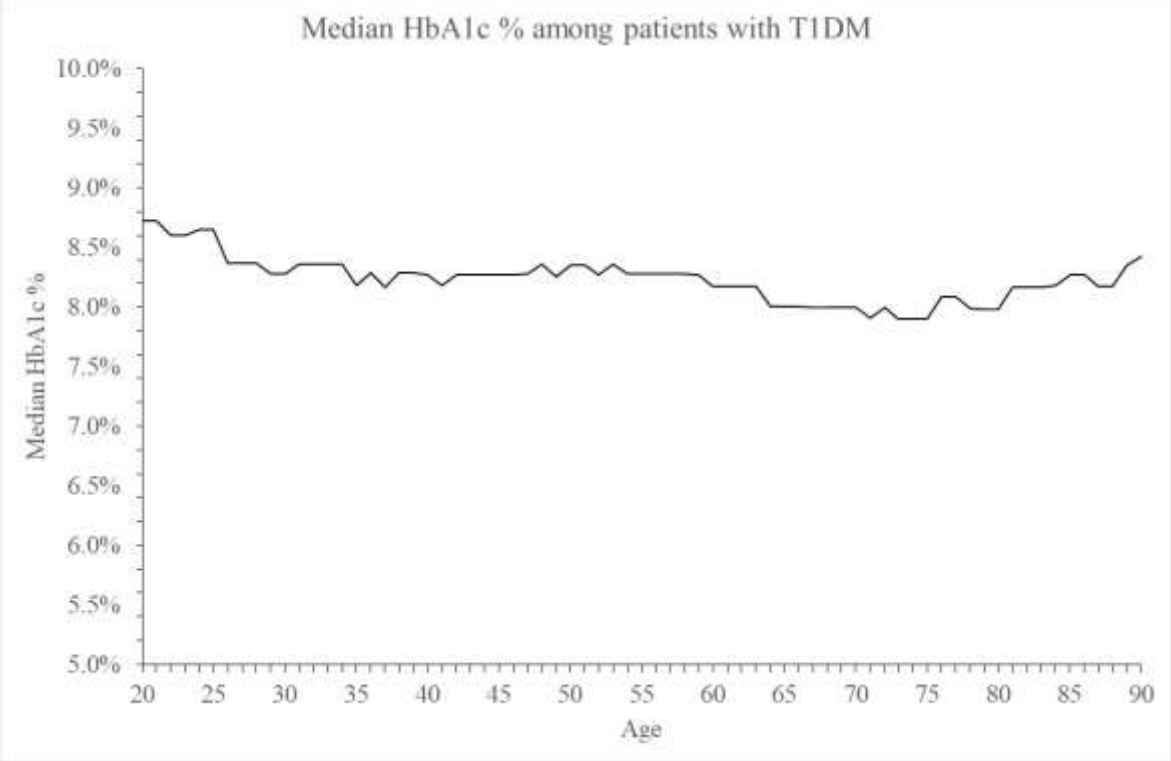


Figure 23: UK Diabetes Audit: Median HbA1c by age

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 1248519680.546.1248519680.546 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 1248519680.546.1248519680.546 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.

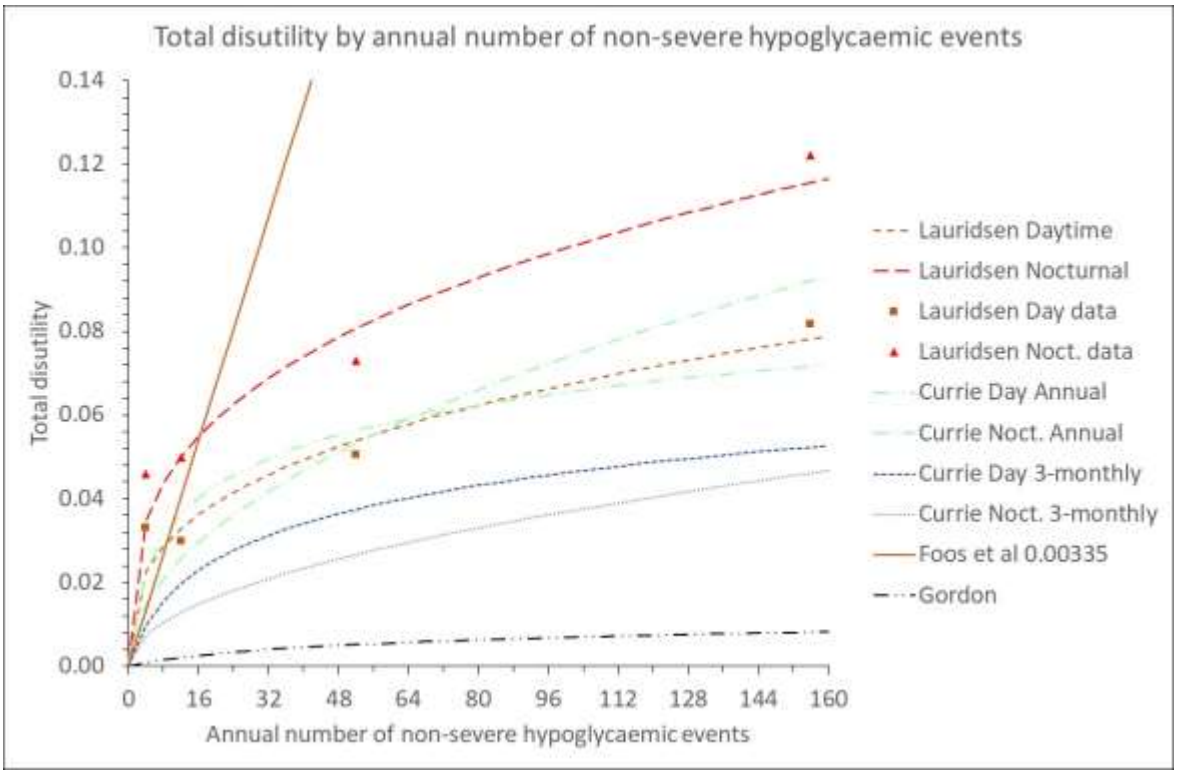


Figure 24: NSHE disutilities for the iQVIA CDM defaults and Gordon et al

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:
---
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:
---
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 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)*

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