NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

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

Final scope

March 2021

1 Introduction

The NICE diagnostics guidance 21 on Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) was reviewed in January 2019. A review decision was made to update the guidance because the technologies assessed previously are no longer available to the NHS and they have been replaced by successor systems with enhanced features. In addition, new potential comparator technologies have become available. The final scope was informed by discussions at the scoping workshop held on 23 February 2021 and the assessment subgroup meeting held on 10 March 2021. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technology based on information provided to NICE by manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

The MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM integrated sensor-augmented insulin pump systems assessed in DG21 are intended to monitor interstitial glucose levels and deliver insulin for people with type 1 diabetes. Both systems are no longer available on the NHS for new patients, however, some people are still using the Veo insulin pump and these will be gradually phased out when they are due for a replacement. Recently, there have been rapid advancements in the use of technologies for

the management of type 1 diabetes, for example, hybrid closed loop systems which rely on a mathematical algorithm to automatically drive insulin delivery in response to continuously monitored interstitial fluid glucose levels have been launched. These systems aim to reduce user or caregiver input in insulin dosing by requiring minimal user interaction. Hybrid closed loop systems are reported to be more effective at improving glycaemic outcomes such as increased time in target range, reduced hypoglycaemic events and a reduction in glycated haemoglobin (HbA1c), than sensor augmented pump systems. (Brown 2019, Akturk 2019). There are more advanced fully closed loop systems that are fully automated, however, none of these systems were identified during scoping as being commercially available.

2.2 Product properties

Hybrid closed loop systems use a combination of real-time glucose monitoring from a continuous glucose monitoring device and a control algorithm to direct insulin delivery through an insulin pump. Some of these systems are built by combining interoperable devices from different manufacturers. Hybrid closed loop systems available in the UK at the time of writing the scope have been highlighted in table 1 and section 2.2.4. Each system has unique features that differentiates it from other systems, but overall, the systems are aimed at achieving optimized time in a desirable glucose range. In addition to a clinician's opinion and funding arrangements, the choice of hybrid closed loop system a person uses is often influenced by their preference, which may be based on factors such as aesthetics, ease of use and how it fits around their daily activities.

2.2.1 Continuous glucose monitoring

This involves measuring interstitial fluid glucose levels throughout the day and night. A continuous glucose monitor typically comprises a disposable sensor with a tiny cannula inserted into the skin to measure glucose levels, and a transmitter connected to the sensor that sends real time readings wirelessly to a receiver or a smart device that displays results. Calibration is required for some continuous glucose monitors, hence they are used in conjunction with capillary blood testing. Most monitors can send alerts for high or low glucose levels. Glucose levels can also be monitored using intermittently scanned glucose monitors (see section 3.2).

2.2.2 Control algorithms

A control algorithm is a software programme that receives data about glucose levels from a continuous glucose monitor and uses this information to increase or decrease the basal insulin (background insulin) infusion rate

delivered by a continuous subcutaneous insulin infusion pump. Control algorithms are usually hosted on a smart device that allows a person to view their glucose level data, and the data is automatically sent to a portal where clinicians and carers can have access to this information. Setting up the algorithm requires inputting a person's weight and daily insulin dose. In hybrid closed loop systems, there is a need to manually programme bolus insulin for mealtimes, while basal insulin is delivered automatically. Some algorithms allow adjustments for activities such as exercise.

2.2.3 Continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion is delivered through a subcutaneously inserted cannula connected to an external pump with a refillable storage reservoir. The insulin pump can be tethered, where insulin is sent from the pump to the cannula through a tubing, or patch where the pump is attached directly to the skin. Typically, the pump can automatically deliver a basal rate of insulin, however, bolus doses at mealtimes are manually delivered by the push of a button. Continuous subcutaneous insulin infusion pumps can be used as standalone pumps or integrated with continuous glucose monitors and a control algorithm to form a closed loop system.

2.2.4 Hybrid closed loop systems

Minimed 670G

Minimed 670G (Medtronic) is a CE marked hybrid closed loop system that uses a predictive low glucose management technology (SmartGuard), whereby insulin delivery can be suspended in response to predicted hypoglycaemia (within the next 30 minutes) and delivery is automatically resumed once blood glucose levels become normal. In addition, it has an 'Auto mode' function, whereby blood glucose level data measured by the continuous glucose monitor is sent wirelessly to the insulin pump, to enable adjustment of basal insulin every five minutes. The system requires some user interaction to administer mealtime bolus doses. During scoping, the company noted that 670G, launched in 2018, will be withdrawn in the next 12 months and replaced by the 780G which has a more advanced algorithm and bluetooth connectivity. The 670G is not licensed for use in children under 7 years old. The device is also not to be used in persons who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

Minimed 780G

Minimed 780G (Medtronic) is a CE marked hybrid closed loop system launched in 2020. It is intended to achieve a tighter glucose target of 5.5 - 6.1 millimoles per litre compared with the 6.7 millimoles per litre target of the

preceding 670G. In addition to the features of its predecessor system, the 780G has an ‘autocorrection feature’ that delivers correction boluses automatically when sustained hyperglycemia is detected, with minimal need for user or carer interaction. The bluetooth functionality of 780G enables it to connect with the continuous glucose monitor and to the Minimed mobile app, which automatically uploads data to the CareLink connect system to notify carers or for clinician review. The 780G is not licensed for use in children under 7 years or for people who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

Control IQ

The Control-IQ (Tandem Diabetes Care) is a CE marked system that combines t:slimX2 insulin pump and Control-IQ technology. This system can be interlinked with a compatible continuous glucose monitor to form a hybrid closed loop system (see table 1) which suspends insulin delivery in response to predicted hypoglycaemia or gives a correction bolus in response to predicted hyperglycaemia. Control-IQ adjusts basal insulin delivery every five minutes based on glucose data and predicted glucose levels for the next 30 minutes. Mealtime bolus doses are administered manually. Data from Control-IQ can be uploaded on Diasend or Tidepool data cloud for clinician review. Control-IQ is not licensed for use in children under 6 years or for people who require less than a total daily insulin dose of 10 units per day or who weigh less than 55 pounds, as those are the required minimum values needed to operate safely.

CamAPS FX

CamAPS FX (Camdiab) is a CE marked android app developed at the University of Cambridge. The app can be interlinked with a compatible continuous glucose monitor and insulin pump (see table 1) to form a hybrid closed loop system. CamAPS FX can operate on an auto mode ‘off’ whereby basal insulin delivery is pre-programmed by the user or an auto mode ‘on’ where insulin delivery is directed by the app. If the auto mode ‘on’ feature is prevented from coming on, an auto mode ‘attempting’ feature is initiated in which insulin delivery is reverted to pre-programmed basal rates. A bolus dose calculator embedded in the app allows the user to initiate the delivery of mealtime insulin dose. Data from CamAPS FX can be uploaded to the Diasend data cloud, for clinician review. CamAPS FX is licensed for use in people aged 1 year and older and in pregnancy, however, other age restrictions may apply depending on the chosen continuous glucose monitor and insulin pump.

Table 1 Hybrid closed loop systems

System	Compatible CGM (sensor duration) *Manufacturer*	Control algorithm *Manufacturer*	Insulin pump *Manufacturer*	Licensed use - Age	Licensed use - Pregnancy	Number of fingersticks	Customizable glucose target
Minimed 670G	Guardian sensor (3 - 7days) *Medtronic*	Smart Guard *Medtronic*	670G *Medtronic*	≥ 7 years	No	4 to 6 per day	Target 6.7 mmol/L (120 mg/dL) non-customizable (optional exercise target at 8.3 mmol/L,150 mg/dL), correction target 8.3 mmol/L (150 mg/dL)
Minimed 780G	Guardian sensor (3 - 7days) *Medtronic*	Smart Guard *Medtronic*	780G *Medtronic*	≥ 7 years	No	4 to 6 per day*	Target 6.7, 6.1 or 5.5 mmol/L, correction target 6 mmol/L, exercise target 8.3 mmol/L
Control-IQ	Dexcom G6 (10 days) *Dexcom*	Control-IQ *Tandem*	t:slimX2 *Tandem*	≥ 6 years	No	Rarely (factory calibrated)	Target range 6.2– 8.9 mmol/L (112.5–160 mg/dL), sleep range 6.2–6.7 mmol/L (112.5–120 mg/dL), exercise range 7.8–8.9 mmol/L (140–160 mg/dL) Non-customizable
CamAPS FX	Dexcom G6 (10 days) *Dexcom*	CamAPS FX *Camdiab*	Dana RS, Dana-I *Advanced therapeutics*	≥ 1 year	Yes	Rarely (factory calibrated)	Target 5.8 mmol/L (105 mg/dL) customizable between 4.4 and 11 mmol/L (80 and 200 mg/dL). Optional activity target set

Information provided by companies, taken from technology's instruction for use document and Leelarathna et al. 2020. CGM- continuous glucose monitor (combination of sensor and transmitter) mmol/L- millimole per litre, mg/dL – milligram per decilitre *A new factory calibrated sensor will soon be launched.

2.2.5 Alternative technologies

During scoping compatible interoperable devices from the manufacturers highlighted in table 2 were identified. It is likely that some of these interoperable, hybrid closed loop systems may become available in the UK in the near future.

Table 2 Hybrid closed loop systems that may become available in the UK

Continuous glucose monitor	Control algorithm	Insulin pump
Dexcom	Diabeloop	Roche Terumo Kaleido Dana
Dexcom	Lilly	Mylife diabetes
Dexcom Abbott (intermittently scanned continuous glucose monitor)	Omnipod	Omnipod
Dexcom Medtronic	Tidepool	Omnipod Medtronic
Abbott (intermittently scanned continuous glucose monitor)	Bigfoot Biomedical	Bigfoot Biomedical
Dexcom	Beta Bionics	Beta Bionics
To be confirmed	Camdiab	*To be confirmed*

Predictive low glucose management systems

During the scoping workshop, stakeholders noted that predictive low glucose management systems may be an option for people who do not meet the criteria for hybrid closed loop systems. These are earlier versions of automated insulin delivery systems that incorporate continuous glucose sensor data into an algorithm and suspend basal insulin before the occurrence of hypoglycaemia.

Do-it-yourself (DIY) artificial pancreas systems

Several DIY artificial pancreas systems (this includes open-source artificial pancreas systems [openAPS] on a computer, androidAPS and Loop for iphone) are being used by people with type 1 diabetes (Ahmed 2020). The control algorithm for these systems is normally developed by freelance algorithm designers and they usually have no regulatory approval. These algorithms can combine with compatible commercially available continuous

glucose monitors and insulin pumps to form a closed loop system (Kesavadev 2020, Diabetes UK).

3 Target condition

3.1 Type 1 diabetes

Blood glucose (a type of sugar) increases when the carbohydrate in food and drink is digested. Insulin is produced by the pancreas in response to an increase in blood glucose levels to regulate blood glucose levels by signalling the liver, muscle, and fat cells to take up glucose from the blood to be used for energy. As the level of glucose in the blood falls. the amount of insulin produced reduces.

It is estimated that approximately 400,000 people in the UK are living with type1 diabetes, including around 29,000 children. In type 1 diabetes, a person's blood glucose level becomes too high (hyperglycaemia) because there is no, or very little, production of insulin by the pancreas. Blood glucose levels can only be regulated by giving insulin to prevent hyperglycaemia. According to the World Health Organisation, hyperglycaemia is defined as blood glucose levels greater than 7.0 millimoles per litre when fasting and greater than 11.0 millimoles per litre 2 hours after meals. In the short term, hyperglycaemia can cause diabetic ketoacidosis. If type 1 diabetes is not well controlled, patients are at risk of long-term complications of hyperglycaemia including microvascular damage such as retinopathy and blindness, nephropathy, neuropathy and are at increased risk of macrovascular complications such as ischaemic heart disease, stroke and peripheral vascular disease. Poorly controlled type 1 diabetes may also result in gastroparesis, a long-term condition in which food passage through the stomach is slower than usual.

Diabetic ketoacidosis is an acute short-term complication faced by people with type 1 diabetes. It happens when there is insufficient insulin in the body to allow the entry of glucose into cells, consequently, the body breaks down other body tissues, such as fat, rather than glucose for energy. The breakdown of fat leads to the production of a substance known as ketone. The build-up of ketones in the blood is harmful and can be life-threatening because it makes the blood become acidic. The presence of ketones is an early sign of diabetic ketoacidosis. Symptoms of diabetic ketoacidosis include frequent passing of urine, thirst, deep and fast breathing, being sick, blurry vision, tummy pain nausea and vomiting, breath that smells fruity, confusion and unconsciousness or even death. A person with diabetic ketoacidosis may need to be admitted to hospital for the condition to be treated with insulin and

intravenous fluids. Ketone testing and early detection is therefore important in the management of diabetes.

The goal of treatment in type 1 diabetes is to keep blood glucose within a healthy range by providing the body with supplemental insulin. If the level of circulating insulin becomes too high, blood glucose levels can become too low leading to hypoglycaemia (also known as a hypo).

Hypoglycaemia is a common complication in the treatment of type 1 diabetes in which a person's blood glucose is usually below 4 millimoles per litre. In its mild form, hypoglycaemia is commonly characterised by symptoms such as blurred vision, dizziness, fatigue, hunger and sweating and it can be corrected by oral intake of sugars. Severe hypoglycaemia is defined as having low blood glucose levels that requires assistance from another person to treat. Symptoms of severe hypoglycaemia include confusion, intense nightmares, convulsions, coma and death. In children, severe hypoglycaemia can cause long-term cognitive impairment. One study showed that children with type 1 diabetes and recurrent severe hypoglycaemia had lower performance in memory and learning than children with diabetes without severe hypoglycaemia (Blasetti 2011). People with type 1 diabetes and parents of children with type 1 diabetes experience fear of recurrent hypoglycaemia and this decreases quality of life in the short term but can also hinder adherence to treatment and the achievement of good glycaemic control (Lawton 2015).

Night-time hypoglycaemia (nocturnal hypoglycaemia) is hypoglycaemia that occurs during sleep in people who use insulin in the management of type 1 diabetes. Symptoms of nocturnal hypoglycaemia, including headaches upon waking up, tiredness, seemingly unprovoked sleep disturbance and waking up in damp clothes from sweating, are often only realised upon waking up. Death resulting from a nocturnal hypoglycaemia is rare, but it is estimated that nocturnal hypoglycaemia is responsible for 6% of all deaths in people with type 1 diabetes who are under 40 years old (diabetes.co.uk).

People who have had type 1 diabetes for several years or who have frequent hypos may experience hypoglycaemia unawareness, a situation in which symptoms of hypoglycaemia are not noticed. Loss of hypo awareness is dangerous because people can go into severe hypoglycaemia without recognizing early warning signs.

Type 1 diabetes in pregnancy

Type 1 diabetes in pregnancy is linked to an increased risk of foetal complications such as still birth, neonatal death, malformation and foetal macrosomia (infant large for gestational age) and maternal complications

such as preeclampsia and delivery by caesarean section (Person 2009). It is estimated that around 5% of the nearly 700,000 women who give birth in England and Wales each year have either pre-existing diabetes or gestational diabetes. It is estimated that 87.5% of women who have diabetes during pregnancy have gestational diabetes and 7.5% have type 1 diabetes. Gestational diabetes commonly occurs in the second and third trimester and it may or may not resolve after giving birth.

Pregnant women with long duration type 1 diabetes are at risk of microvascular complications (retinopathy, nephropathy and neuropathy) and are more likely to have absolute or relative hypoglycaemia unawareness which makes them more vulnerable to episodes of hypoglycaemia.

3.2 Diagnostic and care pathway

The management of type 1 diabetes has several components and typically involves lifestyle adjustments, regular measuring of blood glucose levels, use of multiple daily insulin injections or continuous subcutaneous insulin infusion and periodic assessment of blood glucose control. In addition, ketone testing is undertaken if a person has sustained high blood glucose levels.

The levels of glucose in the blood may vary widely during a 24-hour period and from day to day in a person with diabetes. In the management of diabetes, glycaemic control is assessed by measuring blood glucose levels as well as by measuring HbA1c levels. Blood glucose measurements are taken after several hours of fast, usually in the morning before breakfast (fasting blood glucose level), before a meal (pre-prandial blood glucose level) and at least 90 minutes after a meal (post-prandial blood glucose level) to measure the change in glucose concentration. Blood glucose is measured in 3 ways:

a) Firstly, blood glucose can be checked at any time by testing a drop of blood with a glucose meter (capillary blood glucose testing) also known as self-monitoring of blood glucose.

b) Secondly, continuous or intermittent glucose monitors provide frequent automated testing of interstitial fluid glucose, calibrated to reflect blood plasma glucose.

c) Thirdly, longer-term control is measured by HbA1c, which reflects the average blood glucose levels over 2 to 3 months.

3.2.1 Self-monitoring of blood glucose by capillary blood glucose devices

Self-monitoring of blood glucose is an integral part of therapy in diabetes treated with insulin, it involves the measurement of blood glucose concentration by people with diabetes or their carer using self-monitoring devices such as test strips.

Capillary blood glucose monitoring involves pricking a part of the body (usually the finger) with a lancet device to obtain a small blood sample at certain times of the day. The drop of blood is then applied to a test strip which is inserted into a blood glucose meter for automated determination of the glucose concentration in the blood sample at the time of the test.

The care pathways for monitoring blood glucose for children and adults are outlined in NICE's guidelines on diabetes (type 1 and type 2) in children and young people, type 1 diabetes in adults and diabetes in pregnancy.

3.2.2 Continuous and intermittent glucose monitoring

Continuous glucose monitoring generates an average glucose value every few minutes throughout the day by measuring interstitial fluid glucose levels. Real time glucose level measurements can be sent wirelessly from the monitor to a display device (see section 2.2.1 for further details). NICE guideline on diabetes (type 1 and type 2) in children and young people recommends continuous glucose monitors with alarms for children and young people who have frequent severe hypoglycaemia or impaired hypoglycaemia awareness or who cannot recognise or communicate symptoms of hypoglycaemia.

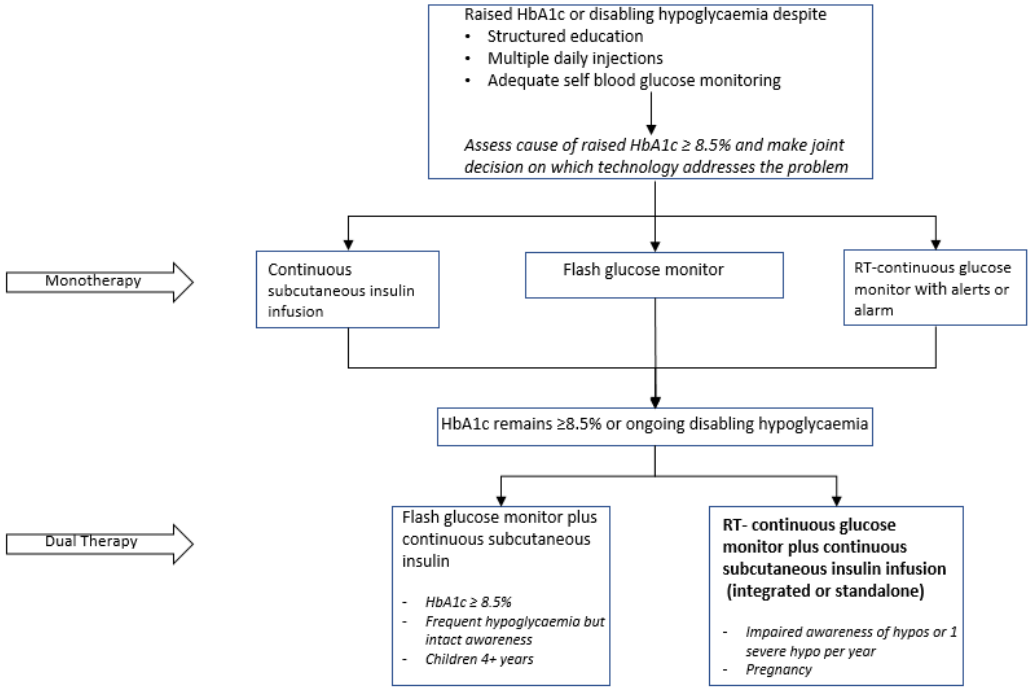
Intermittently scanned continuous glucose monitors, for example flash glucose monitors, automatically monitor interstitial fluid glucose levels throughout the day and night but give glucose readings only when the sensor has been scanned. Intermittently scanned glucose monitoring involves wearing a sensor just under the skin (usually in the upper arm). A sensor can be used for several days. A reader or a mobile device with the appropriate app installed can be used to scan the sensor to obtain glucose readings. The monitor has no alarm so does not give alerts for low or high glucose levels. Intermittently scanned (Flash) glucose monitors became available on the NHS in April 2019 for people with type 1 diabetes. The NHS has published flash glucose monitoring guidelines and set out patient criteria (annex A) for the reimbursement by Clinical Commissioning Groups (CCGs) for the ongoing cost of flash glucose sensors including:

> *"For those with Type 1 diabetes and recurrent severe hypoglycemia or impaired awareness of hypoglycemia, NICE suggests that Continuous Glucose Monitoring with an alarm is the standard. Other evidence-based alternatives with NICE guidance or NICE TA support are pump therapy, psychological support, structured education, islet transplantation and whole pancreas transplantation. However, if the person with diabetes and their clinician consider that a Flash Glucose Monitoring system would be more appropriate for the individual's specific situation, then this can be considered."*

NICE's guideline on diabetes in pregnancy (December 2020 update) recommends continuous glucose monitoring for all pregnant women with type 1 diabetes to help meet their pregnancy blood glucose targets and to improve neonatal outcomes. The guideline recommends intermittently scanned glucose monitoring for pregnant women with type 1 diabetes who are unable to use continuous glucose monitoring or express a clear preference for it.

Diabetes UK has published a position statement on the appropriate use of technology in type 1 diabetes (Choudhary 2019). The statement notes that if blood glucose targets are not met despite optimized use of multiple daily insulin injections and adequate capillary glucose monitoring, then continuous subcutaneous insulin or intermittently scanned glucose monitoring or continuous glucose monitoring should be considered as monotherapy for people with raised HbA1c ≥8.5% or disabling hypoglycaemia. If monotherapy does not improve outcomes or improves outcomes but personalized glucose targets are not met, dual therapy combining continuous subcutaneous insulin infusion with flash glucose monitoring or continuous glucose monitoring should be considered (figure 1).

Figure 1 Technology care pathway for type 1 diabetes



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

3.2.3 Measurement of glycated haemoglobin (HbA1c) levels

Glycated haemoglobin level is an objective measure of glycaemic control, which reflects average plasma glucose over the preceding 3 months. HbA1c has been shown to be strongly correlated to continuous glucose monitoring results over the preceding 8 to 12 weeks (Nathan 2007). NICE guidelines on diabetes (type 1 and type 2) in children and young people, type 1 diabetes in adults and diabetes in pregnancy recommend that people with type 1 diabetes should aim for a target HbA1c level of 48 millimoles per mole (6.5%) or lower to minimise the risk of long term complications from diabetes. HbA1c as a surrogate measure of glycaemic control, has been reported to have several limitations including, not being able to characterise daily fluctuations in glucose levels and inaccuracy in reflecting mean blood glucose levels (Cox 2002, Shrom 2010).

3.2.4 Measurement of time in range

Time in range is a measure of glycaemic control which shows the percentage of time a person spends within a target glucose range. It is obtained from continuous glucose monitor data and gives an idea of changes in glucose patterns within a day and between days. The international consensus on time

in range recommends a time in range of at least 70% in a glucose range of 3.9 – 10 millimoles per litre for people with type 1 diabetes and a tighter glucose range of 3.5 – 7.8 millimoles per litre, in pregnancy (Battelino et al. 2019). Time in range is correlated to HbA1c, and it has been reported that people who spend less time in range are more likely to develop microvascular complications (Beck 2019). Time below range (percentage of time between 3.0 - 3.9 millimoles per litre) is associated with increased risk of severe hypoglycaemia, while time above range (percentage of time between 10 - 13.9mmol/l) may indicate a risk of ketoacidosis.

3.2.5 Ketone testing

Early detection of ketones in the blood allows prompt action to be taken and prevents a person from developing diabetic ketoacidosis. Ketone testing is useful if a person has sustained high blood sugar readings which can often occur during periods of illness and when there is difficulty in controlling glucose levels.

Ketone testing involves measuring the amount of ketones in either urine or blood. Blood ketone testing gives real time results and is thought to be more accurate than urine testing because of a time lag in ketone levels in urine. Moreover, the accuracy of urine testing may be affected by medication and the amount of liquid a person drinks. Dilute urine can lead to false negatives and if the person is dehydrated, a falsely high ketone measurement. NICE guidelines on diabetes (type 1 and type 2) in children and young people, type 1 diabetes in adults and diabetes in pregnancy recommend ketone testing for people with type 1 diabetes.

3.2.6 Insulin therapy

Blood glucose control in type 1 diabetes is achieved by insulin injection. There are various types of insulin, distinguished by their rate of onset and duration of action, that can be combined into different regimens depending on a person's individual needs. Insulin therapy can be delivered by multiple daily insulin injections or by continuous subcutaneous insulin infusion using an insulin pump. NICE guidelines on diabetes (type 1 and type 2) in children and young people, type 1 diabetes in adults and diabetes in pregnancy outline the care pathway for insulin therapy.

NICE's technology appraisal on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus recommends continuous subcutaneous insulin infusion therapy for adults and children over 12 years with type 1 diabetes if attempts to achieve target HbA1c levels with multiple daily injections result in disabling hypoglycaemia or HbA1c levels have remained

high despite a high level of care. In the guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life. The guidance also recommends the use of continuous subcutaneous insulin infusion in children below age 12 where multiple daily injection therapy is considered impractical or inappropriate.

NICE's diagnostic guidance (DG21) on Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes recommends the MiniMed Paradigm Veo system as an option for managing blood glucose levels in people with type 1 diabetes only if they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion.

3.3 Patient issues and preferences

Diabetes is a lifelong condition that significantly affects quality of life. Daily life activities need to be arranged around a relatively rigid structure of mealtimes and insulin therapy. Optimal glucose control may be difficult to maintain because many factors can cause fluctuations in glucose levels, for example activities associated with stress, diet and physical exercise. With increasing duration of illness and the onset of complications, people with diabetes and their carers may experience occupational difficulties, and children may experience difficulties in school performance.

A major challenge for children and adolescents living with diabetes is that they often feel different from their peers. Time spent on clinic visits and managing the condition could result in missed work days for parents and school days for children. Parents of children with diabetes frequently have intense parental anxiety and stress because of the persistent nature of the disease (Lawton 2015). The burden on carers of children with diabetes who are under 12 years old can be high and can substantially impact on their quality of life. Nocturnal hypoglycaemia, particularly, can cause substantial anxiety for parents and may result in them becoming sleep deprived because they stay up all night to monitor their children's glucose levels. Parents and carers of children with diabetes are more likely to seek psychological support for their wellbeing.

People with diabetes also report that the requirement from the Driver and Vehicle Licensing Agency to test glucose levels before driving results in having to perform many additional capillary blood glucose tests, particularly for those in occupations that involve driving. The fear of losing a driving licence may also dissuade a person with diabetes from reporting a hypoglycaemic episode which may mean that the number of episodes of

hypoglycaemia in people with diabetes may be underestimated. If a person experiences hypoglycaemia (glucose levels lower than 3.9 millimoles per litre) when driving, they will have to wait for their glucose level to rise to around 5 millimoles per litre before they can continue driving.

Hybrid closed loop systems may offer improvement in quality of life and mental well-being for people with type 1 diabetes and their carer because the use of technology may reduce the stress that comes with carbohydrate counting, multiple daily insulin injections, self-monitoring of blood glucose, nocturnal hypoglycaemia and sleep deprivation. In addition, a technology that prevents hypoglycaemia may be useful for people with type 1 diabetes whose occupation involves driving.

Patient issues related to closed loop systems include potential difficulty in managing software updates or glitches, security of data, concerns about whether the system can be hacked, frequent exit from auto mode, alarm fatigue and scarring of the skin or allergies from prolonged wearing of sensors. Some people may have a strong preference against wearing devices or using automated technologies or may consider them an added burden, because of the amount of data the systems generate that takes time to be reviewed. People who have limited understanding of English language may have difficulty understanding how to use technology and how to interpret the data.

Older people may choose to remain only on pumps as their cognitive function declines. Children and people with cognitive impairment may need a carer to control the system.

4 Comparators

In UK clinical practice, people who may require hybrid closed loop systems to manage their blood glucose levels may currently use other technologies either individually or combined.

People who are having difficulty maintaining HbA1c of 6.5% or below, or spend less than 70% of time in a glucose range of 3.9 – 10 millimoles per litre, or who have ongoing disabling hypoglycaemia, mainly use the following technologies:

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

In some cases, glucose targets may be achieved using:

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

Children, 5 years and under, are unlikely to use intermittently scanned glucose monitors.

5 Scope of the assessment

Table 3 Scope of the assessment

Decision question	Does the use of hybrid closed loop systems for managing glucose levels in type 1 diabetes represent a clinically and cost-effective use of NHS resources?
Populations	People with type 1 diabetes who are having difficulty managing their condition. These difficulties may include: - not maintaining HbA1c levels of 6.5% or below or - not maintaining at least 70% time in range of 3.9 -10 mmol/l or - ongoing disabling hypoglycaemia If evidence permits the following subpopulations should be included: • Women with type 1 diabetes who are pregnant and those planning pregnancy (not including gestational diabetes) • Children with type 1 diabetes. If possible, evidence should be analysed based on the following age groups: - 5 years and under - 6 - 11 years - 12 -19 years • People with extreme fear of hypoglycaemia • People with diabetes related complications that are at risk of deterioration
Intervention	Hybrid closed loop systems
Comparators	• Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated) • Intermittently scanned glucose monitoring with continuous subcutaneous insulin infusion

	Where evidence permits scenarios assessing the following comparators should be presented for women with type 1 diabetes who are pregnant and those planning pregnancy: • Real time continuous glucose monitoring with multiple daily insulin injections • Intermittently scanned glucose monitoring with multiple daily insulin injections • Self blood glucose monitoring with continuous subcutaneous insulin infusion
Healthcare setting	Self-use supervised by primary or secondary care
Outcomes	Intermediate measures for consideration may include: • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below target range • Time above target range • Change in HbA1c • Rate of glycaemic variability • Fear of hypoglycaemia • Rate of severe hypoglycaemic events • Rate of severe hyperglycaemic events • Episodes of diabetic ketoacidosis • Rate of ambulance call outs • Rate of hospital out-patient visits • Rate of weight gain
	Clinical outcomes for consideration may include: • Long term complications of diabetes and treatment including retinopathy, neuropathy, cognitive impairment and end stage renal disease. • Increased risk of cardiovascular disease • Mortality In pregnant women, additional type 1 diabetes-related clinical outcomes may include: • Premature birth • Miscarriage related to fetal abnormality • Increased proportion of babies delivered by caesarean section • Macrosomia (excessive birth weight) • Respiratory distress syndrome in the new-born Device related outcomes for consideration may include:

	• Adverse events related to the use of devices
	Patient-reported outcomes for consideration may include: • Heath related quality of life • Psychological well being • Impact on patient (time spent managing the condition, time spent off work or school, ability to participate in daily life, time spent at clinics, impact on sleep) • Anxiety about experiencing hypoglycaemia • Acceptability of testing and method of insulin administration Carer reported outcomes for consideration may include: • Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of technology • Cost of consumables (glucose testing strips, sensors, infusion sets, ketone testing strip) • Cost of insulin • Cost of hypoglycaemic events • Cost of diabetic ketoacidiosis • Cost of longer-term complications • Cost of follow up (for example, clinical appointments) • Cost of unscheduled contact (for example with diabetes specialist nurse, A and E etc) • Cost of training, education and ongoing support
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

In DG21 the IMS CORE diabetes model (IQVIA CORE diabetes model) was used to assess the cost effectiveness of MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system in a cohort of adults with type 1 diabetes for a time horizon of 80 years. The model comprises 17 interdependent Markov sub-models that represent the most common diabetes

related complications such as stroke, peripheral vascular disease, diabetic retinopathy, hypoglycaemia and ketoacidosis. A model limitation highlighted in the original guidance was that the model did not adequately capture short term outcomes associated with hypoglycaemia. There are other models that can be used to assess the cost effectiveness of technologies for diabetes, including some specifically for type 1 diabetes, for example the Sheffield type 1 diabetes policy model.

The landscape of technologies used for the management of type 1 diabetes is rapidly advancing with several technologies being superseded by newer technologies. Most technologies appear to have a life span of around 2 to 3 years before they are superseded or replaced.

7 Potential equality issues

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

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

8 Potential implementation issues

A variation in funding arrangements across Clinical Commissioning groups for continuous glucose monitoring technologies may lead to unequal access to technologies for type 1 diabetes. It has been reported that many Clinical Commissioning groups do not have a policy for funding continuous glucose monitoring technologies or have a blanket ban to refuse funding (Choudhary 2019). In addition, some systems are not licensed in certain groups which may limit their options.

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

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

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

9 Authors

Tosin Oladapo
Topic Lead

Frances Nixon
Technical Adviser

March 2021

Appendix A Glossary of terms

Foetal macrosomia	A term used to describe newborn who is larger than the average
Interstitial fluid	The fluid between cell tissues, which act as link between the blood and the cells
Nephropathy	A complication that leads to the deterioration of normal functioning kidneys
Neuropathy	A condition in which nerves are damaged
Pre-eclampsia	A condition associated with pregnancy, in which a person has high blood pressure and possibly protein in their urine
Retinopathy	A disease that damages the retina (back of the eye)
Subcutaneous	Under the skin

Appendix B Abbreviations

DIY	Do it yourself
HbA1c	Glycated haemoglobin
APS	Artificial pancreas system
CCG	Clinical commissioning groups

Appendix C References

Ahmed, S. H., Ewins, D. L., Bridges, J., Timmis, A., Payne, N., Mooney, C., & MacGregor, C. (2020). Do-It-Yourself (DIY) Artificial Pancreas Systems for Type 1 Diabetes: Perspectives of Two Adult Users, Parent of a User and Healthcare Professionals. Advances in Therapy, 37(9), 3929-3941.

Akturk HK, Giordano D, Champakanath A, Brackett S, Garg S, Snell-Bergeon J. Long-term real-life glycaemic outcomes with a hybrid closed-loop system compared with sensor-augmented pump therapy in patients with type 1 diabetes. Diabetes Obes Metab. 2020 Apr;22(4):583-589.

Battelino, T., Danne, T., Bergenstal, R.M., Amiel, S.A., Beck, R., Biester, T., Bosi, E., Buckingham, B.A., Cefalu, W.T., Close, K.L. and Cobelli, C., 2019. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes care, 42(8), pp.1593-1603.

Bally, L., Thabit, H., Hartnell, S., Andereggen, E., Ruan, Y., Wilinska, M. E., ... & Hovorka, R. (2018). Closed-loop insulin delivery for glycemic control in noncritical care. New England Journal of Medicine, 379(6), 547-556.

Beck, R.W., Bergenstal, R.M., Riddlesworth, T.D., Kollman, C., Li, Z., Brown, A.S. and Close, K.L., 2019. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care, 42(3), pp.400-405.

Blasetti, A., Chiuri, R. M., Tocco, A. M., Giulio, C. D., Mattei, P. A., Ballone, E., ... & Verrotti, A. (2011). The effect of recurrent severe hypoglycemia on cognitive performance in children with type 1 diabetes: a meta-analysis. Journal of child neurology, 26(11), 1383-1391.

Boughton, C. K., Bally, L., Martignoni, F., Hartnell, S., Herzig, D., Vogt, A., ... & Hovorka, R. (2019). Fully closed-loop insulin delivery in inpatients receiving nutritional support: a two-centre, open-label, randomised controlled trial. The Lancet Diabetes & Endocrinology, 7(5), 368-377.

Cox, D., Gonder-Frederick, L., McCall, A., Kovatchev, B. and Clarke, W., 2002. The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes. International journal of clinical practice. Supplement, (129), pp.20-26.

Choudhary, P., Campbell, F., Joule, N., Kar, P., & Diabetes UK. (2019). A type 1 diabetes technology pathway: consensus statement for the use of technology in type 1 diabetes. Diabetic Medicine, 36(5), 531-538.

Diabetes UK https://www.diabetes.org.uk/professionals/position-statements-reports/do-it-yourself-closed-loop

Diabetes UK https://www.diabetes.org.uk/professionals/position-statements-reports/statistics

Kesavadev, J., Srinivasan, S., Saboo, B. et al. The Do-It-Yourself Artificial Pancreas: A Comprehensive Review. Diabetes Ther 11, 1217–1235 (2020).

Lawton J, Waugh N, Barnard KD, Noyes K, Harden J, Stephen J, McDowell J, Rankin D. Challenges of optimizing glycaemic control in children with Type 1 diabetes: a qualitative study of parents' experiences and views. Diabet Med. 2015 Aug;32(8):1063-70. doi: 10.1111/dme.12660. Epub 2014 Dec 30. PMID: 25472898.

Leelarathna, L., Choudhary, P., Wilmot, E. G., Lumb, A., Street, T., Kar, P., & Ng, S. M. (2020). Hybrid closed-loop therapy: Where are we in 2021?. Diabetes, Obesity and Metabolism.

Nathan, D.M., Turgeon, H. & Regan, S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 50, 2239–2244 (2007).

Persson, M., Norman, M., & Hanson, U. (2009). Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diabetes care, 32(11), 2005-2009.

Shrom, D., Sarwat, S., Ilag, L. and Bloomgarden, Z.T., 2010. Does A1c consistently reflect mean plasma glucose?. Journal of diabetes, 2(2), pp.92-96.