Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Recommendation
January 2022

In response to an enquiry from the Scottish Diabetes Group

Closed loop systems and the artificial pancreas for the management of type 1 diabetes

Recommendations for NHSScotland

This recommendation applies to single hormone closed loop systems. No evidence was identified for artificial pancreas systems (multi-hormone closed loop systems) available on the UK market.

To minimise inequalities in accessing diabetes technologies, clinicians should pro-actively initiate meaningful discussions with all patients with type 1 diabetes about the suitability of a closed loop system for their individual circumstances.

Single hormone closed loop systems should be available to people with type 1 diabetes (paediatric and adult) who:

- under their current diabetes care plan, continue to have suboptimal glycaemic control, a high risk of severe hypoglycaemia, or impaired awareness of hypoglycaemia, or
- experience diabetes-related distress, measured using a validated tool, that adversely affects quality of life or their ability to manage diabetes, and which is likely to be improved by moving to a closed loop system.

People who can achieve the desired glycaemic targets using finger prick testing, flash glucose monitoring or continuous glucose monitoring plus multiple daily insulin injections, or flash glucose monitoring plus an insulin pump, should be supported to remain on their current diabetes care plan subject to their circumstances and quality of life. People who are currently using continuous glucose monitoring in combination with an insulin pump (non-integrated) should be offered a closed loop system, which may provide them with additional clinical benefits at lower costs.

In their discussions, people with type 1 diabetes and clinicians must consider the day-to-day requirements of managing closed loop systems, for example, responding to alerts or replacing sensors when required. Support on how to use the closed loop system effectively should be provided to everyone offered the technology.

The Scottish Care Information (SCI)-Diabetes database should be used to collect clinical and person-reported outcomes data from people with type 1 diabetes using closed loop systems. These data will be used to inform quality of care improvements and future advice for NHSScotland.

NHSScotland is required to consider SHTG Recommendations.

What were we asked to look at?

We were asked to examine the evidence on using closed loop systems and the artificial pancreas for the management of type 1 diabetes. We were asked to consider the cost-effectiveness of these technologies compared with current diabetes management options, and to consider clinical effectiveness, safety and patient aspects.

Why is this important?

Access to technologies to support people with managing diabetes is a key priority of the Scottish Government's Diabetes Improvement Plan.[1] The 2019 Scottish diabetes survey found that there were 33,452 people living with type 1 diabetes in Scotland.[2] Living with type 1 diabetes is associated with a significant physical and mental health burden caused by the demands of managing the condition every day and worrying about future complications. Poorly controlled diabetes is associated with complications such as leg, toe or foot amputation, nephropathy, neuropathy and retinopathy resulting in sight loss.[3] People with type 1 diabetes are also at increased risk of cardiovascular disease and premature mortality. Approximately 80% of the £10 billion annual spending on diabetes in the UK is used to fund the treatment of complications.[3] Rapidly advancing diabetes technologies, such as closed loop systems and the artificial pancreas, have the potential to transform the lives of people living with type 1 diabetes. 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.

What was our approach?

We produced SHTG Recommendations based on the published evidence on clinical effectiveness and safety, SHTG de novo economic modelling, patient experiences and patient preferences. Information on our SHTG Recommendations product can be found here.

What next?

The recommendations will be shared with the Scottish Diabetes Group and the diabetes managed clinical networks. The recommendations will be circulated throughout NHSScotland as NHSScotland is required to consider SHTG Recommendations.

Key points from the evidence

1. Trials comparing closed loop systems with usual care generally have small sample sizes and evaluate interventions over short time periods with a study population of people with well controlled type 1 diabetes who have lived with the condition for many years. The closed loop systems used in trials have often been superseded by more advanced versions. Meta-analyses show high levels of statistical heterogeneity based on these trials.

2. A network meta-analysis of 14 trials (n=1,043) in adults with type 1 diabetes found that the mean percentage time in normal glycaemic range was significantly greater with closed loop systems compared with other diabetes technologies, including continuous glucose monitoring plus insulin pump therapy. A meta-analysis of 12 trials (n=344) that compared closed loop systems with sensor-augmented pump therapy reached similar conclusions.

3. A meta-analysis of 19 studies (n=364) compared closed loop systems with continuous subcutaneous insulin infusion in adolescents and children with type 1 diabetes. There was a statistically significant difference in mean percentage time in normal glycaemic range that favoured closed loop systems: 11.97%, 95% confidence interval (CI) 5.54% to 18.40%, p=0.0003.

4. A meta-analysis of 41 trials (n=1,042) comparing closed loop systems with continuous subcutaneous insulin infusion or sensor-augmented pump therapy, in people of any age with type 1 diabetes, found a statistically significant improvement in weighted mean percentage time in normal glycaemic range in the closed loop group compared with the control group: 9.62%, 95% CI 7.54% to 11.70%, p<0.001. A subgroup analysis was consistent with the overall meta-analysis for comparisons of an artificial pancreas (a dual hormone closed loop system) with continuous subcutaneous insulin infusion or sensor-augmented pump therapy.

5. The meta-analyses described in key points 3 and 4 found corresponding statistically significant reductions in the mean percentage time spent in hypoglycaemia and hyperglycaemia with closed loop systems.

6. The results of 13 randomised controlled trials (RCTs), published after the most recent meta-analysis, are consistent with the findings reported in the secondary literature. Two of the trials tested closed loop systems in people with a moderate-to-high risk of hypoglycaemia or suboptimal glycaemic control.

7. Clinical safety outcomes, such as severe hypoglycaemia or diabetic ketoacidosis, were rarely reported in the secondary literature. As a result there is uncertainty around the frequency of these outcomes with closed loop systems compared with other diabetes management options.

8. Device-associated safety concerns related to either technical difficulties affecting components within the closed loop system or human factors. The main safety issues reported with closed loop systems were about loss of connectivity between component devices often owing to the devices being too far apart.

9. In the published literature on patient experiences and views of closed loop systems, people with type 1 diabetes described how closed loop systems improved their glycaemic control, gave them increased flexibility around eating and exercise, and provided 'time off' from managing their diabetes. People also described a burden of treatment associated with this technology such as the need to respond to frequent alarms, replace sensors and deal with technical problems. Some people expressed concerns about the trustworthiness of closed loop systems or found the systems challenging to use when exercising.

10. An audit of services in England and Wales for children and young people with type 1 diabetes found that continuous glucose monitors and insulin pumps were significantly more likely to be used by children and young people with diabetes who live in the most affluent areas and are of white ethnicity.

11. The patient organisation Insulin Pump Awareness Group (iPAG) Scotland identified inequalities in access to closed loop systems in Scotland created by the current requirement for people to self-fund the use of these systems. This is a cost that many from lower income areas cannot afford.

12. Three patient organisations (iPAG Scotland, Juvenile Diabetes Research Foundation (JDRF), and Diabetes Scotland) outlined the substantial impact the condition has on those living with type 1 diabetes and all strongly supported access to closed loop systems in Scotland.
    - Managing type 1 diabetes is a daily burden that has a major impact on the daily lives of people with diabetes, their families and carers.
    - The adverse effects of managing type 1 diabetes are both physical and mental and include diabetes-related distress and reduced quality of life.
    - There are currently financial barriers to accessing closed loop systems because of the requirement to self-fund and barriers to education about diabetes and the role of closed loop systems.
    - Equal access to closed loop systems across NHSScotland is highly desirable for people with type 1 diabetes.

13. Two studies reporting interviews with healthcare professionals in NHS England identified the importance of defining priority groups and ensuring consistency of access to closed loop systems in clinical practice.

14. SHTG adapted an economic model comparing closed loop systems with continuous glucose monitoring plus multiple daily injections, flash glucose monitoring plus multiple daily injections, continuous subcutaneous insulin infusion pumps plus continuous

glucose monitoring, and finger prick testing plus multiple daily injections. Based on the available clinical evidence in people with well controlled type 1 diabetes:

- closed loop systems were associated with the highest costs and quality adjusted life years in a Scottish adult population with type 1 diabetes (except in the comparison with continuous glucose monitoring plus continuous subcutaneous insulin infusion, where associated closed loop system costs were lower)
- base case results showed that closed loop systems are cost-effective compared with continuous subcutaneous insulin infusion plus continuous glucose monitoring (non-integrated)
- base case results showed that closed loop systems are unlikely to be cost-effective compared with flash or continuous glucose monitoring plus multiple daily injections. The results are sensitive to baseline HbA1c, technology costs and effects on hypoglycaemia. The model does not capture day-to-day quality of life improvements associated with the use of closed loop systems, and
- the costs associated with closed loop systems (device and consumables cost) should be considered in the context of the reduction in the costs of managing long-term complications of type 1 diabetes.

SHTG Council considerations

1. When formulating their recommendations, the Council took into account the published evidence, SHTG economic modelling, and the views of clinical experts and patients.

2. The Council acknowledged that closed loop systems are a rapidly advancing technology, and that consequently some of the evidence reviewed may relate to devices that have been superseded. The Council felt it important that the published evidence, and outcomes data from the SCI-Diabetes database, should be reviewed regularly by SHTG to allow for updating of the recommendations on closed loop systems for NHSScotland.

3. Particular note was made of current evidence being based on trials that recruited participants who had relatively well controlled type 1 diabetes. The Council recognised that the benefits of closed loop systems may be greater for people with less well controlled type 1 diabetes.

4. The Council were advised by clinical experts that very few people in Scotland with type 1 diabetes currently receive a closed loop system through the NHS.

5. The Council noted that costs and incremental cost-effectiveness ratios (ICERs) in the economic modelling could be lower in the future, particularly if lower device costs are negotiated between NHS National Procurement and device manufacturers.

6. Clinical experts highlighted that glycaemic targets in the published literature were aligned with Scottish definitions. Time spent in glycaemic range has been internationally agreed to be time spent with glucose levels between 3.9 and 10.0 mmol/L. Optimal glycaemic control is defined in the Scottish Diabetes Improvement Plan as <58 mmol/mol (9.4 mmol/L) in adults and <48 mmol/mol (7.2 mmol/L) in children.

7. The Council discussed the most appropriate way of defining and measuring diabetes-related distress. They agreed that validated tools should be used to provide information to facilitate discussions between clinicians and people with type 1 diabetes about whether using a closed loop system would be suitable for the individual. Appropriate tools for measuring diabetes-related distress in people with type 1 diabetes include the Problem Areas In Diabetes (PAID) scale and the Diabetes Distress Scale.

8. The Council discussed the lack of clinical data comparing closed loop systems with flash glucose monitoring plus an insulin pump. As a consequence, any additional clinical benefit of closed loop systems for people currently using flash glucose monitoring and an insulin pump remains unclear.

9. The Council discussed the value of educational programmes that help people with type 1 diabetes to use a closed loop system. These programmes should be designed for people with a range of educational and technological knowledge levels and should be accessible to people with English as a second language.

10. Patient organisations highlighted the daily burden of managing type 1 diabetes and the impact this has on the lives of people with diabetes, with particular reference to effects on physical and mental health, including diabetes-related distress and quality of life.

11. The Council recognised the mental health and wellbeing benefits of using closed loop systems, in addition to their physical health benefits, regardless of people's previous levels of glycaemic control.

12. The Council acknowledged that there are a growing number of people with type 1 diabetes who are using 'do it yourself' (DIY) closed loop systems. DIY closed loop systems are not regulated and are not covered in these SHTG Recommendations. Diabetes UK has developed a position statement on DIY closed loop systems which has been endorsed by the Royal College of Nursing.

13. The Council noted the link between poor glycaemic control and subsequent development of diabetes-related complications, which in addition to the heavy burden placed on individuals with type 1 diabetes, carries a substantial treatment cost to NHSScotland.

14. There is an ongoing trial of closed loop systems in NHS England that should provide useful data to inform an update of this review.

15. The SCI-Diabetes database provides a fully integrated shared electronic record of population level data for all people with diabetes in Scotland. SCI-Diabetes should be used for the robust capture of national data to facilitate decision making and real world assessment of diabetes technologies across NHSScotland.

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Definitions

Diabetic ketoacidosis	a serious state that arises when people with diabetes start to run out of insulin in their body. Ketones from the breakdown of fats build up in the body and this can become life threatening if the person is not treated quickly.[4]
Endogenous insulin	insulin that is produced naturally in the body.[5]
Exogenous insulin	insulin that is injected or infused into the body.[5]
Hyperglycaemia	the medical term for high blood sugar (glucose) levels.[6]
Hypoglycaemia ('hypo')	the medical term for low blood sugar (glucose) levels.[7]
Sensor-augmented pump	when an insulin pump and a continuous glucose monitor used by one person are not integrated. Alerts from the sensor or pump inform the individual when their glucose levels become too high or too low.[8]

Closed loop systems are referred to in the published literature by three terms which are used interchangeably. For the purposes of this review the following technology definitions have been applied to refer to the devices assessed within published studies:

Artificial pancreas	a fully automated closed loop system that administers multiple hormones, for example insulin and glucagon.
Closed loop system	a fully automated, insulin only system where the user is not required to administer an insulin bolus at mealtimes.
Hybrid closed loop system	a closed loop system that requires the user to manually enter estimated carbohydrates at mealtimes in order to prompt the insulin pump to administer an insulin bolus.

Introduction

Type 1 diabetes is a serious condition where blood glucose (sugar) levels become too high because the body cannot make a hormone called insulin. Type 1 diabetes is an autoimmune condition where the body's immune system mistakenly destroys cells in the pancreas that produce insulin.[9] This leads to insufficient insulin production and a life-long dependency on exogenous insulin administration. The role of insulin is to reduce blood glucose levels by facilitating the transport of glucose from the blood into cells throughout the body where it is used as a fuel. In people with type 1 diabetes,

exogenous insulin is required to replicate this process. Additional insulin is needed at mealtimes when glucose levels rise rapidly after the person consumes carbohydrates in their food.

Daily management of type 1 diabetes, including counting carbohydrates, measuring glucose levels and administering insulin, places a substantial burden on people with this condition. People with type 1 diabetes, or the parents of children with the condition, also often experience a reduction in mental health and wellbeing as a result of constantly managing diabetes and worrying about hypoglycaemic events or long-term complications of diabetes.

It is important for people with type 1 diabetes to maintain blood glucose concentrations as close as possible to the normal range in order to avoid complications and harms from hyperglycaemia or hypoglycaemia. In the long-term, hyperglycaemia can lead to blindness, limb amputations, stroke and other serious cardiovascular complications. Hypoglycaemia can result in confusion, seizures, unconsciousness and even death.[10] The artificial pancreas and closed loop systems can potentially help maintain blood glucose in the healthy range for people with type 1 diabetes through continuous monitoring of glucose concentrations and automatic adjustment of insulin delivery.

Research question

What is the clinical effectiveness, cost-effectiveness and safety of closed loop systems and the artificial pancreas in the management of type 1 diabetes?

Literature search

A systematic search of the secondary literature was carried out between 23 June and 1 July 2021 to identify systematic reviews, health technology assessments and other evidence-based reports. The Medline, Medline in process and Embase databases were searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 23 June and 1 July 2021 using the following databases: Medline, Medline in process and Embase. Results were limited to RCTs, economic studies and qualitative studies on patient aspects.

A systematic search of the literature was conducted between 26 and 29 July 2021 to identify economic models, relevant long-term clinical outcomes, costs and utilities to inform the de novo economic modelling. The NHS Economic Evaluation database (NHSEED), Medline and Embase databases were searched.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: type 1 diabetes, artificial pancreas; closed loop system; closed loop pancreas; closed loop insulin system; closed loop therapy. A full list of resources searched and terms used are available on request.

Health technology description

Closed loop systems and the artificial pancreas consist of medical devices that combine three functions: continuous monitoring of interstitial glucose levels (continuous glucose monitoring, CGM), hormone, normally insulin, delivery using a pump and a digital controller. The CGM device sends glucose data to the digital controller, which analyses the data using an algorithm and instructs the pump to adjust hormone delivery accordingly.[11] Integrating these three functions creates an automated hybrid or fully closed loop system.

The digital controller function can be integrated into the pump or CGM device (with a smartphone app providing the user interface), on a separate dedicated mobile device, or it can be an app on a regular smartphone. There are different types of algorithm used by digital controller devices for closed loop systems.[11]

There are six stages of development for closed loop systems and the artificial pancreas (*Table 1*).[11] Research is being conducted on developing devices at all six stages simultaneously. This evidence review focuses on second and third generation devices (stages four to six in *Table 1*).

Table 1: Development stages for closed loop systems and the artificial pancreas[11]

	Stage	Description
First generation	1	**Very low glucose insulin off pump.** The insulin pump shuts off if the user does not respond to low glucose alarms.
	2	**Hypoglycaemia minimiser.** Predicted hypoglycaemia causes an alarm to sound, causing the pump to either reduce or stop administering insulin before blood glucose levels get too low.
	3	**Hypoglycaemia and hyperglycaemia minimiser.** This is essentially the same device as stage 2, but with the added ability to increase insulin therapy when glucose levels get above a pre-specified threshold.
Second generation	4	**Automated basal or hybrid closed loop.** An automated closed loop system at all times that requires users to manually enter estimated carbohydrates prior to mealtimes, resulting in the pump administering an insulin bolus.
	5	**Fully automated insulin closed loop.** An automated closed loop system at all times. Users do not need to manually input carbohydrates at any time.
Third generation	6	**Fully automated multi-hormone closed loop.** Also known as the artificial pancreas. Fully automated administration of insulin and other hormones, such as glucagon, mimics a healthy human pancreas.

In NHSScotland, a small number of people with type 1 diabetes currently have access to a stage four (hybrid closed loop) device (Prof B Kennon, Consultant Diabetologist, NHS Greater Glasgow and Clyde. Personal communication, 06 Aug 2021). At the time of writing (December 2021), there are four commercial hybrid closed loop systems on the market in the UK: the Medtronic MiniMed™ 670G + Guardian™ 3 sensor, the Medtronic MiniMed™ 780G + Guardian™ 3 sensor, the Tandem t:slim X2™ + Dexcom G6 sensor + Control IQ™, and the CamAPS FX + DanaRS + Dexcom G6 sensor. The first three systems are available in NHSScotland.

People with type 1 diabetes are required to perform self management tasks when using a closed loop system or artificial pancreas. For example, replacing CGM sensors, replacing insulin pump infusion sets, inserting new insulin capsules into the pump and responding to alerts or alarms from the devices.

The current flash glucose monitoring technology (Freestyle Libre™) does not form part of a commercial closed loop system, however some people with type 1 diabetes have chosen to use flash glucose monitoring within their DIY closed loop system.

Although both commercial and DIY closed loop systems are available, this SHTG evidence review focuses on the commercially available, regulated systems.

Epidemiology

In 2019, the Scottish diabetes survey recorded 33,452 people with type 1 diabetes living in Scotland.[2] Incidence was estimated at 20 per 100,000 population per year, based on 1,024 people who had received their diagnosis within the previous 12 months.

In the 2019 diabetes survey, 13.8% (n=4,614) of people of all ages who had type 1 diabetes were using an insulin pump. A higher proportion of people aged under 18 used insulin pumps (38.9%) compared with those aged over 18 (11.3%).[2] In October 2021 the SCI-Diabetes database recorded 1.1% of adults with type 1 diabetes, and 9.7% of people aged under 18 with type 1 diabetes, were using a CGM device. Flash glucose monitoring is used by 46.8% of Scottish adults who have type 1 diabetes, and 47.6% of people aged under 18 who have type 1 diabetes (Prof B Kennon, Consultant Diabetologist, NHS Greater Glasgow and Clyde. Personal communication, 30 Dec 2020).

Only 53.5% of adults, 45.5% of children under 11 years and 50.3% of children and adolescents aged 12 to 17, who have type 1 diabetes manage to achieve an HbA1c level within a target range within a year of diagnosis.[2] Poorly controlled diabetes is associated with complications such as leg, toe or foot amputation, nephropathy, neuropathy and retinopathy leading to sight loss.[3] People with type 1 diabetes are also at increased risk of cardiovascular disease and premature mortality. Approximately 80% of the £10 billion annual UK spending on diabetes is for funding the treatment of complications.[3]

In a cohort of 33,547 people in Scotland with type 1 diabetes (2006–2015), mortality increased with increasing socioeconomic deprivation measured using the Scottish Index of Multiple Deprivation

(SIMD).[12] The age standardised mortality rate in people with type 1 diabetes was statistically significantly higher in the most deprived SIMD quintile compared with the least deprived quintile for both sexes: rate ratio (RR) 2.81, 95% confidence interval (CI) 2.27 to 3.47 in men and RR 2.86, 95% CI 2.22 to 3.69 in women. Compared with the general population, age standardised mortality was statistically significantly higher in the population with type 1 diabetes within every SIMD quintile.

Both a systematic review and a retrospective cohort study analysing Scottish data identified inequalities affecting the rate of diabetic ketoacidosis, a severe adverse event in people with type 1 diabetes.[13, 14] The Scottish study (n=37,939) found that diabetic ketoacidosis events were more common in women, people living in more deprived areas, people on antidepressants and people with a prescription for methadone.[13] Access to an insulin pump and completion of structured education on diabetes were associated with lower diabetic ketoacidosis event rates. Similarly, the systematic review found evidence that repeat diabetic ketoacidosis events were associated with being female, living in more deprived areas and poor mental health.[14]

Clinical effectiveness

Adults

A network meta-analysis (NMA) compared multiple technologies for managing type 1 diabetes in adults.[15] A literature search conducted by the meta-analysis authors in April 2019 identified RCTs with a minimum intervention duration of 2 weeks and participants aged 18 or older, for inclusion in the NMA. Studies in pregnant women were excluded. Cross-over trials were treated as if they were parallel RCTs if there was no evidence of a carryover effect.

Interventions in the RCTs involved insulin delivery, glucose monitoring, insulin dosing advice or multiple daily injections of insulin and self monitoring of blood glucose. Any combination of CGM and continuous subcutaneous insulin infusion (CSII, insulin pumps) that facilitated automated adjustment of insulin delivery was considered to be a closed loop system. Multiple daily injections was defined as at least three bolus injections and one basal injection of insulin per day. Outcomes were defined as percentage time in range (3.9 to 10.0 mmol/L or 70 to 180 mg/dL), percentage time above range (hyperglycaemia, >10.0 mmol/L or >180 mg/dL), and percentage time below range (hypoglycaemia, <3.9 mmol/L or <70 mg/dL).

The NMA authors used the Cochrane risk of bias tool to assess the quality of the included RCTs. The majority of trials were judged to have an overall high or unclear risk of bias and all studies were considered to have a high risk of performance bias as a result of the lack of blinding of participants and outcome assessment. The authors of the NMA assessed the three assumptions underpinning NMA by evaluating effect modifiers (transitivity assumption), measuring inconsistency using side-splitting and measuring heterogeneity using the I^2 statistic. Inconsistency was found to be significant in the network for time below range (hypoglycaemia) indicating a difference in results between direct and indirect evidence. Heterogeneity was considerable in all three analyses: I^2=87% for time in range, I^2=73% for time above range, and I^2=97% for time below range. The GRADE certainty of

treatment effects was very low for all comparisons in the NMA after the evidence was downgraded for risk of bias, inconsistency, indirectness and heterogeneity.

Fourteen RCTs (n=1,043), published between 2014 and 2018, were included in the NMA. Comparisons within the NMA were largely based on indirect evidence, with only one or two RCTs providing direct evidence for each pairwise comparison. Four RCTs assessed a closed loop system; three of these trials had one or more UK sites and all four used a cross-over design. Trials evaluating a closed loop system used CGM plus CSII as the comparator; in one trial the control group included using flash glucose monitoring or finger prick testing in place of CGM. In three of the RCTs the closed loop system was the Florence system, which uses an algorithm developed by Cambridge University. All RCTs involving a closed loop system were conducted in an outpatient setting. Mean sample size in the 14 included RCTs was 55 (standard deviation (SD) 33). The mean duration of intervention was 5 months (SD 3.0) and all trials received industry funding or material support. Mean age of trial participants was 43.3 (SD 7.0), mean baseline HbA1c was 7.7% (SD 0.7%) and mean duration of type 1 diabetes was 21.4 years (SD 5.7).

Results from the NMA on mean percentage time in range are presented in *Table 2*. Mean percentage time in range was significantly greater based on 24-hour use of closed loop systems compared to all other technologies in the analysis (10 RCTs, n=710), and for most technologies compared with nocturnal-only closed loop systems. In the analyses for mean percentage time above range (10 RCTs, n=705) and below range (12 RCTs, n=872), the 95% confidence interval for each comparison included zero, suggesting that no intervention performed significantly better than any other. The one exception was the comparison of 24-hour closed loop systems with CGM plus CSII: mean difference (MD) 7.97%, 95% CI 0.82% to 15.11%. Closed loop systems had the highest probability of being best at increasing percentage time in range (91%) and nocturnal-only closed loop systems had the highest probability of being second best for this outcome (86.3%). Closed loop systems had the highest probability of being best for reducing time above range (71.8%). Probability values were similar for all interventions for the outcome of percentage time below range.

Table 2: Results from an NMA showing mean difference in percentage time in range for comparisons including closed loop systems in adults with type 1 diabetes[15]

Comparison	Mean difference % time in range	95% Confidence interval
24h closed loop systems versus:		
MDI+SMBG	17.85	9.28 to 26.42
MDI+FGM	13.29	3.86 to 22.71
MDI+CGM	12.76	4.87 to 20.64
CSII+CGM	8.77	4.18 to 13.35
CSII+CGM/FGM/SMBG*	10.60	6.46 to 14.74
Night only closed loop	3.87	1.71 to 9.46
Nocturnal closed loop systems versus:		
MDI+SMBG	13.98	6.01 to 21.94
MDI+FGM	9.41	0.30 to 18.52
MDI+CGM	8.88	1.71 to 16.05

CSII+CGM	4.89	1.73 to 8.05
CSII+CGM/FGM/SMBG*	6.73	-0.22 to 13.67

**CGM/FGM/SMG (an RCT where participants in the control group could use an insulin pump plus any glucose monitoring approach). CSII = continuous subcutaneous insulin infusion, CGM = continuous glucose monitoring, FGM = flash glucose monitoring, SMBG = self monitoring blood glucose, MDI = multiple daily injections.*

A pairwise meta-analysis (12 RCTs, n=344) comparing closed loop systems with sensor-augmented pump therapy in adults with type 1 diabetes reported similar results to the NMA.[16] The meta-analysis authors conducted a literature search in March 2021, but did not include any trials published after 2017. Unlike the NMA, the pairwise meta-analysis found that studies had a low risk of bias based on the Cochrane tool and that evidence quality, based on GRADE, was moderate or high for all outcomes. Mean difference in percentage time in range was 7.91% (95% CI 4.45% to 11.37%, $p<0.00001$, $I^2=67\%$, seven studies) and favoured closed loop systems.

Adolescents and children

A pairwise meta-analysis compared closed loop systems, including the artificial pancreas, with what is describe as an 'open loop' (sensor-augmented CSII) in adolescents and children with type 1 diabetes.[17] Closed loop systems and the artificial pancreas were defined as technologies where an algorithm connects a CGM device and an insulin pump, thereby determining insulin doses without input from the user. A literature search was conducted by the meta-analysis authors in April 2018. Studies that compared glycaemic control using a closed loop system (single or dual hormone) with sensor-augmented CSII in people aged <18 who had type 1 diabetes, were eligible for inclusion in the meta-analysis. The primary outcome of interest was percentage time in range (4.0 to 10.0 mmol/L). Secondary outcomes included mean glucose levels, percentage time in hypoglycaemia (<4.0 mmol/L) and percentage time in hyperglycaemia (not defined). The meta-analysis authors assessed the quality of included studies using the Cochrane risk of bias tool. Although the study designs of included studies are not reported, the use of the Cochrane tool suggests they are RCTs. All included studies were found to have a high risk of performance bias because of lack of blinding. The meta-analysis authors also identified potential publication bias based on the inspection of funnel plots.

Twenty-five studies (n=504), from 2010 to 2018, were included in the qualitative synthesis and 19 studies (n=364) were included in the meta-analysis. Sample size ranged from four to 54 participants. Mean age of study participants ranged from 5 years (SD 1.4) to 18.6 years (no SD reported). Duration of type 1 diabetes ranged from 2.1 years (SD 1.1) to 13.5 years (SD 11.9). Baseline HbA1c ranged from 7.3% (SD 0.9%) to 9.0% (SD 1.1%). Twenty-one studies were conducted in an outpatient setting; six included one or more UK sites. The intervention duration ranged from 8 hours to 84 days (median 48 hours, mean 154 hours).

The meta-analysis reported greater mean percentage time in range with the closed loop system compared with sensor-augmented CSII (*Table 3*). The sensor-augmented CSII group had statistically significantly higher mean glucose levels, and spent a greater percentage time in hypoglycaemia and hyperglycaemia, compared with the closed loop group. There was substantial statistical heterogeneity for all outcomes. The results in favour of closed loop systems remained statistically significant across all sensitivity analyses that reduced between-study heterogeneity. Excluding seven

studies that were considered outliers by the meta-analysis authors reduced heterogeneity to I^2=0%. In this analysis of 11 studies with no heterogeneity, people using a closed loop system spent an average of 11.85% (95% CI 9.57% to 14.13%) increased time in the target glycaemic range. Excluding three studies from the analysis of time in hypoglycaemia reduced heterogeneity to 28%: MD 0.76%, 95% CI 0.25% to 1.27%. Heterogeneity in the hyperglycaemia analysis was 40% after excluding four studies: MD 2.96%, 95% CI 0.76% to 5.17%.

Table 3: Results of a meta-analysis comparing closed loop systems with sensor-augmented CSII therapy in children and adolescents[17]

	n studies	Mean difference (95% CI)	p value	I^2
% time in range (4.0 to 10.0 mmol/L)	18	11.97% (5.54% to 18.40%)	0.0003	96%
% time in hypoglycaemia (<4.0 mmol/L)	11	0.67% (0.21% to 1.13%)	0.004	73%
% time in hyperglycaemia (not defined)	11	3.01% (1.68% to 4.34%)	<0.00001	95%
Mean glucose (mmol/L)	20	0.75 (0.18 to 1.33)	0.01	93%

All age groups

A pairwise meta-analysis compared closed loop systems with any insulin-based intervention for managing type 1 diabetes in people of any age.[18] Sixteen of the studies in this meta-analysis were not included in the NMA or pairwise meta-analysis described above, possibly as a result of differing search strategies and inclusion criteria. A literature search was conducted by the meta-analysis authors in February 2018. Studies eligible for inclusion were RCTs that incorporated adults, children or adolescents with type 1 diabetes, and were conducted in an outpatient setting. Studies in pregnant women were excluded.

Closed loop systems and the artificial pancreas were defined as a combination of an insulin pump and CGM, using a control algorithm that determined delivery of insulin or multiple hormones. Data were extracted from included trials for 24-hour and overnight-only use of closed loop systems. Data on single and dual hormone closed loop systems were also extracted separately. The review authors assessed study quality using the Cochrane risk of bias tool. Only nine out of 39 studies were considered to have a low risk of bias. Most included studies were deemed to have a high risk of bias because they reported median instead of mean values. The meta-analysis authors detected potential publication bias based on a funnel plot and the Egger statistic, however the results of the meta-analysis were not affected by adjusting for publication bias.

Thirty-nine publications, describing 41 RCTs published between 2013 and 2017, were included in the meta-analysis. Thirty-two trials compared closed loop systems with sensor-augmented pumps, five trials compared closed loop systems with CSII plus blinded CGM, and four studies compared single and dual hormone closed loop systems against a control group. The trials described 45 comparisons

with a total of 1,042 participants. Thirteen studies recruited adults, 17 studies recruited adolescents and children, and 11 studies recruited a mixed population. Seven RCTs used a parallel design and all other studies were cross-over RCTs. Thirty-six trials were described by the meta-analysis authors as lasting less than 4 weeks; the remaining five trials lasted 8 to 30 weeks. The follow up duration reported for individual trials ranged from one day to 12 weeks. Sixteen trials evaluated an overnight-only closed loop system. Thirty-two trials used a single hormone closed loop system, five studies used a dual hormone artificial pancreas, and four studies trialled both single and dual hormone devices. Sample size ranged from eight to 75 people, with all but three studies recruiting less than 35 participants. Mean age of participants ranged from 7 to 47 years and mean baseline HbA1c ranged from 6.9% to 8.6%. Participants' duration of type 1 diabetes is not reported. Twenty-six trials involved people using the devices at home.

Compared with the control group, closed loop systems were associated with a statistically significant improvement in mean absolute time in range: an additional 2 hours 20 minutes spent in the target range of 3.9 to 10.0 mmol/L over a 24-hour period (*Table 4*). There were corresponding statistically significant reductions in the mean absolute time spent in hyperglycaemia (2 hours) and hypoglycaemia (20 minutes) using the closed loop systems. Results of the meta-analysis remained similar in sensitivity analyses based on RCTs at low risk of bias, analyses that excluded trials conducted in diabetes camps, and analyses that only included studies conducted in the home setting. Heterogeneity was moderate-to-high for all outcomes.

Table 4: Results from a meta-analysis comparing closed loop systems with sensor-augmented pump therapy or CSII plus blinded CGM in people of any age who have type 1 diabetes[18]

Outcome	n studies	Effect estimate (95% CI)	p value	I^2
Over 24 hours				
Weighted mean difference in % time in range (3.9 to 10.0 mmol/L)	32	9.62 (7.54 to 11.70)	<0.001	78%
Weighted mean difference in % time above range (>10.0 mmol/L)	22	8.52 (5.90 to 11.14)	<0.001	80%
Weighted mean difference in time below range (<3.9 mmol/L)	29	1.49 (1.11 to 1.86)	<0.001	74%
Overnight-only				
Weighted mean difference in % time in range (3.9 to 10.0 mmol/L)	31	15.15 (12.21 to 18.09)	<0.001	73%
Weighted mean difference in % time above range (>10.0 mmol/L)	23	11.12 (8.44 to 13.8)	<0.00001	71%
Weighted mean difference in % time below range (<3.9 mmol/L)	29	2.22 (1.65 to 2.78)	<0.00001	72%

Results of a subgroup analysis separately comparing single hormone closed loop systems and a dual hormone artificial pancreas with a control group are presented in *Table 5*. All results were

statistically significant and favoured the single hormone closed loop system or dual hormone artificial pancreas over the control group (sensor-augmented pump or CSII plus blinded CGM).

Table 5: Summary of subgroup meta-analyses results based on type of closed loop system used (single hormone or dual hormone) compared with sensor-augmented pump or CSII plus blinded CGM[18]

	n studies (single/dual)	Closed loop system* vs. control (WMD (95% CI); I^2)	
		Single hormone	Dual hormone (artificial pancreas)
% time in range (3.9 to 10.0 mmol/L)			
24h	26/6	8.53 (6.34 to 10.72); 78%,	15.16 (10.68 to 19.63); 43%,
Overnight	23/8	12.77 (9.82 to 15.71); 68%	2.84 (15.08 to 30.60); 74%
% time in hyperglycaemia (>10.0 mmol/L)			
24h	16/6	7.52 (4.66 to 10.38); 80%,	11.58 (4.99 to 18.17); 81%,
Overnight	15/8	8.4 (6.58 to 10.22); 24%	17.21 (8.85 to 25.58); 87%,
% time in hypoglycaemia (<3.9 mmol/L)			
24h	24/5	1.28 (0.92 to 1.65); 72%	2.95 (1.87 to 4.03 to 1.87); 30%
Overnight	24/7	1.82 (1.27 to 2.38); 70%	4.04 (2.48 to 5.59); 47%
Mean sensor glucose (mmol/L)			
24h	25/7	0.41 (0.20 to 0.61); 83%	0.76 (0.22 to 1.31); 89%
Overnight	29/8	0.67 (0.45 to 0.89); 76%	1.47 (0.79 to 2.14); 80%

**Between 5 and 7 studies on dual hormone artificial pancreas; 15 to 19 studies on single hormone closed loop system. WMD = weighted mean difference.*

Randomised controlled trials

Thirteen RCTs comparing closed loop systems with a relevant comparator were published after the most recent literature search within the secondary literature described above.[19-31] Five trials related to adults, four to children and adolescents, and four included people of any age. A summary of the key findings from these RCTs is presented in *Appendix 2*. The trials report similar results to those found in the secondary literature: statistically significant improvements in mean percentage time in range favouring closed loop systems over the comparator. Statistically significant reductions in mean percentage time in hypoglycaemia favouring closed loop systems were reported in all the RCTs on adults; results were more variable in trials in children, adolescents and mixed age groups.

Eleven trials involved people with well controlled type 1 diabetes. Two trials involved people who had less well controlled type 1 diabetes.[19, 29] Adults (n=44) with type 1 diabetes in one RCT were described as being at moderate or high risk of hypoglycaemia.[19] Participants in this trial were randomised to either a hybrid closed loop system or sensor-augmented pump therapy. Mean percentage time in target range (3.9 to 10 mmol/L) showed a statistically significant increase in the

closed loop group and decrease in the sensor-augmented pump group. A similar pattern occurred for percentage time above and below target range. The second RCT was conducted in people of any age (n=86) who were described as having suboptimally controlled type 1 diabetes.[29] Participants were randomised to a hybrid closed loop system or sensor-augmented pump therapy. Mean percentage time in target range (3.9 to 10.0 mmol/L) was significantly greater in the hybrid closed loop group. Reductions in percentage HbA1c were significantly greater in the hybrid closed loop group compared with the control group.

Real world evidence

Two studies, with an overlapping group of authors, assessed the use of a hybrid closed loop system in clinical practice using data uploaded to the CareLink™ Personal system.[32, 33] The CareLink™ Personal system is a free web-based service provided by Medtronic Ltd. People using Medtronic Ltd diabetes technologies can automatically upload data from their diabetes management system to the CareLink™ Personal software platform. Both studies provide data from multiple countries, including the UK. Neither study was able to report demographic, socioeconomic or clinical background data, as this is not recorded on CareLink™ Personal.

One study reported data on the use of the Medtronic MiniMed™ 780G hybrid closed loop system uploaded to CareLink™ Personal between August 2020 and March 2021.[33] Data were available from Belgium, Finland, Italy, the Netherlands, Qatar, South Africa, Sweden, Switzerland and the UK. Data are presented in *Table 6* for percentage time in range, above range and below range, reported prior to initiation of the hybrid closed loop function and after the hybrid closed loop was activated (at mean follow up of 54 ± 32 days). All changes to percentage time in, above, or below range, from pre- to post initiation of the hybrid closed loop system were statistically significant. Data from people in the UK using the hybrid closed loop are reported separately in *Table 6*. Additional data in the study showed that percentage time in range and below range improved significantly more during the night compared with during the day ($p<0.0001$). The average number of self monitoring blood glucose measurements decreased from 4.7 ± 2.0 to 3.6 ± 1.2 per day from pre- to post hybrid closed loop initiation ($p<0.0001$). The results reported in this study were similar to those reported in the pivotal trial on this device and did not vary substantially between individual countries despite variations in access, reimbursement, indications and healthcare systems.

The second study reported data on the use of the Medtronic MiniMed™ 670G hybrid closed loop system uploaded to CareLink™ Personal between October 2018 and July 2020.[32] Data were available from Austria, Belgium, Switzerland, Germany, Denmark, Spain, Finland, the UK, Italy, Luxembourg, the Netherlands, Sweden and Slovenia. Data are presented in *Table 6* for time in range, above range and below range reported pre- and post initiation of the hybrid closed loop function (at 1 year follow up). Additional data in the study showed that percentage time in range and below range improved significantly more during the night compared with during the day ($p<0.0001$). The results reported in this study were similar to those reported in the pivotal trial for this device and did not vary substantially between individual countries despite variations in access, reimbursement, indications and healthcare systems.

Table 6: Real world data on use of the Medtronic MiniMed™ hybrid closed loop systems[32, 33]

	MiniMed™ 670G		MiniMed™ 780G	
	Pre-auto mode initiation	Post auto mode initiation	Pre-auto mode initiation	Post auto mode initiation
Merged data from all included countries				
n users providing data	880	880	812	812
% time in range (3.9 to 10.0 mmol/L)	62.4	72.2*	63.4	75.5*
% time below range (<3.9 mmol/L)	2.0	1.8	2.0	1.7*
% time below range (<3.0 mmol/L)	0.5	0.5	0.6	0.5 (p<0.005)
% time above range (>10.0 mmol/L)	25.5	19.8	25.6	18.1*
% time above range (>13.9 mmol/L)	9.6	5.7	8.4	4.2*
Data from UK patients				
n users providing data	–	1,323	–	356
% time in range (3.9 to 10.0 mmol/L)	–	69.8	–	74.3
% time below range (<3.9 mmol/L)	–	1.8	–	2.0
% time below range (<3.0 mmol/L)	–	0.6	–	0.5
% time above range (>10.0 mmol/L)	–	20.2	–	17.5
% time above range (>13.9 mmol/L)	–	7.6	–	4.9

**p<0.0001 compared with pre-auto mode initiation*

Safety

The main adverse clinical outcomes for people with type 1 diabetes are severe hypoglycaemia that requires assistance from a third party or hospitalisation, and diabetic ketoacidosis. One systematic review of 27 studies (n=804) found that the incidence of severe hypoglycaemia reported in trials was very low, both in people using a closed loop system (six episodes) and in the control group using other insulin therapies (three episodes).[18]

Another systematic review reported adverse events as any hypoglycaemic event, respiratory tract infections, allergic rhinoconjuntivitis, skin irritations and viral gastroenteritis.[16] In studies comparing closed loop systems with sensor-augmented pump therapy, statistically significant differences in adverse event risk favouring closed loop systems were reported for hypoglycaemic events: risk ratio (RR) 0.27, 95% CI 0.09 to 0.81. No other statistically significant differences were reported for adverse events.

Two low quality narrative overviews explored potential device-related faults and safety concerns relating to closed loop systems and their constituent devices.[34, 35] Both overviews conducted a basic literature search of PubMed and did not report clinical or patient outcomes. The faults and safety concerns identified are summarised in *Table 7*.

Table 7: Summary of potential device-related safety issues relating to closed loop systems and their constituent devices[34, 35]

Component	Description of the potential safety issue
CGM	Inaccuracy of glucose sensor calibration and readings (where required), especially during hypoglycaemia.
	Foreign body reactions from newly inserted CGM sensors, which can result in inaccurate sensor readings for several hours.
	Delay between a change in blood glucose and a change in interstitial glucose readings, which can be exacerbated by rapidly changing glucose levels.
	The sensor is unavailable because of loss of connection or the sensor being replaced.
	Pressure on the sensor from a user lying on it at night can result in attenuation of CGM sensor signals for approximately 15-30 minutes.
Controller device	Loss of communication with the CGM sensor or insulin pump. In a 4 week trial of closed loop system overnight in 24 patients, 112 events were recorded where the closed loop ceased to operate, 68% of these events were caused by a lack of pump connectivity.[35]
	Delayed effect of subcutaneously infused insulin on blood glucose levels, which can lead to hypoglycaemia if, for example, exercise is not announced well in advance of activity.
	Variability in insulin sensitivity between users.
	Missing or incorrect announcements from the user regarding exercise or food intake.
	Missing glucose values because of lost connectivity between CGM and controller devices.
	Overdosing of insulin because of software or hardware failures.
Infusion pumps (CSII)	Kinking or occlusion of the infusion set (tubing connecting insulin pump with the body).

Incidents affecting the pump can result in hyperglycaemia, diabetic ketoacidosis or severe hypoglycaemia.	Leaking or dislocation of the infusion set. Dislocation is a more common problem with patch pumps.
	Software or hardware failures affecting communication with controller devices.
	In a dual hormone pump, the risk of accidentally switching between insulin and glucagon.
	Human error when filling cartridges with hormones for use in the pump.
	Infusion site reactions, such as inflammation, affect subcutaneous absorption of insulin. People have reported bleeding, bruising, pain or soreness, adhesion issues and irritation or itchiness at the site of insulin infusion.
	Dual hormone pumps may present an added risk if glycogen stores in the liver are depleted, resulting in blood glucose levels remaining low regardless of the amount of glucagon administered.
Closed loop system	Reliability and security of wireless communication between devices.
	Low batteries in any device in the system.
	The complexity of the system combines the potential issues from all the constituent devices.
Alarms	Alarm fatigue occurs when users are presented with too many alarms requiring them to take action.
	No response by users to alarms from the system.
Patient/user	Physiological changes, such as sleep, alcohol consumption and physical activity, can present a challenge to components of the closed loop system.
	Human error, for example miscalibration of a CGM sensor (where applicable).
	Incorrect carbohydrate intake estimates, or forgetting to announce a meal or exercise.

Patient and social aspects

Two systematic reviews explored the values and preferences relating to closed loop systems among people with type 1 diabetes.[36, 37] Four qualitative studies presented evidence on experiences and preferences for closed loop systems in UK-based populations.[10, 38, 39,40] Three studies provided evidence on quality of life outcomes[30, 41, 42] and two observational studies reported on discontinuation of closed loop system use and patient satisfaction.[43, 44]

Systematic reviews

The most recent systematic review explored the values and preferences of adults with type 1 diabetes in relation to the use of CSII or a hybrid closed loop system.[37] The 19 studies included in the systematic review consisted of eight cross-sectional surveys and 11 qualitative studies that used semi-structured interviews and focus groups to elicit values and preferences. The qualitative studies

were assessed for quality by the review authors using the appraisal tool from the critical appraisal skills programme (CASP). The main limitations of the qualitative studies were small sample sizes leading to a lack of data saturation, and recruitment of participants from RCTs that potentially biased the sample in favour of well educated people with well controlled type 1 diabetes. Four of the qualitative studies included people from the UK. Sample size ranged from five to 113, with mean duration of diabetes ranging from 18.3 (SD 6.9) to 29.0 (SD 11.0) years.

Two main themes were identified from the cross-sectional studies on hybrid closed loop systems: clinical efficacy and treatment burden. Additional themes extracted from qualitative studies included increased flexibility around eating and exercise, challenges with exercising, advantages and disadvantages relating to sleep, and the feeling of taking a break from diabetes self care.

The main perceived benefit of closed loop systems was improved blood glucose control. Study participants reported being impressed with how stable their glucose levels were and felt that the closed loop system helped them avoid complications resulting from poor glucose control. For a few people, the closed loop system failed to meet their expectations and this was given as a reason to discontinue using the system. Other people said they trusted the hybrid closed loop system, but not completely or without double checking its actions. Participants expressed a desire to be able to override decisions made by the control algorithm or expressed surprise that they needed to intervene manually when having a meal or exercising.

Although most participants felt that the closed loop system gave them more freedom to eat and exercise as they wished, some reported an increase in hypoglycaemic events associated with sports activities. These participants said that it 'knocked their confidence' in the system. People who exercised regularly reported a negative effect of the closed loop system on their exercise caused by frequent alarms and the inability to elevate their glucose levels before exercising. While some participants reported improved sleep with the closed loop system compared with CSII and CGM, others reported their sleep was interrupted more often by alarms and frequent buzzing from the insulin pump. The majority of participants, particularly women, expressed worries about the size, weight and appearance of devices, which made them difficult to conceal.

The majority of participants reported experiencing technical difficulties with the closed loop system, such as loss of connectivity, pump catheter problems or the control algorithm not responding as expected. Required tasks that were considered burdensome by people using the closed loop system included responding to alarms, entering carbohydrate information for meals, confirming meal boluses, providing corrective insulin doses, and calibrating the CGM sensor (where relevant).

The second systematic review explored the psychosocial impact of hybrid closed loop systems in people of all ages who have type 1 diabetes.[36] The review included 13 studies: nine in adults, three in adolescents or children, and one in pregnant women. Three studies described in this systematic review were also included in the more recent review reported above. The systematic review authors noted that most studies had a small sample size and were conducted in people participating in RCTs.

Studies in adults with type 1 diabetes identified themes that are consistent with those reported in the systematic review described above. Additional themes included a perceived reduction in the burden of self monitoring of glucose levels and less worry about hypoglycaemia. Participants noted improved overnight glucose control, and consequently improved sleep, as having a positive effect on their daily functioning and diabetes control. The lowest levels of user satisfaction were recorded for exercising and bathing.

Similar themes were identified in the three studies recruiting adolescents, children and their parents. There were some additional perceived benefits of closed loop systems in this group, such as improved child safety, reduced parental anxiety about hypo- and hyperglycaemia, and 'time off' from diabetes management. Negative perceptions among participants in this review focused on needing to carry multiple devices, calibration difficulties and concerns about the accuracy and trustworthiness of the system.

Qualitative studies

Three qualitative studies described the results of a series of interviews with people in the UK who have type 1 diabetes and were participating in a 3 month trial of a hybrid closed loop system (APCam11).[10, 38, 39] The trial participants had all been using the CamAPS closed loop system. The three studies used the same qualitative methodology: semi-structured interviews were conducted using a topic guide, with recruitment continuing until data saturation was reached. Participants were interviewed at baseline and at 3 months follow up. Interviews took an average of 1-2 hours. In two studies, interviews were conducted with ten adults (aged 18 or older), five adolescents aged 13-17 and nine parents of children aged 12 or under. In the third study, interview participants consisted of 12 adults (aged 16 or older), three adolescents aged 13-15, and nine parents of children with type 1 diabetes (five parents of children aged 12 or under, four parents of children aged 13-15). Participants had previous experience of using insulin pumps and the study sample was skewed towards educated and highly motivated individuals.

One of the qualitative studies explored the effects of using a closed loop system on food choices and eating habits.[38] Overall, people ate similar meals before and after using the closed loop system, but many described feeling more normal and less burdened by their diabetes. The main concerns noted by participants were that they might become deskilled in carbohydrate counting or develop unhealthier eating patterns over time. At 3 months follow up, participants said they felt more confident and less anxious, especially about eating out, because they were less worried about incorrectly estimating the carbohydrate content of food. Others described consuming treats and takeaways more often as they found they could eat high fat, energy dense foods without experiencing adverse consequences. People felt liberated from the need to weigh and measure food, and felt they could snack more without needing to administer a corrective insulin dose. Parents of children and teenagers with type 1 diabetes felt that the closed loop system protected their child from prolonged hyperglycaemia and acted as a safety net.

The second qualitative study explored experiences of using a closed loop system in daily life.[39] Participants described the need to develop trust and confidence in the system, which could involve

several weeks of observing the system making decisions and adjusting blood glucose levels. In hindsight, some people felt that their anxieties and fiddling with the system had probably been counterproductive to the system's learning. People reported feeling less burdened by diabetes self management tasks, such as finger prick testing, and also found that their glucose levels were more stable when using the closed loop system. Parents of children with type 1 diabetes noted that their relationship with the child improved when the burden of diabetes care was reduced by the closed loop system. People felt reassured that the closed loop system could manage their glucose levels appropriately, even if they miscounted the carbohydrate content of meals, forgot to take insulin before eating, or undertook unplanned exercise. In adolescents, the closed loop system was felt to provide a safety net at a time of life when diabetes self management may be neglected. People felt that overall, they could lead more flexible and active lives with the closed loop system. Several participants indicated they would like to be able to communicate with or collaborate with the closed loop system, for example entering information about plans on atypical days or discriminating between intensities of exercise.

Participants in this second study were asked about their training and support needs for using a closed loop system. People felt the training session delivered at the start of the trial was sufficient, although they did not remember all of the information passed on at the time. They valued the opportunity to contact staff for glycaemic support or troubleshooting of the closed loop system. In the long-term people felt their need for support would be no greater than that required for using an insulin pump.

The third study described benefits experienced by the parents of children or adolescents with type 1 diabetes who used a closed loop system.[10] The main benefit felt by parents was respite from managing their child's diabetes. They worried less about hypoglycaemic events and could sleep more at night without worrying about their child's glycaemic safety. The reduction in glucose fluctuations as a result of using the closed loop system led to improved mood among children and adolescents with type 1 diabetes, with consequent reductions in conflict within the family. Parents were glad not to have to constantly remind their child to undertake diabetes management tasks, and felt able to allow their child more freedom to participate in sports, go to parties or socialise with their peers.

A fourth qualitative study described the experiences of adolescents and their parents of using a hybrid closed loop device as part of the CLOuD (closed loop from onset in type 1 diabetes) trial.[40] The authors of this study overlapped with the three studies reported above, but described semi-structured interviews with a different patient population. Purposive sampling recruited adolescents and their parents from six UK sites involved in the CLOuD trial. Unlike other trials of closed loop systems, the adolescents recruited for the CLOuD trial had been diagnosed with type 1 diabetes within the preceding 21 days. Recruitment continued until data saturation was reached. Interviews were conducted 12 months after the adolescent started using the closed loop system. In total 18 adolescents (aged 11 to 17 years) and 21 parents were interviewed.

Interviewees described little or no family conflict around food choices and finger prick testing when using a hybrid closed loop system. Parents expressed fewer concerns about their child's food choices because they felt reassured that the closed loop system would correct any imbalances. Although

some parents reporting needing to prompt their child about finger prick testing before going to bed, they were less worried about their child failing to test at other times of the day. Parents did however need to prompt their child to perform the practical tasks involved in keeping the closed loop system functioning optimally.

Both parents and adolescents described improved sleep as a result of confidence that the closed loop system would manage insulin levels overnight. Parents were also less worried about their child being away from home overnight when they had a closed loop system. Adolescents described how the closed loop system helped them to lead normal lives, with the ability to discretely administer insulin when needed. The ability of the closed loop to automatically adjust insulin levels resulted in adolescents being able to engage in physical activities, eat what they wanted and socialise with their friends. Some adolescents reported feeling self conscious about the visibility of the closed loop devices and consequently tended to wear loose fitting clothes and avoid certain activities, such as swimming. Parents described how their child would chose to manually administer insulin when playing sports or leave the handset behind when going out to avoid being embarrassed by alarms going off in public. Some adolescents felt that the system did not respond fast enough to high blood sugar readings and would instruct the system to give an additional insulin bolus to bring glucose levels down faster. Others described feeling happy that they could leave their glucose management to the closed loop system.

Quality of life

Three studies were identified that assessed quality of life in children and young people using closed loop systems.[30, 41, 42]

One study described improved quality of life among parents and caregivers of 20 young children (aged 1 to 7 years) with type 1 diabetes who used a hybrid closed loop system.[42] Parents or caregivers filled in a survey after their child had completed two 3-week periods of unrestricted 24-hour use of a hybrid closed loop system. The survey consisted of two parts; one considering overall experience and the other looking at perceived benefits of the closed loop system. Ninety percent of caregivers would strongly recommend the hybrid closed loop system to others and 95% were satisfied that their child's glucose levels were being controlled appropriately. Eighty-five percent of caregivers reported spending less time managing their child's diabetes and 90% reported less worry. Caregivers viewed the closed loop system positively, experienced improved quality of sleep for both them and their child, felt reassured about their child's safety, and felt that the closed loop system had a positive impact on their child's wellbeing.

A second study considered health-related quality of life and treatment satisfaction in 101 children aged 6 to 13 years who participated in a trial of the Tandem t:slim™ Control IQ™ closed loop system.[41] The study participants had been diagnosed with type 1 diabetes at least one year prior to the trial. Person-reported outcomes (PRO) were used to assess the utility of the closed loop system and the impact on quality of life. Satisfaction measures were obtained from children and their parents or caregivers prior to the start of the trial, at the end of the randomisation phase (week 16), and at the end of the cross-over extension phase (week 28). There were no statistically significant

changes in PRO measures in the children on the closed loop system, nor their parents, compared with the sensor-augmented pump group. Sleep scores for parents and caregivers of the closed loop system group improved between the baseline measurement and 16 weeks, although the changes were not statistically significant.

The third study was a six month multi-centre RCT of the Medtronic MiniMed™ 670G hybrid closed loop system in children and adolescents (n=135) with type 1 diabeties.[30] Secondary outcomes in the trial included psychosocial measures collected using a diabetes-specific paediatric quality of life questionnaire. Quality of life scores were found to be higher in the group using the hybrid closed loop system compared with the conventional therapy group. The improved quality of life scores were attributed by the study authors to reduced worry, increased confidence and trust in the hybrid closed loop system. Overall, participants found the hybrid closed loop system helpful for the day-to-day management of their diabetes.

Discontinuation of closed loop system use

A prospective observational study explored discontinuation of using a hybrid closed loop system among young people with type 1 diabetes.[44] The study sought to identify predictors of discontinuation and to describe the reasons for it among a group of young people enrolled in the first 6 months of a real world observational study assessing the Medtronic MiniMed™ 670G hybrid closed loop system. Data collection for this study occurred simultaneously with routine clinical care at baseline, 1 month follow up, at routine clinic visits and at approximately 3 and 6 months follow up. At the 6 month follow up, participants were stratified into continuers and discontinuers (<10% of their time on the hybrid closed loop system at any visit). Participants completed the Hypoglycaemia Fear Survey Worry subscale, the PAID survey and a questionnaire developed for the study. Open questions from the surveys were analysed thematically, with *a priori* categories assigned to the raw data.

Ninety-two people, with a mean age of 15.7 years (SD 3.6) and mean duration of diabetes of 6.8 years (range 4.6 to 9.8) were included in the study. The majority of participants (83%) had used insulin pumps for more than a year and 61% had used CGM for more than 1 year. Twenty-eight young people in the study (30%) discontinued using the hybrid closed loop system within 6 months. Only baseline HbA1c was a statistically significant predictor of discontinuation (p=0.026). The odds of an individual discontinuing hybrid closed loop therapy was 2.7 times greater (95% CI 1.1 to 6.3) for every 1% increase in baseline HbA1c. It is possible that other predictors of discontinuation were not detected in this study.

Ten participants who discontinued closed loop therapy and 13 caregivers of young people who discontinued hybrid closed loop therapy entered free text responses about why they stopped using the system. The most common reasons for were technical issues, too much work to maintain the system, expense or reimbursement of devices (caregivers only), and frequency of alarms. Eight young people who discontinued using the device perceived the system to not be working correctly, with poor CGM accuracy, failed sensor calibrations, sensor errors, trouble staying in auto mode and transmitters not working. Six participants described needing to enter too many blood glucose

readings for calibration and frequent 'blood glucose required' alerts, plus the hassle of replacing sensors. Four young people described alarms as affecting their ability to sleep at night.

Another observational study conducted a satisfaction survey among adults with type 1 diabetes who had been using the Medtronic MiniMed 670G hybrid closed loop system.[43] Surveys were administered to 21 adults during a routine clinic visit. Four participants were using the CGM sensor and insulin pump separately. All participants had good glucose control, with an average HbA1c of 6.7%. Eleven people stated they were very satisfied or satisfied with the hybrid closed loop system. The features they liked most about the system were better, more consistent blood glucose levels (nine people), and ease of use (5 people). The least liked features of the system were the pump allowing blood glucose to remain elevated (five people), high frequency of alerts or alarms (four people), dissatisfaction with insulin administration (three people) and lack of flexibility of system settings (two people). Reasons given for swapping from the hybrid closed loop to manual mode (pump and CGM no longer connected to each other) included four people being recommended to do so by the pump, four people having to change sensors, two people correcting for high blood glucose, and two people who had calibration issues.

Summary of submissions from patient organisations

Three patient organisations tendered a submission on closed loop systems: iPAG Scotland, the JDRF and Diabetes Scotland. The full submissions can be found here and are summarised below.

iPAG Scotland

- Burden of diabetes for patients, carers and families

  The advent of closed loop systems demonstrates clearly that, for many people, the complexities of controlling blood glucose levels are too great to be managed conventionally. This is illustrated by the failure of three quarters of the type 1 diabetes population in Scotland to achieve even the minimum acceptable measure of control, as determined by HbA1c levels. Automated systems are capable of making the ongoing changes to insulin delivery needed to achieve good glycaemic control. Many users attempt to micromanage their blood glucose levels using conventional systems by spending many hours testing, taking corrective insulin doses, eating extra carbohydrates and consulting with diabetes clinical teams, all of which has a substantial impact on their daily life and on NHS resources.

- Reduced anxiety and improved mental health

  Fluctuating blood glucose levels not only have adverse effects on physical health, they also cause mental health issues for patients, carers and their families. These mental health issues can be a direct symptom of either high or low blood glucose, as well as the burden of managing type 1 diabetes.

- Equity of access and variations in access

  The cost of self-funding CGM effectively excludes the majority of the type 1 diabetes population from the benefits of closed loop systems. This problem is exacerbated by barriers

to attending education courses, such as time off work and lost earnings when attending structured education, clinic appointments and training. For many people with lower levels of educational achievement, lack of confidence is another barrier to education and training. With no national pathway for access to closed loop systems there is a postcode lottery in Scotland with each health board using different criteria for providing insulin pumps, CGM sensors and closed loop systems, with different 'approved lists' of available technology.

- Cost

  Self-funding costs are beyond the budget of most people with type 1 diabetes, particularly those from lower SIMD areas. This is inequitable, with lower income patients being excluded from the best treatment options for their condition, reducing their quality of life, putting them at risk of long-term diabetes complications, and requiring a higher level of input from their clinical teams.

JDRF

- Closed loop systems would substantially improve the quality of life of people living with type 1 diabetes, allowing them more freedom and flexibility in their daily lives, without the need to constantly think about their diabetes. This improvement would manifest as both improved psychological wellbeing through a reduction in diabetic fatigue, and a reduction in physical symptoms caused by high or low HbA1c levels, given the evidence that technology can assist in stabilising these.
- The long-term benefit of closed loop systems is significant, both in the value to patients and in reduced cost to the NHS from treating complications relating to type 1 diabetes and reducing hospitalisations for diabetic ketoacidosis.
- All people with type 1 diabetes could benefit from closed loop systems and it is important that all patients are offered an informed discussion with their clinicians to make sure it is a viable option for them, ensuring that people who have not accessed diabetes technologies in the past are not left behind.
- In England, closed loop systems are currently being piloted among 1,000 people with type 1 diabetes. The results of this pilot will be instrumental in demonstrating the value of such technologies given they are not currently widely accessible and many people are DIY-ing their own technology, which is unregulated and therefore not as rigorous as official assessments.

Diabetes Scotland

- Hybrid closed loop technology is one of the most exciting developments in type 1 diabetes care in recent years. It represents what some describe as a 'practical cure' for the condition.
- Technologies like flash, CGM, insulin pumps and, now, hybrid closed loop systems are evidenced to lower HbA1c levels, improve time in range and reduce levels of diabetes distress.

- People with experience of using closed loop systems have reported the enormous benefits and improved quality of life for not just them but also their families and carers.
- More routine access to hybrid closed loop technology would mean those unable to use DIY technology do not face unfair health inequalities.
- The use of diabetes technology could significantly reduce the strain on the NHS in the long-term including preventing avoidable short- and long-term complications.

Inequalities

A diabetes audit from England and Wales provides evidence on inequalities in access to diabetes technologies, such as insulin pumps and CGM.[45, 46] Although this literature does not relate specifically to closed loop systems, evidence on access to constituent devices suggests that similar inequalities could arise when closed loop systems enter routine clinical practice. The literature identified relates only to children and young people, however it seems reasonable to assume that similar inequalities could exist in adult populations. As closed loop systems evolve, concerns over inequalities in access may be addressed by a reduced need for user expertise to manage these systems.

The Royal College of Paediatrics and Child Health collate annual audit data on paediatric diabetes care in England and Wales.[45, 46] Data are collected for all children and young people aged 0-24 on the first day of the audit period who have attended a paediatric diabetes unit during the audit year. Data from 27,653 children and young people with type 1 diabetes were collated in the 2019–2020 audit. The audit found that, despite overall increases in insulin pump use in all quintiles of deprivation, the gap between children and young people in the most and least deprived quintiles has widened over the past 6 years. In the 2014–15 audit, there was a 7.9% difference between insulin pump use in the most and least deprived quintiles, compared with a 12.6% difference in the 2019–20 audit. In 2019–20, insulin pumps were used by 44.3% of children and young people living in the least deprived areas, compared with 31.7% of those living in the most deprived areas. White children and young people were more likely to be using insulin pumps (39.8%) compared with children and young people from Asian (29.7%) or black (26.7%) ethnic groups.

A similar pattern was found for CGM use. Higher levels of CGM use were associated with living in less deprived areas and white ethnicity. Children and young people living in the most deprived areas and children and young people from black ethnic groups were the least likely to have access to CGM. Twenty percent of white children and young people use CGM, compared with 11.7% of black children and 15.1% of Asian children. Children and young people in the least deprived areas were almost twice as likely to use CGM compared with those living in the most deprived areas: 25.5% versus 14.0%.

Two observational studies from the US reported similar inequalities in access to diabetes technologies among children with type 1 diabetes.[47, 48]

Organisational issues/Context

Two studies explored UK healthcare professionals' views on closed loop systems.[49, 50]

The first study conducted interviews with healthcare professionals participating in a 24-month trial of a hybrid closed loop system in children and young people with type 1 diabetes.[49] Interviews were based on a topic guide and conducted by an independent research team. Recruitment continued until data saturation and good representation of doctors (n=7), diabetic nurses (n=9) and research nurses (n=6) were achieved. Interviews lasted an average of 70 minutes and were analysed thematically. The interviews identified five overarching themes: closed loop systems are less work but still work; preconceptions about candidacy; revisiting or revising candidacy in light of RCT experiences; use of closed loop systems in routine clinical care; and who should be given priority access.

In order to benefit from hybrid closed loop systems people with diabetes, or their caregiver, still need to undertake essential tasks, such as administering insulin before meals or replacing CGM sensors. Prior to the RCT, interviewees felt that young people with close-knit families, who were well educated and keen to be involved in their own care, would be the best candidates for a hybrid closed loop system. After the RCT was underway, some interviewees noticed that the people they had previously thought would benefit most, actually over-interacted with the system, which had detrimental effects on system learning and their blood glucose levels. People who left the system alone attained more benefit and interviewees felt that closed loop systems may therefore encourage people who struggle to manage their diabetes, to attain better glucose control without as much interaction with the device. The interviewees felt that everyone with type 1 diabetes should be given a chance to try a hybrid closed loop system in clinical practice, but that the system should be withdrawn if people neglected to engage with the system and perform key tasks. Deciding on priority access to closed loop systems was regarded as a complex issue, with interviewees identifying multiple potential priority groups, including teenagers, young children and infants (who have unpredictable eating habits and require tiny amounts of insulin), and adults who meet current criteria for insulin pump therapy. Interviewees acknowledged that financial constraints may mean that difficult decisions need to be made on prioritising access to closed loop systems in clinical practice.

The second study explored clinicians' attitudes towards eligibility for closed loop systems in mainstream care in England.[50] Thirty-six interviews, based on a topic guide, were conducted with healthcare professionals working with adults, pregnant women and children with type 1 diabetes. Interviews were conducted in person (n=29) or by telephone (n=7) and lasted an average of 47.5 minutes (range 28 to 73 minutes). Participants were grouped into three categories based on their responses: access to closed loop systems will be more restricted than eligibility for current diabetes technologies (n=10); eligibility for closed loop systems will be similar to that for CGM and insulin pumps (n=14); and eligibility will be wider than for current technologies (n=9).

The ten people expecting more restricted access to closed loop systems felt that eligibility should be limited to those who would clearly benefit. Reasons for this view included the greater technical

challenges involved in using these systems, the psychological impact of using a closed loop system (for example, anxiety over relinquishing control), unrealistic expectations about the system, and funding issues. Explanations offered by the 15 people who thought access would be similar to current technologies included organisational continuity as people would receive closed loop systems though similar service pathways, funding challenges similar to CGM and insulin pump provision, user engagement and motivation, and challenges surrounding predicting user experiences. The challenges of predicting how people would respond to closed loop systems were highlighted as it was thought possible that the technology would trigger increased user engagement amongst a wider patient group. Nine people hoping for wider access to closed loop systems compared with current technologies cited the expectation of widespread benefits from closed loop systems, the potential for liberal national access guidelines, potential cost savings if people used a closed loop, and the unpredictability of how people will react to the new technology. Interviewees in this last group felt that up to 80% of people with diabetes could benefit from closed loop systems, and that better glycaemic control using the closed loop system would reduce complications and subsequently long-term healthcare spending.

Cost-effectiveness

Review of published economic literature

One study compared the cost-effectiveness of a hybrid closed loop system (MiniMed™ 670G) and CSII pump therapy in people with type 1 diabetes in the UK.[51] The analysis was performed using clinical input data from a 3-month before and after trial in 124 adults and adolescents with type 1 diabetes who use insulin pumps.[52] Treatment effects in the model included the reduction in % HbA1c (-0.5%) and rates of severe hypoglycaemia. Since no severe hypoglycaemic events were observed in the study, a rate of zero events was assumed in the hybrid closed loop arm of the model. In the CSII arm, the rates of severe hypoglycaemia (25 events per 100 patient years requiring medical assistance and 65 events per 100 patient years not requiring medical assistance) came from a non-UK source.[53] The IQVIA CORE® diabetes model, which is an individual patient simulation model, was used for the long-term extrapolation of treatment effects, prediction of diabetes-related micro- and macro-vascular complications, and associated lifetime costs and quality adjusted life years (QALYs). A utility benefit of 0.0552 associated with reduced fear of hypoglycaemic events was applied in the hybrid closed loop arm only, based on a previous hypoglycaemia fear survey among users of sensor-augmented insulin pumps.[54] In the base case results, the hybrid closed loop system was found to be cost-effective, with an ICER of £20,421 per QALY. The hybrid closed loop was associated with 1.73 additional QALYs, higher lifetime device costs (+£50,932) and lower costs of severe hypoglycaemia (-£9,171), microvascular complications (-£5,940) and cardiovascular disease (-£415).

The authors of the cost-effectiveness study presented a range of scenario analyses around the assumed utility benefit in the closed loop arm. When the utility benefit from a reduced fear of hypoglycaemia was removed, the ICER increased to £55,012 based on a reduction in incremental QALYs from 1.73 to 0.68. In another scenario, no reduction in hypoglycaemia was assumed, which increased the ICER to £37,955. It is unclear if the utility benefit associated with reduced fear of

hypoglycaemia was retained in the closed loop arm in the latter scenario. A combined scenario analysis where no reduction in hypoglycaemia and no additional utility benefit associated with reduced fear of hypoglycaemia were assumed in the hybrid closed loop arm would fully reflect the uncertainty around differences in severe hypoglycaemic events, however this analysis was not presented in the study. Additionally, the assumption of no difference in HbA1c levels had a minimal impact on the ICER (£28,253).

It should be noted that the published economic analysis is has several limitations. The nature of the evidence base is associated with uncertainties around relative treatment effects. The lack of severe hypoglycaemic events associated with the hybrid closed loop system may be a result of the short duration of the study, and the assumption of no lifetime severe hypoglycaemic events may be too optimistic, which likely creates a bias favouring the closed loop system in the economic model. It is unclear if the assumed severe hypoglycaemic event rates in the CSII arm of the economic model are appropriate. They appear to come from a non-UK source, where most participants (64%) had impaired hypoglycaemia awareness or were hypoglycaemia unaware, and it was unclear if they were all insulin pump users.

A further limitation is that the assumed utility benefit in the closed loop arm associated with a reduced fear of hypoglycaemia is uncertain. The benefit was derived using the reported reduction of 6.9 units in the Hypoglycaemia Fear Survey II in the INTERPRET study[55] and another study,[56] which found that a one unit reduction is associated with a 0.008 decrease in EQ-5D utility score. The latter study only used the Worry subscale of the Fear of Hypoglycaemia Survey when deriving this association and not the overall survey score. The reduction in the Worry scale reported in the INTERPRET study was 4.992, which yields a utility gain of 0.0399 and not 0.0552 as used in the model. It should also be noted that the baseline HbA1c value in the model, which although reflecting HbA1c in the underlying primary study, is likely to be lower than that of the population of people with type 1 diabetes in Scotland.

Given the paucity of relevant published cost-effectiveness evidence, it was considered appropriate to conduct an in-house economic evaluation on the use of closed loop systems in NHSScotland.

SHTG economic analysis

Model design

The published and validated Sheffield type 1 diabetes model was selected as appropriate for adaptation to assess the cost-effectiveness of closed loop systems compared with a range of technologies for diabetes management in adult patients with type 1 diabetes in Scotland.[57] The comparators included in the model for Scotland were self monitoring of blood glucose ('finger prick testing' referred to as SMBG in the model) plus multiple daily injections (MDI), CGM plus MDI, flash glucose monitoring (FGM) plus MDI, CGM plus CSII and FGM plus CSII.

The economic model is a cohort simulation with 5,000 iterations, a lifetime time horizon and annual cycles. It was executed in Microsoft Excel® using Monte Carlo methods. In each cycle, the probability

of an event was compared to a random number. If the random number was lower than the probability, a patient was modelled as experiencing that event and priority rules were set out as advised in published guidance.[58]

People with type 1 diabetes transitioned through cohort Markov models, which simulated disease progression and diabetes-related complications based on individual characteristics or observed rates in the Scottish type 1 diabetes population. The first Markov model is a simple two-state model (alive and dead) to predict mortality in each cycle. If alive, the individual can develop microvascular complications or cardiovascular disease (CVD) and can experience hypoglycaemic events (severe or non-severe). Only severe hypoglycaemic events requiring hospitalisation were included as severe events in the model. The progression of microvascular complications is captured using a five state Markov model for nephropathy (no nephropathy, microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD) and death from ESRD), a three state neuropathy model (no neuropathy, neuropathy, and amputation) and a five state retinopathy model (no retinopathy, background retinopathy, proliferative retinopathy, macular oedema and blindness). Cardiovascular disease was modelled using a published algorithm where the 5-year risk of CVD was dependent on individual patient characteristics such as age, duration of diabetes, HbA1c levels, systolic blood pressure, cholesterol levels, previous CVD and the presence of macroalbuminuria.[59]

Baseline annual probabilities of microvascular events in the Sheffield type 1 diabetes model were derived from various sources such as the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), UK Diabetes Control and Complications Trial (DCCT) and the UK prospective diabetes study (UKPDS) (*Appendix 3, Table A*).[57] Annual probabilities were calculated based on an HbA1c of 10%, and the treatment effect (reduction in HbA1c) was applied to the model using a published algorithm.[60] The type of cardiovascular event was based on the distribution reported in the DCCT/EDIC study, which was 53% myocardial infarction, 28% angina, 12% heart failure, and 7% stroke.[61]

Treatment effects

Percentage time in glycaemic range (3.9 to 10.0 mmol/L) has become the most commonly reported primary outcome in recent clinical trials in diabetes because of the increasing availability of devices able to capture continuous glucose measurements, and recognition of the benefits of time in range compared with HbA1c. Previously, HbA1c has been considered the gold standard measure. An economic model directly incorporating time in range as an efficacy input was considered unfeasible because of the lack of previously published validated models and the lack of long-term data on the association of time in range and diabetes-related complications. Improvements in time in range associated with closed loop systems compared with a range of comparators in an NMA are reported in *Table 2* and were converted to reduction in baseline HbA1c using a published algorithm (see *Appendix 3, equation 1*).[62] The baseline HbA1c of 7.7% in the NMA was assumed for all comparators in the SHTG model and the estimated reduction in HbA1c was assumed in the closed loop system arm in pairwise comparisons. The closed loop system arm was assumed to be using a hybrid closed loop system, since these devices are currently available in Scotland and the clinical efficacy from the

NMA mostly reflected these devices. Predicted device-specific reductions in HbA1c from baseline are presented in *Table 8*.

Table 8: Estimated treatment effects used in the SHTG model – reduction in HbA1c based on improvement in % time in range

Closed loop vs:	Mean HbA1c reduction (95% CI for the predicted value)	Source
SMBG + MDI	-0.62 (-1.60 to 0.36)	Pease 2020; Beck 2019[15, 62]
FGM + MDI	-0.49 (-1.47 to 0.49)	Pease 2020; Beck 2019[15, 62]
CGM + MDI	-0.48 (-1.46 to 0.50)	Pease 2020; Beck 2019[15, 62]
CGM + CSII	-0.37 (-1.40 to 0.61)	Pease 2020; Beck 2019[15, 62]

FGM = flash glucose monitoring; MDI = multiple daily injections; CGM = continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion

No studies comparing closed loop systems with FGM plus CSII were identified. The NMA in the clinical effectiveness section included one study where the comparator was CGM/FGM/SMBG plus CSII, but only 17% of participants were using FGM and the majority (66%) were not using a sensor.[63] The results from the study were used in an exploratory cost-effectiveness analysis comparing closed loop systems with FGM plus CSII.

The NMA did not find significant differences in time below range for any of the comparators.[15] Other pairwise meta-analyses for the comparison of closed loop systems with CSII or sensor-augmented pump, discussed in the clinical effectiveness section above, found statistically significant improvements in time below range associated with the closed loop system.[18] No studies were identified showing a direct association between time below range and hypoglycaemic events. In order to populate the economic model, rates of non-severe hypoglycaemic events and severe hypoglycaemic events requiring medical assistance, as observed in the Scottish population, were assumed for people with type 1 diabetes treated with SMBG plus MDI.[64,65] All person-reported non-severe hypoglycaemic events were experienced during daytime. Device-specific proxy reductions in hypoglycaemic events were assumed based on reduction in time with glucose concentration <70 mg/dL (<3.9 mmol/L) for non-severe events, and glucose concentration <50/<40 mg/dL (<2.8/<2.2 mmol/L) for severe events for each technology compared with SMBG plus MDI where possible (*Table 9*).

Table 9: Treatment effects – reductions in annual rate of hypoglycaemic events vs SMBG plus MDI

Technology	NSHE	Source	SHE*	Source
SMBG + MDI	41.74	Estimated from Donnelly, 2005[64]	0.115	Leese, 2003[65]
Reduction: closed loop (CL)	50%	Approximation based on McAuley, 2020[28]	55%	Approximation based on McAuley, 2020[28]
Reduction: CGM + MDI	35%	Approximation based on Beck, 2017[66]	55%	Approximation based on Dicembrini, 2020[67]
Reduction: FGM + MDI	25%	Approximation based on Bolinder, 2016[68]	55%	Approximation based on Bolinder, 2016[68]

Reduction: CGM + CSII	30%	Assumption	55%	Assumption

SMBG = self monitoring of blood glucose (via finger prick testing); CL = closed loop; CGM = continuous glucose monitor; FGM = flash glucose monitor; CSII = continuous insulin infusion; MDI = multiple daily injections; NHSE = non-severe hypoglycaemic events; SHE = severe hypoglycaemic events
**defined as requiring emergency medical care*

Baseline characteristics

Baseline characteristics in the model were mostly drawn from a Scottish type 1 diabetes cohort study from 2017 and are presented in *Table 10*.[69] Baseline age, HbA1c and duration of diabetes were taken from the NMA used to populate the economic model.[15] Mean age (43.3 years) and duration of diabetes (21.4 years) in the NMA were similar to those in the Scottish population. Mean HbA1c in the NMA (7.7%, SD 0.7%) was lower compared with the Scottish population (8.6%, SD 0.6%).

Table 10: Baseline characteristics of the Scottish adult population with type 1 diabetes used in the SHTG economic model

Characteristics	Mean value	Source
Age (years)	43	Scottish diabetes cohort study, 2017[69]
Male (%)	55.6	Scottish diabetes cohort study, 2017[69]
Duration of diabetes (years)	21	Scottish diabetes cohort study, 2017[69]
HDL:TCL	4.5	Assumption
Systolic blood pressure (mmHg)	129	Scottish diabetes cohort study, 2017[69]
Smoker (%)	19.1	Scottish diabetes survey, 2019[2]
Background retinopathy (%)	36.9	Scottish diabetes cohort study, 2017[69]; Assumption
Proliferative retinopathy (%)	14.7	Scottish diabetes cohort study, 2017[69]; Assumption
Microalbuminuria (%)	14.8	Scottish diabetes cohort study, 2017[69]
Macroalbuminuria (%)	3.8	Scottish diabetes cohort study, 2017[69]
ESRD (%)	1.5	Scottish diabetes cohort study, 2017[69]

HDL = high density lipoprotein, TCL = total cholesterol levels

Costs

Costs in the model captured the costs of the technologies (devices, consumables, lancets, and strips), microvascular complications (nephropathy, neuropathy, and retinopathy), CVD and hospital treatment of severe hypoglycaemia. Costs of devices and consumables were sourced from National Procurement Scotland and the National Tariff (*Table 11*). Costs were discounted at 3.5% per year as per NICE methods of technology appraisal guidance.[70]

In the closed loop systems arm, intervention costs included the cost of an insulin pump (replaced every 4 years in line with the length of warranty), cost of pump consumables (infusion sets), a transmitter (one per 4-12 months), sensors (one per 7-10 days), a charger and materials for finger

prick testing of blood glucose three times a day for CGM calibration. The annual costs of CGM and FGM included the cost of sensors (replaced every 7-10 days for CGM and every 14 days for FGM) and cost of finger prick testing (approximately twice a day for CGM and approximately 90% reduction versus SMBG for FGM based on the IMPACT study).[68] The intervention costs in the CGM plus CSII arm included the average cost of CSII pumps (replaced every 4 years), CGM and consumables available in Scotland. People with type 1 diabetes who self monitor their blood glucose using finger prick testing and inject insulin multiple times a day were assumed to check their blood glucose approximately six times a day based on the recommended frequency of testing of 4-10 times a day.

Table 11: Mean annual intervention costs

Costs	Mean (SE) annual cost	Source (personal communications)
Closed loop – year 1 (every 4 years)	£6,747 (£176)	National procurement, 2021*
Closed loop – consumables – years 2-4	£4,273 (£199)	National procurement, 2021*
Closed loop – self testing for CGM calibration	£206 (£53)	National procurement, 2021*
CGM (sensors, transmitters)	£2,800 (£296)	National procurement, 2021*
CGM (self testing for calibration)	£206 (£53)	National procurement, 2021*
FGM sensors	£910	National Tariff, 2021
FGM self testing	£62 (£21)	National procurement, 2021*
CSII pump (every 4 years)	£2,340 (£130)	National procurement, 2021*
CSII – consumables (infusion sets)	£1,364 (£122)	National procurement, 2021*
Strips (individual)	£0.26 (£0.03)	National procurement, 2021*
Lancets (individual)	£0.03 (£0.01)	National procurement, 2021*
SMBG + MDI cost of self testing	£619.44 (£211)	National procurement, 2021*

CGM = continuous glucose monitoring; FGM = flash glucose monitoring; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; SMBG = self monitoring of blood glucose via finger prick testing; SE = standard error
**costs accurate as of 6th July 2021*

The cost of insulin, user training, and scheduled or unscheduled clinical contact have not been included in the analysis. Unit costs for complications (*Table 12*) are consistent with those in the published Sheffield type 1 diabetes model, indexed to 2020 prices using the average annual Hospital and Community Health Services (HCHS) inflation index.[71]

Table 12: Unit costs for diabetes-related complications (indexed to 2020 prices)

Diabetes-related complications	Unit cost	Source
Microalbuminuria (ongoing)	£41	BNF and McEwan et al (2007)[72, 73]
Macroalbuminuria (ongoing)	£41	BNF and McEwan et al (2007)[72, 73]
ESRD (ongoing)	£27,777	NHS Reference Costs (2007-8)[74]
Clinically confirmed neuropathy	£308	Currie et al (2007)[75]
PAD with amputation (year 1)	£8,208	NHS Reference Costs (2007-8)[74]
PAD with amputation (ongoing)	£499	McEwan et al (2007)[73]
Background retinopathy	£165	McEwan et al (2007)[73]
Proliferative retinopathy	£752	McEwan et al (2007)[73]
Macular oedema	£752	Assumed equal to proliferative retinopathy

Blindness (year 1)	£1,801	UKPDS 65 (2003)[76]
Blindness (ongoing)	£590	UKPDS 65 (2003)[76]
Myocardial infarction (year 1)	£7,715	UKPDS 65 (2003)[76]
Myocardial infarction (ongoing)	£1,028	UKPDS 65 (2003)[76]
Fatal myocardial infarction	£2,388	UKPDS 65 (2003)[76]
Stroke (year 1)	£4,957	UKPDS 65 (2003)[76]
Stroke (ongoing)	£635	UKPDS 65 (2003)[76]
Fatal stroke	£6,461	UKPDS 65 (2003)[76]
Heart failure (year 1)	£4,340	UKPDS 65 (2003)[76]
Heart failure (ongoing)	£1,333	UKPDS 65 (2003)[76]
Fatal heart failure	£4,340	UKPDS 65 (2003)[76]
Angina (year 1)	£3,862	UKPDS 65 (2003)[76]
Angina (ongoing)	£1,081	UKPDS 65 (2003)[76]
Severe hypoglycaemia requiring hospitalisation	£838	UKPDS 65 (2003)[76]

BNF= British National Formulary; PAD= peripheral arterial disease; UKPDS= UK prospective diabetes study; ESRD = end-stage renal disease

Utilities

Baseline utility values included adults with type 1 diabetes and diabetes-related complications. Utility decrements associated with complications and adverse events (hypoglycaemia) were applied annually and on an additive basis in the analysis (*Table 13*). Annual utilities were adjusted for age and sex using the Ara and Brazier algorithm.[77] Utilities were discounted at 3.5% per year as per NICE methods of technology appraisal guidance.[70]

Table 13: Utility values adjusted for age and sex

Utility	Value	Source
Baseline utility value	0.866	Peasgood, 2014[78]
Utility decrements associated with complications:		
Background retinopathy	-0.027	Peasgood, 2014[78]
Proliferative retinopathy	-0.070	Beaudet, 2014[79]
Macular oedema	-0.040	Beaudet, 2014[79]
Blindness	-0.208	Coffey, 2002[80]
Macroalbuminuria	-0.017	Coffey, 2002[80]
ESRD	-0.078	Coffey, 2002[80]
Neuropathy	-0.055	Coffey, 2002[80]
PAD with amputation	-0.116	Coffey, 2002[80]
Myocardial infarction	-0.058	Coffey, 2002[80]
Stroke	-0.165	Alva, 2014[81]
Heart failure	-0.101	Alva, 2014[81]
Angina	-0.090	Coffey, 2002[80]
Severe hypoglycaemic event (per daytime event)	-0.047	Evans, 2013[82]
Non-severe hypoglycaemic event (per daytime event)	-0.004	Evans, 2013[82]

Mortality

Mortality in the model was based on age and sex-adjusted general population all-cause mortality tables for Scotland, and the additional rate of mortality association with ESRD and fatal cardiovascular events.[83]

Results

Base case results from the economic model are presented in *Table 14*. The analysis shows that in a population with well controlled type 1 diabetes, closed loop systems are associated with the highest costs and QALYs of all technologies in the model, except in the comparison with CSII plus CGM. The ICERs comparing closed loop systems with SMBG plus MDI, CGM plus MDI, and FGM plus MDI are £44,920, £58,996, and £79,664 respectively. These ICERs are above conventional ICER thresholds used in the UK. Closed loop systems were associated with lower costs and higher QALYs than CSII plus CGM, and are therefore cost-effective in this group. Disaggregated predicted event rates for the comparator and associated rate reductions associated with closed loop systems are presented in *Appendix 3, Table B*.

Table 14: Base case results (pairwise comparisons)

	Total costs	Total QALYs	Total LY	Incremental costs	Incremental QALYs	ICER
Closed loop vs:	£120,471	12.970	18.736			
SMBG + MDI	£40,117	11.181	18.602	£80,354	1.789	£44,920
Closed loop vs:	£120,557	12.949	18.757			
CGM + MDI	£83,547	12.332	18.602	£37,010	0.627	£58,996
Closed loop vs:	£120,607	12.951	18.760			
FGM + MDI	£45,378	12,009	18,602	£75,093	0.943	£79,664
Closed loop vs:	£119,801	12.987	18.755			
CGM + CSII	£120,753	12.164	18.602	-£953	0.823	Dominating*

MDI = multiple daily injections; SMBG = self monitoring of blood glucose via finger prick testing; CGM = continuous glucose monitoring; FGM = flash glucose monitoring; CSII = continuous subcutaneous insulin infusion; LY = life years; QALY = quality adjusted life years; ICER = incremental cost-effectiveness ratio;
**closed loop is more effective and less costly*

The biggest cost driver in the closed loop system arm of the model is the intervention cost (*Appendix 3, Table C*). Some of these costs are likely to be offset by long-term savings associated with the reduced need for treatment of microvascular complications and CVD (*Appendix 3, Table D*).

A range of deterministic scenario analyses are presented in *Table 15*. The ICERs are shown to increase after removing the assumed effects on hypoglycaemia and reducing the per event disutility

value associated with non-severe hypoglycaemic events. Using the utility decrement associated with non-severe hypoglycaemic events derived from the general population reduces the ICER (scenario 3 in *Table 15*). There are a range of possible HbA1c reduction values associated with the same improvement in time in range; scenario 4 in *Table 15* shows the effect on the ICER when the greatest predicted reduction is used. When a baseline HbA1c of 8.6% is used, consistent with the average value in the Scottish type 1 diabetes population in 2017, the ICERs decrease substantially. This is a result of the greater predicted reduction in HbA1c levels associated with improvement in time in range for the closed loop system as reported in the NMA (*see Appendix 3, Table E*).

Table 15: Deterministic scenario analyses (ICERs)

	Scenario	vs. SMBG + MDI	vs. CGM + MDI	vs. FGM + MDI	vs. CGM + CSII
0	Base case	£44,920	£58,996	£79,664	Dominating
1	Excluding effect on NSHE	£331,103	£215,447	£422,677	Dominating
2	Assuming 50% reduction in the value of disutility associated with NSHE	£80,177	£94,970	£136,905	Dominating
3	Using the disutility values for NSHE derived from the general population (0.005 per episode)	£37,154	£50,710	£66,610	Dominating
4	Using highest predicted reduction in HbA1c (lower end of 95% CI)	£41,878	£48,548	£69,877	Dominating
5	Using baseline HbA1c of 8.6% and the associated predicted reductions in HbA1c	£31,688	£26,370	£48,224	Dominating
6	Using baseline HbA1c of 8.6% and the associated predicted reductions in HbA1c and excluding effects on hypoglycaemia	£90,488	£41,397	£95,994	Dominating

NSHE = non-severe hypoglycaemic events; MDI = multiple daily injections; SMBG = self monitoring of blood glucose via finger prick testing; CGM = continuous glucose monitoring; FGM = flash glucose monitoring; CSII = continuous subcutaneous insulin infusion; ICER = incremental cost-effectiveness ratio; CI = confidence interval

An exploratory analysis, where the efficacy in the NMA for closed loop systems compared with FGM/CGM/SMBG plus CSII is assumed to be equivalent to that of closed loop systems versus FGM plus CSII, was conducted. The estimated reduction in HbA1c from baseline associated with the closed loop system in the base case was -0.42 (95% CI for the predicted value -1.40 to 0.56). The reduction in NSHE events for FGM plus CSII compared with SMBG plus MDI was assumed to be 20%. The ICER was £33,475 (incremental costs: £38,098; incremental QALYs: 1.138). The associated scenario analyses are presented in *Appendix 3, Table F*.

A probabilistic sensitivity analysis with 30,000 iterations was conducted (*Appendix 3, Tables G-J)*. The findings were consistent with the base case results.

Limitations

The economic analysis is based on results from an NMA showing improvements in percentage time in range associated with closed loop systems compared with each comparator, which is converted to a reduction in HbA1c levels. Long-term data on the association between percentage time in range and diabetes-related complications is lacking. One study was identified which reported a 10% increase in time in range was associated with a 64% reduction in retinopathy progression and 40% reduction in microalbuminuria.[84] It used data from the DCCT trial to estimate time in range from quarterly seven point SMBG testing and found that the difference between patients who developed and did not develop microvascular complications was 10% to 12% time in range and 1.0% to 1.4% HbA1c. It should be noted that percentage time in range derived from quarterly seven-point SMBG testing may not be directly comparable with values generated with CGM or FGM.[85] Several recent studies have found that, on average, a 10% change in time in range is associated with a 0.5% change in HbA1c, but confidence intervals were wide.[62, 86-88] The extent of reductions in HbA1c levels associated with the same improvement in time in range was found to depend on the baseline HbA1c levels (see *Appendix 3, Equation 1*).[62]

The extent of improvements in time in hypoglycaemia associated with the closed loop system and each comparator in the analysis is unclear. The NMA found no significant differences in time below range between comparators.[15] Pairwise meta-analyses reported improvements in time below range associated with the closed loop system in comparison with CGM plus CSII.[16-18] Improvements in hypoglycaemia were included in the economic model based on studies comparing each device with SMBG plus MDI and the reported improvements in time below range. The extent of the correlation of percentage time below range and rate of hypoglycaemic events remains unclear.

Studies have shown that fear of hypoglycaemia has a negative impact on quality of life. Fear of hypoglycaemia has not been captured in the SHTG model. Only one study quantified the reduction in the Worry scale of the Fear of Hypoglycaemia survey in people who were using an insulin pump and added CGM.[54] The disutility associated with each hypoglycaemic event in the economic model may capture some of the ongoing fear of future events.

The SHTG economic model may not fully capture the positive impact of reducing the burden of day-to-day diabetes management associated with using a closed loop system as a result of the lack of relevant quality of life studies. A time trade-off study has shown improvements in quality of life associated with reduced finger prick testing as a result of the use of glucose monitoring devices (FGM).[89] It could be expected that more automated management of type 1 diabetes would yield even greater utility benefit, however such studies were not been identified in the published literature.

Finally, clinical efficacy data (direct or indirect) for FGM plus CSII are lacking, making the results of the exploratory analysis highly uncertain.

Conclusion

The current evidence on the clinical effectiveness of closed loop systems and the artificial pancreas consists 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 have had the condition for several years and who often had experience with using insulin pumps. In clinical practice, people considered for a closed loop system could include the newly diagnosed and the system would potentially be used over a lifetime.

The primary outcome reported in the secondary literature on closed loop systems is mean percentage time in normal glycaemic range. Studies have previously demonstrated an association between percentage time in range and HbA1c levels, and between HbA1c levels and diabetes-related complications. An NMA and three pairwise meta-analyses found statistically 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. Given the rapidly changing nature of these systems, some of the secondary evidence reviewed may be based on technologies that have since been superseded by newer models. The newer closed loop systems can have more complex algorithms that allow finer adjustments for exercise, automatic correction boluses, individual glycaemic targets and learning based on an individual's history.

The limited use of closed loop systems in routine clinical care makes it difficult to estimate device-related adverse event rates. Adverse events were rarely reported in either the closed loop system or control groups within trials. Device-related safety issues in the literature focused on technical difficulties and human factors affecting closed loop system performance.

People with type 1 diabetes described both positive and negative aspects of using closed loop systems. These systems improved glycaemic control, gave people more flexibility in daily life, and offered people with type 1 diabetes 'time off' from managing their condition. Closed loop systems also presented a burden of treatment in the form of frequent alarms, the need to replace sensors and insulin infusion sets, and dealing with technical problems. Submissions from three patient organisations supported the findings from published studies and emphasised the potential of closed loop systems to have a major positive impact on people's lives.

Audit data from England and Wales identified inequalities in access to diabetes technologies among children and adolescents from different ethnic and socioeconomic backgrounds. White children from affluent areas were the most likely to use CGM or insulin pumps, and black children from the poorest areas were the least likely. It is possible that introducing closed loop systems into clinical practice could increase these inequalities, particularly if closed loop systems are associated with improved glycaemic control in those who can access them.

In the SHTG economic model, 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. The analysis is associated with some uncertainties because of a lack of published studies underpinning assumptions in the model around reductions in hypoglycaemic events, effects on long-term diabetes-related complications, rates of severe and non-severe hypoglycaemia, and quality of life. Device-specific adverse events and quality of life associated with day-to-day management of diabetes are not captured in the model. The available clinical evidence relates to people with well controlled type 1 diabetes and does not allow for analyses in populations with less well controlled diabetes who arguably may benefit more from closed loop systems.

Identified research gaps

Additional RCTs are needed that explore using closed loop systems in larger samples of people, over a much longer time period, and in daily life. Trials assessing the artificial pancreas are also required as there are currently few RCTs on multi-hormone systems. 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 closed loop systems, such as HbA1c effects and quality of life scores (especially resulting from the reduced burden of day-to-day diabetes management), in the UK would be very beneficial. Studies should ideally use CGM plus CSII or FGM plus CSII as the control group, as these are the most relevant comparators. Studies exploring the association between improvements in time in glycaemic range and long-term diabetes-related complications would be beneficial. Ongoing trials that may address some of these evidence gaps are presented in Table 16.

Table 16: Ongoing trials involving people with type 1 diabetes using closed loop systems

Trial ID	Participants	Interventions	Intervention duration	Expected completion date
NCT04243629	Adults	Rapid insulin + pramlintide in two insulin pumps vs. rapid insulin + placebo in two insulin pumps	4 weeks	April 2022
NCT04914910	Adults currently using insulin pumps and CGM/FGM who are not meeting glycaemic targets	MiniMed 780G vs. usual care	28 weeks	June 2023

NCT04510506	Pubertal adolescents	Tandem t:slim™ X2 with Control IQ™ vs. usual care + CGM	2 years	August 2024
NCT04053712	Aged >15 and using insulin pump	Single hormone closed loop system versus dual hormone closed loop system (artificial pancreas)	33 hours	July 2029

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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Appendix 1: abbreviations

BNF	British national formulary
CASP	critical appraisal skills programme
CEAC	cost-effectiveness acceptability curve
CGM	continuous glucose monitoring
CI	confidence interval
CLOuD	closed loop from onset in type 1 diabetes
CSII	continuous subcutaneous insulin infusion
CVD	cardiovascular disease
DCCT	UK diabetes control and complications trial
DDS	diabetes distress scale
ESRD	end stage renal disease
FGM	flash glucose monitoring
GRADE	grading of recommendations assessment, development and evaluation
HCHS	hospital and community health services
HCL	hybrid closed loop
HDL:TCL	high density lipoprotein : total cholesterol levels
ICER	incremental cost-effectiveness ratio
iPAG	Insulin Pump Awareness Group
IQR	inter-quartile range
JDRF	Juvenile Diabetes Research Foundation
LY	life years
MD	mean difference
MDI	multiple daily injections
NHSEED	NHS economic evaluations database
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSHE	non-severe hypoglycaemic event
OR	odds ratio
PAD	peripheral arterial disease
PAID	problem areas in diabetes
PRO	patient reported outcomes

QALY	quality adjusted life years
RCT	randomised controlled trial
RR	relative risk/risk ratio
SCI	Scottish care information
SD	standard deviation
SE	standard error
SHE	severe hypoglycaemic event
SHTG	Scottish Health Technologies Group
SIMD	Scottish index of multiple deprivation
SMBG	self monitoring blood glucose
SUCRA	surface under the cumulative ranking
TBR	time below range
TIR	time in range
UKPDS	UK prospective diabetes study
WESDR	Wisconsin epidemiological study of diabetic retinopathy
WMD	weighted mean difference

Appendix 2: Relevant RCTs published 2018–2022

Table A: Relevant RCTs published after the most recent literature search in the secondary evidence (2018)

Study	Participants	Comparison	Key findings
Adults			
Haider (2021)[27] Cross-over RCT; Outpatient free-living with no remote monitoring; Canada	n=36 Mean age 39 (SD 16) 61% female Mean duration of diabetes 23 years (SD 13) Mean % HbA1c 7.5 (SD 0.9)	Hybrid closed loop system; iPancreas system (Dexcom CGM, t:slim™ TAP3 pump, Nexus 5 smartphone) vs. Sensor-augmented pump therapy Intervention duration 12 days	Hybrid closed loop system increased percent time in range (3.9 to 10 mmol/L) from 61% (IQR 53 to 74) to 69% (IQR 60 to 73), p=0.006. Hybrid closed loop system reduced percent time in hypoglycaemia from 3.5% (IQR 0.8 to 5.4) to 1.6% (IQR 1.1 to 2.7), p=0.0021.
Blauw (2021)[22] Cross-over RCT; Outpatient free-living with alarm-based monitoring; Netherlands	n=23 Median age 43.0 (IQR 26.5 to 51.0) 35% female Median diabetes duration 23.0 years (IQR 14.0 to 34.5) Mean % HbA1c 7.3 (IQR 7.1 to 8.1)	Artificial pancreas (Inreda Diabetic, two Enlite™ devices and a wearable device integrating CGM, accelerometer, control algorithm, insulin pump, and glucagon pump) vs. Usual care (open loop with CGM/FGM and insulin pump) Intervention duration 2 weeks	Percent time in range was significantly higher with artificial pancreas: median 86.6% (IQR 84.9 to 88.5) versus 53.9% (49.7 to 67.2), p<0.0001. Percent time in hypoglycaemia (<3.9 mmol/L) reduced with artificial pancreas: 0.4% (IQR 0.1 to 0.8) versus 2.0% (IQR 0.7 to 3.6), p<0.0001. Percent time in hyperglycaemia (>10 mmol/L) reduced with artificial pancreas: 12.8% (IQR 11.1 to 14.4) versus 38.8% (IQR 30.5 to 48.9), p<0.0001. No severe hypoglycaemia, ketoacidosis or other serious adverse events.

McAuley (2020)[28] Parallel RCT; Australia	n=120 Mean age 44.2 (SD 11.7) 53% female Duration of diabetes range 1 to 59 years % HbA1c range 5.7 to 10.4	Hybrid closed loop system; Medtronic 670G (Enlite™ 3 CGM, GST3c MiniLink™) vs. Multiple daily injections or insulin pump Intervention duration 26 weeks	Hybrid closed loop system resulted in increased percent time in range (3.9 to 10.0 mmol/L): difference in time in range 15%, 95% CI 11 to 19, p<0.0001. HbA1c levels were lower with the hybrid closed loop system: median difference 0.4%, 95% CI 0.2 to 0.6, p<0.0001. Diabetes-specific positive wellbeing scores were higher with the hybrid closed loop system. 17 (9 device-related) vs. 13 serious adverse events with hybrid closed loop and control group respectively.
Benhamou (2019)[20] Cross-over RCT; Outpatient free-living; France	n=63 Mean age 48.2 (SD 13.4) 62% female Mean duration of diabetes 28.0 years (SD 13.6) Mean % HbA1c 7.6 (SD 0.9)	Hybrid closed loop system (DBLG1 system) vs. Sensor-augmented pump therapy Intervention duration 12 weeks	Percent time in range was significantly higher in DBLG1 group compared with sensor-augmented pump group: mean difference 9.2%, 95% CI 6.4 to 11.9, p<0·0001. Five severe hypoglycaemic episodes in the DBLG1 group and three in the sensor-augmented pump group.
Anderson (2019)[19] Parallel RCT; Home; US	n=44 Mean age closed loop group 38.3 (SD 3.3) Mean age control group 38.0 (SD 3.3) 47.6% female in closed loop group	Hybrid closed loop system (Diabetes Assistant [DiAs] smartphone platform, Dexcom G4 Platinum CGM, Roche Accu-Chek® Spirit Combo insulin pump) vs. Sensor-augmented pump therapy	Percent time below range (<3.9 mmol/L) decreased on hybrid closed loop system (7.2% ± 5.3% to 2.0% ± 1.4%) but not on sensor-augmented pump (5.8% ± 4.7% to 4.8% ± 4.5%), p=0.001. Percent time in range (3.9 to 10 mmol/L) increased on hybrid closed loop (67.8% ±

	71.4% female in control group Mean duration of diabetes closed loop group 21.1 (SD 2.6) Mean duration of diabetes control group 18.2 (SD 2.3) years Mean % HbA1c closed loop group 7.5 (SD 0.2) Mean % HbA1c control group 7.2 (SD 0.2)	Intervention duration 4 weeks	13.5% to 78.2% ± 10%) but decreased on sensor-augmented pump (65.6% ± 12.9% to 59.6% ± 16.5%), p<0.001. Percent time above range (>10 mmol/L) decreased on hybrid closed loop (25.1% ± 15.3% to 19.8% ± 10.1%) but increased on sensor-augmented pump (28.6% ± 14.6% to 35.6% ± 17.6%), p=0.009.
Children and adolescents			
Abraham (2021)[30] Parallel RCT; Australia	n=135 Mean age 15.3 years (SD 3.1) 56% female Mean duration of diabetes 7.7 years (SD 4.3) Mean % HbA1c 8.0 (SD 1.0)	Hybrid closed loop system (MiniMed™ 670G pump, Guardian™ 3 sensor, Guardian™ Link 3 transmitter) vs. Standard care (CSII or multiple daily injections, with or without CGM) Intervention duration 26 weeks	Percent time in range increased from a mean of 53.1% (SD 13.0) to 62.5% (SD 12.0) in the hybrid closed loop group and from 54.6% (SD 12.5) to 56.1% (SD 12.2) in the control group. Mean adjusted difference in percent time in range 6.7% (95% CI 2.7 to 10.8, p=0.002). Hybrid closed loop reduced the percent time in a hypoglycaemia (<3.9 mmol/L) range: mean difference 1.9%, 95% CI 1.3 to 2.5. Hybrid closed loop therapy was associated with improved diabetes-specific quality of life. No episodes of severe hypoglycaemia or diabetic ketoacidosis in either group.

Breton (2020)[23] Parallel RCT; US	n=101 Mean age in closed loop group 11.3 ± 2.0 Mean age in sensor-augmented pump group 10.8 ± 2.4 49% female Mean duration of diabetes in closed loop group 5.0 ± 2.8 Mean duration of diabetes in sensor-augmented pump group 6.0 ± 2.8 % HbA1c range 5.7 to 10.1	Hybrid closed loop system (t:slim X2™ insulin pump, with Control IQ™ algorithm, and Dexcom G6 CGM) vs. Sensor-augmented pump therapy Intervention duration 16 weeks	Percent time in range (3.9 to 10.0 mmol/L) increased more in the hybrid closed loop group: mean adjusted different 11%, 95% CI 7 to 14, p<0.001. Mean adjusted between-group difference in the % HbA1c at 16 weeks was −0.4%, 95% CI −0.9 to 0.1, p=0.08. 16 adverse events were reported in 15 patients (19%) in the hybrid closed loop group and three adverse events were reported in two patients (9%) in the control group.
Forlenza (2019)[26] Parallel RCT; Home (remote monitoring); US	n=24 Mean age 9.6 (SD 1.9) 50% female Duration of diabetes 4.5 years (SD 1.9) Mean % HbA1c 7.35 (SD 0.68)	Hybrid closed loop system (t:slim X2™ insulin pump, Control IQ™ algorithm, Dexcom G6 CGM) vs. Sensor-augmented pump therapy Intervention duration 3 days	Percent time in range (3.9 to 10.0 mmol/L) significantly improved in hybrid closed loop group compared with the control group: 71.0% ± 6.6% versus 52.8% ± 13.5%, p=0.001. Percentage time in hypoglycaemia (<3.9 mmol/L) was not significantly different between groups: 1.7%, 95% CI 1.3 to 2.1 versus 0.9%, 95% CI 0.3 to 2.7.
Ware (2022)[31] Cross-over RCT; Home (remote monitoring); Austria, Germany, Luxembourg, UK	n=74 Mean age 5.6 (SD 1.6) 42% female Mean duration of diabetes 2.6 (SD 1.8) years Mean % HbA1c 7.3 (SD 0.7)	Hybrid closed loop system (Galaxy S8 smartphone, CamAPS FX, Dana Diabecare RS pump, Dexcom G6 CGM) vs. Sensor-augmented pump therapy Intervention duration 16 weeks	Percent time in range was 8.7% (95% CI 7.4 to 9.9) higher with hybrid closed loop. during the closed loop period (p<0.001). Mean adjusted difference (closed loop minus control) in percent time spent in a hyperglycaemic state was −8.5% (95% CI −9.9 to −7.1), p=0.74.

			One event of severe hypoglycaemia occurred during the closed loop period. One serious adverse event that was deemed to be unrelated to treatment occurred.
Mixed age population			
Collyns (2021)[25] Cross-over RCT; Outpatient free-living; New Zealand	n=60 Mean age 23.3 (SD 14.4) 58% female Duration of diabetes 13.2 years (SD 10.2) Mean % HbA1c 7.6 (SD 0.9)	MiniMed™ advanced hybrid closed loop system (MiniMed 670G 4.0 insulin pump, Guardian™ CGM sensors and transmitters, CONTOUR® NEXT LINK 2.4 blood glucose metre) vs. Sensor-augmented pump therapy Intervention duration 8 weeks	Percent time in range (3.9 to 10 mmol/L) favoured the hybrid closed loop over sensor-augmented pump therapy by 12.5% ± 8.5%, p<0.001, with greater improvement overnight (18.8% ± 12.9%, p<0.001). All age groups (children 7-13 years, adolescents 14-21 years, and adults >22 years) demonstrated improvement, with adolescents showing the largest improvement (14.4% ± 8.4%). One episode of mild diabetic ketoacidosis attributed to an infusion set failure in combination with illness occurred in the sensor-augmented pump group.
Brown (2019)[24] Parallel RCT; Outpatient; US	n=168 Mean age in closed loop group 33.0 (SD 16.0) Mean age in control group 33.0 (SD 17.0) 50% female Median duration of diabetes in closed loop group 17 years (IQR 8 to 28)	Hybrid closed loop system (t:slim X2™ insulin pump, Control IQ™, Dexcom G6 CGM) vs. Sensor-augmented pump therapy Intervention duration 26 weeks	Percent time in range increased more in the closed loop group than the sensor-augmented pump group: mean difference 11%, 95% CI 9 to 14, p<0.001. Mean difference in % HbA1c at 26 weeks was 0.33%, 95% CI 0.13 to 0.53, p=0.001.

	Median duration of diabetes in control group 15 years (IQR 7 to 23) % HbA1c range ranged from 5.4 to 10.6		Mean difference in percent time above range (>10.0 mmol/L) was 10%, 95% CI 8 to 13, p<0.001. Mean difference in percent time below range (<3.9 mmol/L) was 0.88%, 95% CI 0.57 to 1.19, p<0.001. 17 adverse events in 16 patients in the closed loop group and two adverse events in two patients in the control group (p=0.05). Severe hypoglycaemia did not occur in either group.
Biester (2019)[21] Cross-over RCT; Home	n=48 Median age 16.1 (IQR 13.2 to 18.5) 60% female Median duration of diabetes 9.4 years (IQR 5.0 to 12.7) Median % HbA1c 7.6 (IQR 7.0 to 8.1)	Hybrid closed loop system (Paradigm® Veo™, Enlite™ 3 sensor with MiniLink® 2, glucometer CONTOUR® Next LINK, MD-Logic closed loop algorithm on a PC tablet platform) vs. Sensor-augmented pump therapy Intervention duration 60 hours	A significant increase in percent time in range (3.9 to 10.0 mmol/L) for the hybrid closed loop system versus control: 66.6% versus 59.9%, p=0.002. No significant change in percent time below range (<3.9 mmol/L): 2.3% versus 1.5%, p=0.369. No serious adverse events were reported. No ketosis or severe hypoglycaemia.
Tauschmann (2018)[29] Parallel RCT; Free-living; UK and US	n=86 Median age in closed loop group 22 (IQR 13 to 36) Median age in control group 21 (IQR 11 to 36) 51% female Median duration of diabetes in closed loop group 13 years (IQR 7 to 20)	Hybrid closed loop system (FlorenceM closed loop system; Enlite™ 3 CGM, MiniMed™ 640G insulin pump, Galaxy S4 mobile phone running the control algorithm) vs. Sensor-augmented pump therapy Intervention duration 12 weeks	Percent time in range (3.9- to 10.0 mmol/L) was significantly greater in the hybrid closed loop group: 10.8%, 95% CI 8.2 to 13.5, p<0·0001. Reductions in HbA1c percent were significantly greater in the hybrid closed loop group compared with the control group:

	Median duration of diabetes in control group 10 years (IQR 7 to 19) Mean % HbA1c closed loop group 8.3 (SD 0.6) Mean % HbA1c control group 8.2 (SD 0.5)		mean difference in change 0.36%, 95% CI 0.19 to 0.53, p<0·0001. No severe hypoglycaemia. One diabetic ketoacidosis event in the hybrid closed loop group because of infusion set failure. Thirteen other adverse events in the hybrid closed loop group and three in the control group.

Appendix 3: Cost-effectiveness

Table A: Baseline transition probabilities from Sheffield type 1 diabetes model – microvascular complications

Annual transition probabilities	Baseline probability at HbA1c of 10%	Beta coefficient	Source[57]
No complications to microvascular complications			
No neuropathy to neuropathy	0.0354	5.3	Sheffield type 1 diabetes model
No neuropathy to PAD with amputation	0.0003		
Neuropathy to PAD with amputation	0.0154		
No albuminuria to microalbuminuria	0.0436	3.25	
No albuminuria to macroalbuminuria	0.0037	7.95	
No albuminuria to ESRD	0.0002		
No albuminuria to death from ESRD	3.30E-06		
No retinopathy to retinopathy	0.0454	10.1	
No retinopathy to proliferative retinopathy	0.0013	6.3	
No retinopathy to macular oedema	0.0012	1.2	
No retinopathy to blindness	0.0000019		
Progression of microvascular complications			
Neuropathy to amputation	0.0154		Sheffield type 1 diabetes model
Micro to macroalbuminuria	0.1565	7.95	
Microalbuminuria to ESRD	0.0133		
Microalbuminuria to death from ESRD	0.0004		
Macroalbuminuria to ESRD	0.1579		
Retinopathy to proliferative retinopathy	0.0595	6.3	
Retinopathy to macular oedema	0.0512	1.2	
Retinopathy to blindness	0.0001		
Proliferative retinopathy to blindness	0.0038		
Macular oedema to blindness	0.0016		
Diabetes-related mortality			
No complications to death from ESRD	3.30E-06		Sheffield type 1 diabetes model
Microalbuminuria to death from ESRD	0.0004		
Macroalbuminuria to death from ESRD	0.007		
Death from ESRD	0.0884		

PAD = peripheral arterial disease; ESRD = end stage renal disease

Table B: Predicted event rates and reductions associated with the closed loop in the economic model (n=5,000 patients)

	Comparator (HbA1c = 7.7%)	CL vs SMBG + MDI	CL vs CGM + MDI	CL vs FGM + MDI	CL vs CGM + CSII	CL vs FGM + CSII
Microalbuminuria	2,307	-323	-262	-270	-203	-232
Macroalbuminuria	946	-430	-362	-368	-284	-325
ESRD	770	-196	-198	-196	-204	-196
Death from ESRD	586	-120	-121	-121	-128	-123
Nephropathy	1,214	-384	-296	-298	-296	-298
Amputation	358	-103	-80	-80	-79	-80
Background retinopathy	2,089	-123	-99	-101	-87	-98
Macular oedema	1,210	-62	-44	-43	-32	-40
Proliferative retinopathy	810	-134	-116	-119	-93	-103
Blindness	123	-16	-15	-15	-10	-12
CVD	2,883	-134	-110	-112	-79	-96
All myocardial infarctions	2,493	-146	-125	-128	-91	-106
Fatal myocardial infarctions	1344	-91	-83	-85	-64	-75
Angina	1132	-80	-69	-70	-56	-60
All heart failure	601	-33	-26	-26	-18	-22
Fatal heart failure	29	1	2	2	2	2
Stroke	414	-21	-13	-14	-14	-17
Fatal stroke	46	-1	1	1	1	0

SMBG = self monitoring of blood glucose; CL= closed loop; CGM = continuous glucose monitor; FGM = flash glucose monitor; CSII = continuous insulin infusion; ESRD = end stage renal disease; CVD = cardiovascular disease

**efficacy for closed loop vs CGM/FGM/SMBG + CSII and assumptions*

Table C: Model predicted lifetime intervention costs

	Comparator	Closed loop	Difference
Undiscounted costs			
SMBG + MDI	£19,452	£163,418	+£143,966
CGM + MDI	£94,411	£163,327	+£68,917
FGM + MDI	£29,894	£163,355	+£133,462
CGM + CSII	£156,481	£163,212	+£6,731
FGM* + CSII	£91,963	£163,246	+£71,283
Discounted costs			
SMBG + MDI	£11,523	£96,604	+£85,081
CGM + MDI	£55,928	£96,576	+£40,649
FGM + MDI	£17,708	£96,587	+£78,880
CGM + CSII	£93,084	£96,561	+£3,477
FGM* + CSII	£54,865	£96,568	+£41,704

SMBG = self monitoring of blood glucose; CL = closed loop; CGM = continuous glucose monitor; FGM = flash glucose monitor; CSII = continuous insulin infusion
**efficacy for closed loop vs CGM/FGM/SMBG + CSII and assumptions*

Table D: Model predicted per patient lifetime costs and associated cost savings

	Comparator	CL vs SMBG + MDI	CL vs CGM + MDI	CL vs FGM + MDI	CL vs CGM + CSII	CL vs FGM* + CSII
Undiscounted costs						
Microvascular complications	£42,267	-£8,194	-£8,119	-£8,036	-£8,144	-£8,039
CVD	£14,886	-£224	-£35	-£41	£97	£14
Discounted costs						
Microvascular complications	£21,750	-£3,666	-£3,628	-£3,588	-£3,652	-£3,573
CVD	£5,153	-£144	-£67	-£70	-£11	-£40

SMBG = self monitoring of blood glucose; CL= closed loop; CGM = continuous glucose monitor; FGM = flash glucose monitor; CSII = continuous insulin infusion
**efficacy for closed loop vs CGM/FGM/SMBG + CSII and assumptions*

Table E: Estimated reduction in HbA1c from baseline HbA1c of 8.6%

Closed loop vs	Mean HbA1c reduction (95% CI for the predicted value)	Source
SMBG + MDI	-1.21 (-2.19 to -0.23)	Pease 2020; Beck 2019[15, 62]
FGM + MDI	-1.08 (-2.06 to -0.10)	Pease 2020; Beck 2019[15, 62]
CGM + MDI	-1.07 (-2.05 to -0.09)	Pease 2020; Beck 2019[15, 62]
CGM + CSII	-0.96 (-1.94 to 0.02)	Pease 2020; Beck 2019[15, 62]
FGM + CSII*	-1.01 (-1.99 to -0.03)	Pease 2020; Beck 2019[15, 62]

FGM = flash glucose monitoring; MDI = multiple daily injections; CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion
**efficacy for closed loop vsCGM/FGM/SMBG + CSII and assumptions*

Table F: Deterministic scenario analyses – closed loop versus FGM plus CSII

	Scenario	vs. FGM + CSII (ICERs)
0	Base case	£33,475
1	Excluding effect on NSHE	£178,138
2	Assuming 50% reduction in the value of disutility associated with NSHE	£57,414
3	Using the disutility values for NSHE derived from the general population (0.005 per episode)	£28,191
4	Using the largest predicted reduction in HbA1c (lower end of 95% CI)	£29,919
5	Using baseline HbA1c of 8.6% and the associated predicted reductions in HbA1c	£19,238
6	Using baseline HbA1c of 8.6% and the associated predicted reductions in HbA1c and excluding effects on hypoglycaemia	£42,355

NSHE = non-severe hypoglycaemic events; FGM = flash glucose monitoring; CSII = continuous subcutaneous insulin infusion; ICER = incremental cost-effectiveness ratio; CI = confidence interval

Table G: Relative treatment effects

Relative treatment effect (time in range)		95% CI			
Closed loop vs	**Mean % TIR longer**	**Low end**	**High end**	**Standard error**	**Distribution**
SMBG + MDI	17.85	9.28	26.42	5.25	Normal
FGM + MDI	13.29	3.86	22.71	5.76	Normal
CGM + MDI	12.76	4.87	20.64	4.85	Normal
CGM + CSII	8.77	4.18	13.35	2.94	Normal
FGM (based on SMBG/CGM/FGM) + CSII	10.6	6.46	14.74	2.70	Normal
Severe hypoglycaemi events (SHE)	**Mean**	**95% CI**		**Standard error**	**Distribution**
Annual incidence of SHE in Scotland per person	0.115	0.094	0.136		
Annual probability of SHE in Scotland (assumed for SMBG + MDI)	0.109	0.090	0.127	0.009	Normal
		alpha	**beta**		Beta
% reduction closed loop	55%	7.5	2.5		Beta
% reduction CGM + MDI	55%	5.5	4.5		Beta
% reduction CGM + CSII	55%	5.5	4.5		Beta
% reduction FGM + MDI	55%	5.5	4.5		Beta
% reduction FGM + CSII	55%	5.5	4.5		Beta
Non-severe hypoglycaemic events		**95%CI**		**Standard error**	
Annual incidence of non-SHE in Scotland per person (assumed for SMBG + MDI)	41.74	37.323	45.64	2.13	Beta
		alpha	**beta**		
% reduction closed loop	50%	5.0	5.0		Beta
% reduction CGM + MDI	35%	3.5	6.5		Beta
% reduction CGM + CSII	30%	3.0	7.0		Beta
% reduction FGM + MDI	25%	2.5	7.5		Beta
% reduction FGM + CSII	20%	2.0	8.0		Beta

CSII = continuous subcutaneous insulin infusions; CGM = continuous glucose monitor; FGM = flash glucose monitor; SMBG = self monitoring of blood glucose; SHE = severe hypoglycaemic events; MDI = multiple daily injections; TIR = time in range

Table H: Utility values

	Mean	Standard error			Distribution
Baseline utility value for a person with type 1 diabetes	0.866	0.01			Normal
Utility decrements associated with diabetes-related complications			**alpha**	**beta**	
Background retinopathy	-0.027	0.011	5.84	210.28	Beta
Proliferative retinopathy	-0.07	0.015	20.18	268.15	Beta
Macular oedema	-0.04	0.013	9.05	217.17	Beta
Blindness	-0.208	0.13	1.82	6.93	Beta
Macroalbuminuria	-0.017	0.01	2.82	163.29	Beta
End stage renal disease	-0.078	0.027	7.62	90.03	Beta
Neuropathy	-0.055	0.01	28.53	490.22	Beta
Peripheral arterial disease with amputation	-0.116	0.023	22.37	170.47	Beta
Myocardial infarction	-0.058	0.022	6.49	105.40	Beta
Stroke	-0.165	0.035	18.39	93.08	Beta
Heart failure	-0.101	0.032	8.85	78.82	Beta
Angina	-0.09	0.018	22.66	229.12	Beta
Severe hypoglycaemic event	-0.047	0.0076	36.40	738.07	Beta
Non-severe hypoglycaemic event	-0.004	0.001	15.93	3,967.07	Beta

Table I: Unit costs for diabetes-related complications

Diabetes-related complications	Unit costs indexed to 2020	Gama distribution	
		Alpha	**Beta**
Microalbuminuria (ongoing)	£41	100	0.42
Macroalbuminuria (ongoing)	£41	100	0.42
End stage renal disease (ongoing)	£27,777	100	277.77
Clinically confirmed neuropathy	£308	100	3.08
Peripheral arterial disease with amputation (year 1)	£8,208	100	82.08
Peripheral arterial disease with amputation (ongoing)	£499	100	4.99
Background retinopathy	£165	100	1.65

Proliferative retinopathy	£752	100	7.52
Macular oedema	£752	100	7.52
Blindness (year 1)	£1,801	100	18.01
Blindness (ongoing)	£590	100	5.90
Myocardial infarction (year 1)	£7,715	100	77.16
Myocardial infarction (ongoing)	£1,028	100	10.28
Fatal myocardial infarction	£2,388	100	23.88
Stroke (year 1)	£4,957	100	49.58
Stroke (ongoing)	£635	100	6.35
Fatal stroke	£6,461	100	64.61
Heart failure (year 1)	£4,340	100	43.41
Heart failure (ongoing)	£1,333	100	13.33
Fatal heart failure	£4,340	100	43.41
Angina (year 1)	£3,862	100	38.62
Angina (ongoing)	£1,081	100	10.81
Severe hypoglycaemic event	£838	100	8.38

Table J: Probabilistic sensitivity analysis results

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Closed loop vs	£125,218	12.871			
SMBG + MDI	£44,960	11.092	£80,258	1.779	£45,121
Closed loop vs	£123,022	12.926			
CGM + MDI	£88,131	12.221	£34,891	0.705	£49,496
Closed loop vs	£123,028	12.926			
FGM + MDI	£50,358	11.916	£74,860	1.010	£74,091
Closed loop vs	£123,143	12.962			
CGM + CSII	£125,067	12.068	-£1,924	0.895	Dominating*
Closed loop vs	£122,937	12.967			
FGM + CSII	£87,127	11.759	£35,810	1.208	£29,637

MDI = multiple daily injections; SMBG = self monitoring of blood glucose; CGM = continuous glucose monitoring; FGM = flash glucose monitoring; CSII = continuous subcutaneous insulin infusion; LY = life years; QALY = quality adjusted life years; ICER = incremental cost-effectiveness ratio;
**closed loop is more effective and less costly*

Figure 1: Cost-effectiveness acceptability curve –closed loop versus SMBG plus MDI

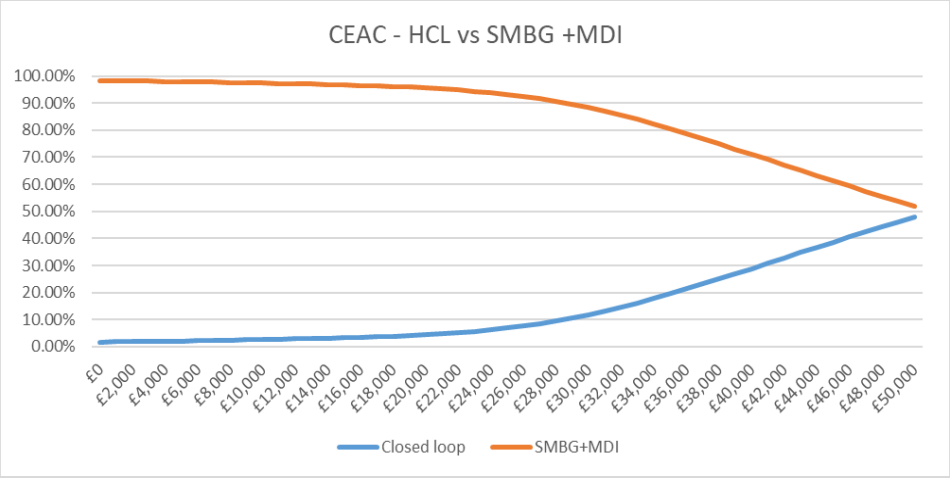


Figure 2: Cost-effectiveness acceptability curve – closed loop versus FGM plus MDI

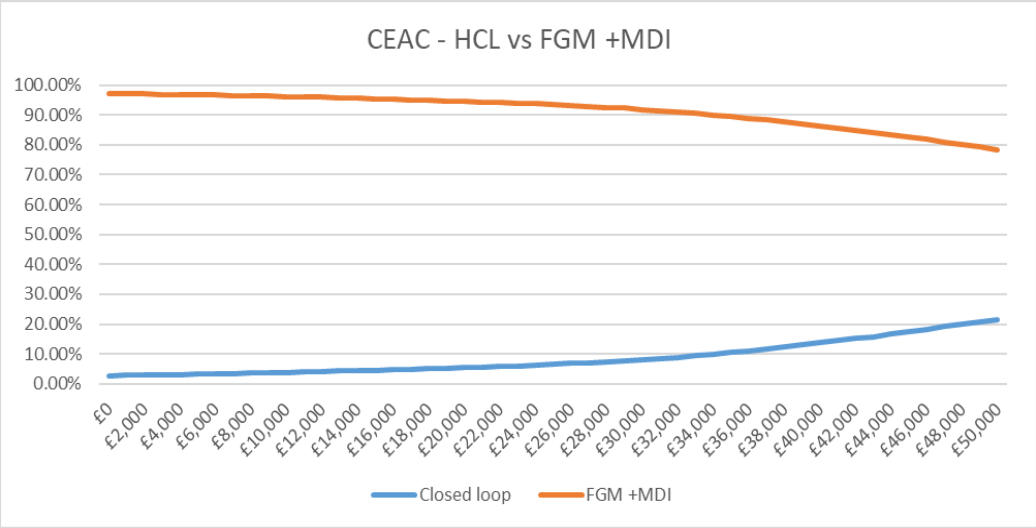


Figure 3: Cost-effectiveness acceptability curve – closed loop versus CGM plus MDI

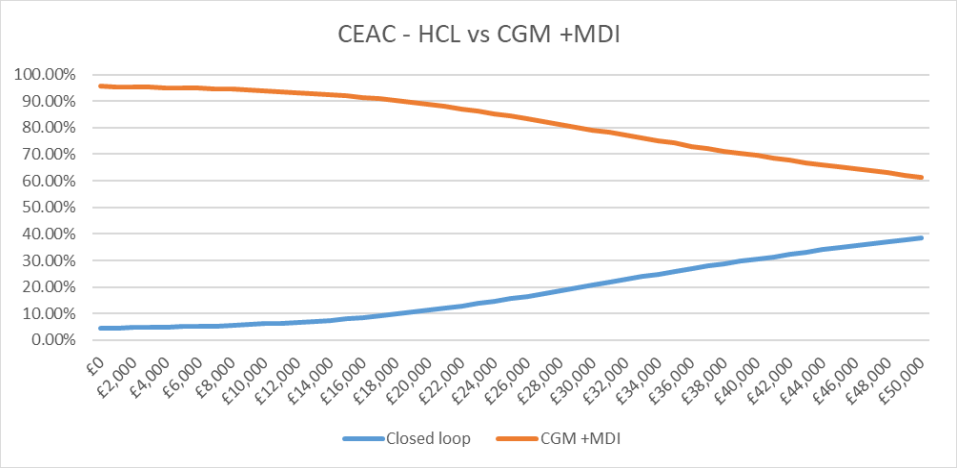


Figure 4: Cost-effectiveness acceptability curve – closed loop versus CGM plus CSII

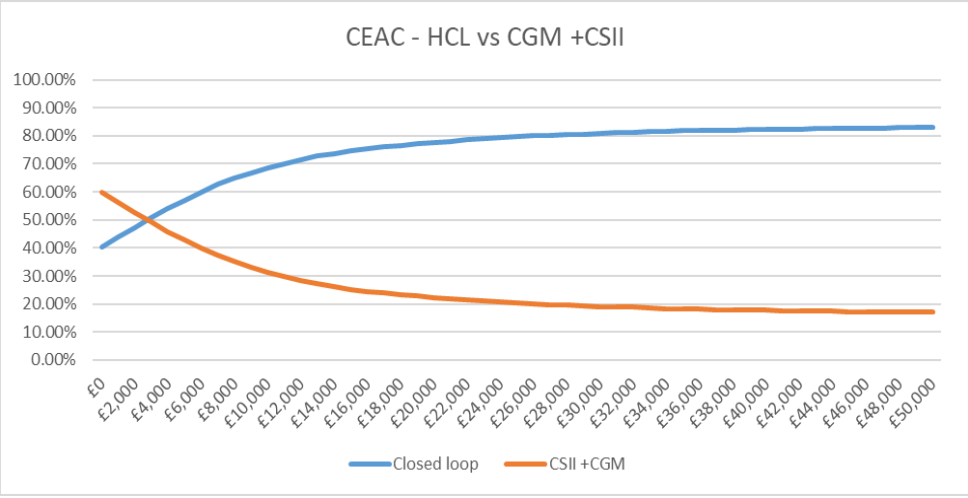
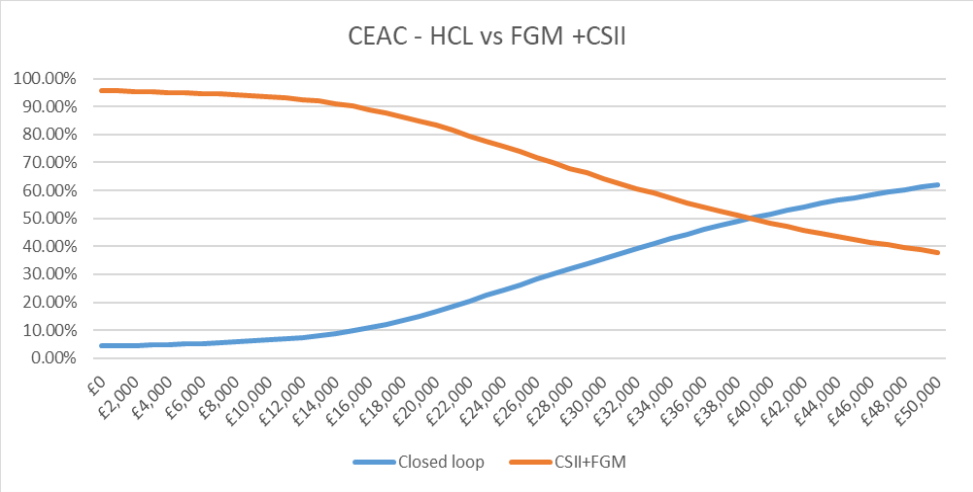


Figure 5: Cost-effectiveness acceptability curve – closed loop versus FGM plus CSII



Equation 1

ΔHbA1c = -0.12-0.028*ΔTIR (if baseline HbA1C = 7.0%-7.9%) and ΔHbA1c = -0.71-0.028*ΔTIR (if baseline HbA1C >8.0%); common root square error= 0.5