

Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – final protocol

Title of project

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

Name of External Assessment Group (EAG) and project lead

Produced by: Warwick Evidence

Authors: Mary Jordan
Lena Alkhudairy
Karoline Freeman
Felix Achana
Anna Brown
Sharin Baldwin
Fatai Ogunlayi
Norman Waugh
Sian Taylor-Phillips
Tim Omer
Ambika Karthikeyan
Chris Stinton

Correspondence to: Dr Lena Al-Khudairy
Associate Professor

Date completed: 10.03.22

The views expressed in this protocol are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors. The authors have no conflicts of interest.

Glossary of terms

CEAC	Cost effectiveness acceptability curve
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion (insulin pump)
DKA	Diabetic ketoacidosis
HbA1c	Haemoglobin A1c or glycated haemoglobin
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
MDI	Multiple daily injections
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
T1DM	Type 1 diabetes mellitus
QALY	Quality adjusted life year

1. Plain English Summary

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

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

Management of Type 1 Diabetes

Management of Type 1 Diabetes is done via lifestyle adjustments and reviewing multiple sources of data about the individual to help calculate the amount of insulin to deliver. This commonly covers the following:

- *Lifestyle*
 - A balanced diet including complex carbohydrates, fats and proteins avoiding processed food slows the impact of food on blood glucose level reducing the possibility of sudden high or lows.
 - Exercise improves the body's sensitivity to insulin, therefore, reducing the amount to be injected. This can reduce the possibility of unexpected sudden blood glucose changes that a larger dose of insulin may bring, as well as general well-being in reducing stress that can cause insulin resistance.
- *Data*
 - Patients' understanding and monitoring their bodies reaction to insulin and foods to calculate their sensitivity to insulin and carbohydrates.
 - Monitoring of blood glucose levels via “finger pricks” where the individual draws a small amount of blood to get a point in time reading or continuous glucose monitors that provide a real-time reading of blood glucose.
- *Insulin Delivery*
 - Via daily injections or insulin pump that is connected to the body 24/7. Injections can be of rapid acting insulins that take effect within a short time frame (bolus) and long-

acting insulins that release over a 12-to-24 hour period providing an amount of background insulin in the body (basal). Insulin pumps provide rapid acting insulin with the ability to deliver complex bolus quickly and easily and continuous background basal delivery that can be precisely adjusted for example every 5 minutes to form a unique 24-hour profile for the individual.

Processing of this information and deciding the best action is an ongoing challenge for the individual, example of such challenges:

- Diet: Poor diet education, cost of access to fresh food and the challenge of avoiding easily accessible cheap highly processed foods.
- Exercise: Lifestyle habits and motivation to exercise, along with the management of changes to insulin sensitivity while and after exercise.
- Insulin Delivery: The inconvenience of injections and their limited control of insulin delivery, Pumps with an overwhelming number of options for consideration.
- Blood Glucose Monitoring: Uncomfortable and limited visibility of trend provided by manual blood glucose tests, continuous glucose monitors providing an overwhelming amount of real-time data for the individual to process.
- Alarm fatigue: Frustration of alarms informing the individual of high or low blood glucose and lack of proactive information to help prevent such events.
- Overtreatment: Miscalculation, frustration or unexpected sensitivity/resistance to Insulin that can result in multiple highs and lows within a short timeframe.
- Changes in sensitivity to insulin, food and many other factors that change over time and day to day.

Hybrid closed loop systems

Hybrid closed loop systems provide a control algorithm that reviews data, along with reviewing the impact of its past actions, and actioning minor frequent adjustments of insulin delivery to managing blood glucose levels. The system is proactive versus reactive with the information that is provided and can make calculations and actions by utilising the real-time feed of data provided by a continuous glucose monitor and a high level of controlled delivery offered by an insulin pump at a frequency that is unattainable by a human being. As a result, such systems can significantly reduce the burden on the patient by supporting them with handling the volume of data and technology available in the management of their condition with intervention only when needed.

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

2. Decision problem

2.1 Purpose of the decision to be made

Type 1 diabetes mellitus (T1DM) is the result of an autoimmune process leading to destruction of insulin-producing beta cells in the pancreas. This causes high blood glucose levels (hyperglycaemia), which needs to be treated with injected insulin to lower blood glucose. The aim of insulin treatment is to keep plasma glucose within the normal range and so prevent the development of complications of diabetes such as retinopathy, nephropathy, and neuropathy. However, insulin treatment can cause abnormally low glucose (hypoglycaemia). Hypoglycaemia is characterised by symptoms such as blurred vision, fatigue, and sweating. Severe hypoglycaemia can lead to confusion, unconsciousness, and convulsions, and can be fatal.

Good control of plasma glucose requires regular monitoring of blood glucose levels either by finger prick tests or continuous blood glucose monitors (CGM) to adjust insulin levels accordingly.

Glycaemic control is also assessed using glycated haemoglobin, HbA1c, which reflects average blood glucose levels over 2-3 months. For people with poor glycaemic control, continuous subcutaneous insulin infusion (CSII or 'insulin pump') therapy is recommended as a treatment option for adults and children 12 years and older, or for children under 12 if multiple daily insulin injections are impractical or not appropriate (NICE guidance [TA151]). Integrated sensor-augmented pump therapy systems (which combined glucose monitors with insulin pumps) are recommended as an option for managing blood glucose levels only for people with T1DM who have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion (NICE DG21). The MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM integrated sensor-augmented insulin pump systems assessed in DG21 are no longer available on the NHS for new patients. New systems (hybrid closed loop systems) are available in which the glucose monitor communicates with the insulin pump via a control algorithm to adjust insulin levels. These have been reported to help patients to keep their glucose levels within a healthy range and reduce the number of hyper- and hypoglycaemic events, which may prevent the long-term complications of T1DM.

The External Assessment Group (EAG) will evaluate these hybrid close loop systems in terms of their clinical and cost-effectiveness in managing T1DM.

2.2 Population and target condition

People with Type 1 diabetes

There are about 400,000 people with T1DM in the UK, including around 29,000 children.¹ T1DM usually presents in late childhood or early adolescence, but can occur at any age. The highest incidence observed is in children aged 10-14 years.² Around half of newly diagnosed cases of T1DM

are in people over the age of 18. Risk factors for T1DM include genetic predisposition and environmental factors. However, the findings on the possible risk factors of T1DM are inconsistent.

T1DM develops due to destruction of pancreatic beta cells. When 80% to 90% of beta cells have been destroyed, hyperglycaemia develops.² Long-term hyperglycaemia contributes to microvascular and macrovascular complications. Untreated T1DM causes death due to diabetic ketoacidosis. Poorly controlled T1DM is a risk factor for chronic complications such as blindness, renal failure, foot amputations, heart attacks, strokes, and enhanced morbidity and mortality from infectious diseases (both viral and bacterial). Intensive glycaemic control with insulin has been shown to reduce rates of some types of microvascular and macrovascular complications.²⁻⁴ If the level of circulating insulin becomes too high, blood glucose levels can become too low leading to hypoglycaemia.

Hypoglycaemia is a common complication in the treatment of T1DM, presenting in its mild form as blurred vision, dizziness, fatigue, hunger and sweating. It can be corrected by oral intake of glucose. Symptoms and complications of severe hypoglycaemia require assistance from another person. In children, severe hypoglycaemia might be associated with long-term cognitive impairment.⁵

People who have had T1DM for several years or who have frequent hypoglycaemia may experience hypoglycaemia unawareness, in which symptoms of hypoglycaemia are not noticed. Loss of hypoglycaemic awareness is dangerous because people can go into severe hypoglycaemia without recognizing early warning signs.

T1DM 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.⁶

2.3 Interventions

The intervention of interest is a class of automated insulin delivery systems which consists of three components – a CGM, a microprocessor with control algorithms, and a pump. The microprocessor receives data from the CGM and adjusts the infusion rate from the pump, to help keep glucose levels in a healthy range. These systems are aimed at reducing user or caregiver input in insulin dosing. The systems are called hybrid closed loop systems and only require users to deliver meal boluses by entering the estimated amount of carbohydrates for meals at the time they are eaten.

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

representative of the intervention of interest and have been identified by NICE as currently available in the UK.

2.3.1 MiniMed 670G

MiniMed 670G (Medtronic) is a CE marked hybrid closed loop system that uses a control algorithm called SmartGuard. SmartGuard technology has a manual mode and an auto mode. In manual mode, the 670G works just like other sensor-augmented pump systems. In auto-mode function, blood glucose level data measured by the CGM (Guardian sensor) is sent wirelessly to the insulin pump (670G), to enable adjustment of basal insulin every five minutes to maintain sensor glucose levels near a target glucose of 120 mg/dL (6.7 mmol/L). The system requires some user interaction to administer mealtime bolus doses. The 670G is not licensed for use in children under 7 years old. The device is also not to be used in people who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

2.3.2 MiniMed 780G

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

2.3.3 Control IQ

The Control-IQ (Tandem Diabetes Care) is a CE marked system that combines t:slimX2 insulin pump and Control-IQ technology. This system can be interlinked with a compatible CGM to form a hybrid closed loop system which suspends insulin delivery in response to predicted hypoglycaemia, or gives a correction bolus in response to predicted hyperglycaemia. Control-IQ has 6 settings, including optional settings for sleep and exercise, to adjust basal insulin delivery depending on user need. Mealtime bolus doses are administered manually. Data from Control-IQ can be uploaded on 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.

2.3.4 CamAPS FX

CamAPS FX (Camdiab) is a CE marked android app developed at the University of Cambridge. The app can be interlinked with a compatible CGM (Dexcom G6) and insulin pump (Dana RS or Dana-I) to form a hybrid closed loop system. CamAPS FX can operate on an auto mode ‘off’ whereby basal insulin delivery is pre-programmed by the user or an auto mode ‘on’ where insulin delivery is directed by the app. In auto mode on, a bolus dose calculator embedded in the app allows the user to initiate the delivery of mealtime insulin dose. If the auto mode ‘on’ feature is prevented from coming on, an auto mode ‘attempting’ feature is initiated in which insulin delivery is reverted to pre-programmed basal rates. Data from CamAPS FX can be uploaded to the Diasend data cloud, for clinician review. CamAPS FX is licensed for use in people aged 1 year and older and in pregnancy, however, other age restrictions may apply depending on the chosen CGM and insulin pump.

2.4 Care pathway

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

NICE guidelines recommend that adult and pregnant women with T1DM should be empowered to self-monitor their blood glucose, supported by structured education packages (e.g., Dose Adjustment for Normal Eating) on how to measure glucose levels and interpret the results. NICE also recommends that children and young people with T1DM and their families or carers should be offered a continuing programme of education from diagnosis. Several systems of monitoring glucose levels and delivering insulin are available in clinical practice. The system recommended for individuals is based on the individual’s age, whether they are pregnant, their glycaemic control, and personal preferences (Figure 1).

Management of type 1 diabetes mellitus (T1DM)			
Education and Information NICE guidelines recommend that all people with T1DM should be offered continuing programme of education from diagnosis			
Glucose monitoring to obtain information on blood glucose levels and ensure a therapeutic insulin regimen			
Glucose monitoring	Finger-prick capillary blood glucose monitoring	Real-time continuous glucose monitoring (rtCGM) using a sensor, transmitter and display device	Flash glucose monitoring using a sensor and scanner
	NICE recommends routine monitoring of blood glucose levels at fingertips for all adults, children and young people and pregnant women with T1DM as first line management together with MDI.	NICE recommends automated rtCGM with alarms (low or high glucose level warnings) for: <ul style="list-style-type: none"> adults with T1DM when standard management of blood glucose levels has not worked resulting in poor glycaemic control with severe hypoglycaemia or impaired hypoglycaemia awareness pregnant women with T1DM children and young people with T1DM, for specific indications 	NICE recommends intermittently scanned CGM (flash monitoring) without alarms to pregnant women with T1DM who are unable to use rtCGM or express a clear preference for it. NICE guidelines for adults, children and young people does not comment on the use of flash glucose monitoring.
Insulin regimen to achieve glycaemic control (measured as glycated haemoglobin levels) in order to minimize the risk of chronic diabetes complications			
Insulin regimen	Multiple daily insulin injections (MDI)	Continuous subcutaneous insulin infusion (CSII)	
	NICE recommends MDI insulin regimens as the insulin injection regimen of choice for all adults, children and young people with T1DM.	NICE recommends CSII for: <ul style="list-style-type: none"> adults and children 12 years and older with T1DM provided that they have not been able to reach target glycated haemoglobin levels with MDI or have disabling hypoglycaemia children younger than 12 years with T1DM if MDI therapy is considered to be impractical or inappropriate pregnant women with insulin-treated diabetes who are using MDI and do not achieve blood glucose control without significant disabling hypoglycaemia 	
Integrated sensor-augmented pump therapy systems (SAP) Using a CGM which "talks to" the pump to automatically suspend insulin rate when blood glucose levels are dropping			
Integrated	NICE recommends SAP as an option but not routinely for adults and children 12 years and older with T1DM provided that they have not been able to reach target glycated haemoglobin and have episodes of disabling hypoglycaemia despite optimal management with CSII. People who have started using the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained.		

Figure 1. Management of type 1 diabetes mellitus

2.4.1 Blood glucose monitoring

Capillary blood glucose monitoring

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

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

Real time continuous blood glucose measurement (rtCGM)

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

A rtCGM system comprises three parts:

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

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

NICE does not recommend offering rtCGM routinely to adults with T1DM. Instead, rtCGM with an alarm should be considered for adults with T1DM for whom standard management of blood glucose levels has not worked or been difficult, i.e., those with recurrent severe hypoglycaemia or impaired

awareness of hypoglycaemia. The users must also be willing to commit to using the technology at least 70% of the time and to calibrate it as needed. For children and young people with T1DM, NICE recommends that ongoing rtCGM with alarms should be offered to those who continue to have severe hypoglycaemia or impaired hypoglycaemia awareness, or those who are not able to recognise or communicate symptoms of hypoglycaemia. The NICE recommendation is to offer rtCGM to all pregnant women with T1DM to help them meet their pregnancy blood glucose targets and improve neonatal outcomes.

Flash glucose monitoring

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

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

HbA1c

Longer-term control is measured by glycated haemoglobin levels (HbA1c), which reflects the average blood glucose levels over 2 to 3 months. HbA1c is correlated to CGM results over the preceding 8-to-12 weeks.⁷ NICE guidelines on diabetes (type 1 and type 2) in children and young people, adults, and diabetes in pregnancy recommend that people with T1DM should aim for a target HbA1c level of 6.5% (48 mmol/mol) or lower to minimise the risk of long term complications from diabetes. Poor glycaemic control may trigger a discussion about different options for insulin administration.

2.4.2 Insulin regimens

Multiple daily injections

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

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

Continuous subcutaneous insulin infusion

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

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

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

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

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

Integrated sensor-augmented pump therapy systems

Integrated sensor-augmented pump therapy systems combine rtCGM with CSII. The systems are designed to measure interstitial glucose levels (every few minutes) and allow immediate real-time adjustment of insulin therapy. The systems may produce alerts if the glucose levels become too high or too low. NICE's diagnostic guidance (DG21) on integrated sensor-augmented pump therapy systems for managing blood glucose levels in T1DM recommends the MiniMed Paradigm Veo system as an option for managing blood glucose levels in people with T1DM only if they have episodes of disabling hypoglycaemia despite optimal management with CSII. As with other pumps the user can program one or more basal rate settings for different times of the day/night. A built-in bolus calculator works out how much insulin is needed for a meal following the input of

carbohydrates consumed. The advanced feature of sensor-augmented pump is that the rtCGM – patient – pump loop is augmented by direct communication between the rtCGM device and the pump. If blood glucose is falling too low, the rtCGM device communicates with the pump and automatically switches off (suspends) the insulin infusions. Depending on the device, the user either must restart insulin delivery or the pump resumes insulin delivery after 2 hours.

3. Decision questions and objectives

3.1 Decision questions

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

Key question 1

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

Sub questions

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

continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring?

Key question 2

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

Sub questions

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

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

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

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

4. Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Cochrane Handbook of Diagnostic Test Accuracy⁸ and the NICE Diagnostic Assessment Programme manual.⁹

4.1 Identification and selection of studies

4.1.1 Search strategy

The search strategy will comprise the following main elements:

- 1) Searching of electronic bibliographic databases and other online sources,
- 2) Contacting experts in the field, and
- 3) Scrutiny of references of included studies, relevant systematic reviews, and the most recent NICE guidance on systems that combine CGM and CSII.¹⁰

A comprehensive search will be developed iteratively and undertaken in a range of relevant bibliographic databases and other sources, following the recommendations in Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions.¹¹ Search terms will relate to T1DM (including a separate set of terms relating to pregnant women and women planning pregnancy) and technologies to manage blood glucose levels. The main MEDLINE search strategies will be independently peer reviewed by a second Information Specialist.

Date limits will be used, in order to identify records added to databases since the searches for the previous DAR (run on 5th September 2014).¹² Searches will be conducted in a range of databases, including: MEDLINE All (Ovid); Embase (Ovid); Cochrane Database of Systematic Reviews (Wiley); CENTRAL (Wiley); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science); and websites of the US Food and Drug Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA). The search will be developed in MEDLINE (Ovid) and adapted as appropriate for other resources. Draft search strategies relating to T1DM, the pregnancy/planning pregnancy population, and the interventions/comparators of interest are provided in Appendix 1.

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

4.1.2 Study eligibility criteria

Studies that satisfy the following criteria will be included:

Populations	People who have T1DM who are having difficulty managing their condition despite prior use of at least one of the following technologies: continuous subcutaneous insulin infusion, real time continuous glucose monitoring, flash glucose monitoring ^{ab} If evidence permits the following T1DM subpopulations will be included:
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	<ul style="list-style-type: none"> • Pregnant women and those planning pregnancies (excluding gestational diabetes).^b • Children (5 years and under, 6 – 11 years, 12 - 19 years). • People with extreme fear of hypoglycaemia. • People with diabetes related complications that are at risk of deterioration. <p>^a For the purpose of this review, difficulty refers to (1) not maintaining HbA1c levels of 6.5% (48 mmol/mol) or below (for pregnant women/those planning pregnancies: not maintaining fasting plasma glucose levels of 5.2 mmol/l or below, or not maintaining non-fasting plasma glucose of 7.7 mmol/L (one hour after eating)/ 6.3 mmol/L (two hours after eating)), (2) not maintaining at least 70% time in range of 3.9 -10 mmol/l, or (3) repeated hypoglycaemia that causes anxiety about recurrence and is associated with a significant adverse effect on quality of life.</p> <p>^b Pregnant women and those planning pregnancies will not be required to have previously used CSII and self-monitoring of blood glucose or glucose monitoring (rt-CGM/flash glucose monitoring) with multiple daily injections.</p>
Target condition	Type 1 diabetes mellitus
Intervention	Hybrid closed loop systems
Comparator	<ul style="list-style-type: none"> • Real time continuous glucose monitoring with continuous subcutaneous insulin infusion (non-integrated). • Intermittently scanned (flash) glucose monitoring with continuous subcutaneous insulin infusion. <p>Where evidence permits, scenarios assessing the following comparators will be presented for women with type 1 diabetes who are pregnant/planning pregnancy:</p> <ul style="list-style-type: none"> • Real time continuous glucose monitoring with multiple daily insulin injections. • Intermittently scanned (flash) glucose monitoring with multiple daily insulin injections. • Self-blood glucose monitoring with continuous subcutaneous insulin infusion.
Outcomes	<p><u>Intermediate measures</u></p> <ul style="list-style-type: none"> • Time in target range (percentage of time a person spends with blood glucose level in target range of 3.9-10 mmol/l) • Time below and above target range • Change in HbA1c • Rate of glycaemic variability

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

Clinical outcomes

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

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

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

Device related outcomes

- Adverse events related to the use of devices

Patient-reported outcomes

- Health-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

	<ul style="list-style-type: none"> Impact on carer (fear of hypoglycaemia, time spent managing the condition, time spent off work, ability to participate in daily life, time spent at clinics, impact on sleep)
Study design	<p><u>Hybrid closed loop systems studies</u></p> <ul style="list-style-type: none"> Any design <p><u>All comparator studies</u></p> <ul style="list-style-type: none"> Comparative effectiveness study designs
Healthcare setting	Self-use supervised by primary or secondary care
Publication type	Peer reviewed papers
	Abstracts and manufacturer data will be included only if they provide numerical data and sufficient detail on methodology to enable assessment of study quality/risk of bias. Further, only data on outcomes that have not been reported in peer-reviewed full text papers will be extracted and reported.
Language	English

Where it cannot be established if all study participants have difficulty managing their condition (defined by HbA1c, fasting plasma glucose, non-fasting plasma glucose, or time in range as above), but the group mean meets this criterion, these studies will be included.

Papers that fulfil the following criteria will be excluded:

Non-human studies, letters, editorials, and communications. Qualitative studies. Studies conducted outside of routine clinical care settings, e.g., inpatient research facilities, diabetic summer camps. Studies where more than 10% of the sample do not meet the inclusion criteria. Studies without extractable numerical data. Studies that provided insufficient information for assessment of methodological quality/risk of bias. Articles not available in the English language. Studies evaluating individual components and not complete hybrid close loop systems. Studies of DIY closed loop systems, which are not approved by regulatory bodies.¹³ Studies of dual pump (e.g. insulin plus glucagon) hybrid closed loop systems. Studies in which hybrid closed loop systems are only used periodically (e.g. overnight only). Studies evaluating automated insulin delivery systems which only suspend insulin delivery when glucose levels are low/ are predicted to get low.

4.1.4 Review strategy

4.1.4.1 Prioritization strategy for full text assessment

We will apply a two-step approach for identifying and assessing relevant evidence. We will apply stricter criteria at the point of data extraction/risk of bias than title and abstract assessment to prioritise and select the best available evidence.¹⁴⁻¹⁶ The elements used to prioritise evidence (study design, study length, sample size) were chosen in collaboration with NICE and diabetes clinicians as those that will provide the most applicable evidence.

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

Step two: studies identified from step one will go through the standard systematic reviewing approach of full text assessment. We will follow the pre-defined PICO (see 4.1.2. for study eligibility criteria) to assess the eligibility of studies.

4.1.4.2 Prioritization strategy for data extraction and risk of bias

In the view of the potentially high number of studies that might meet the inclusion criteria of this review and the limited time and resources available to assess these studies, the most rigorous and relevant studies will be prioritised for data extraction and quality assessment.¹⁶ Studies will be prioritised by study design, study duration, and sample size. RCTs will be prioritised over controlled trials. Non-randomised controlled trials/comparative effectiveness studies will be prioritised over non-comparative studies. In terms of study duration, longer term studies (12 months or more) will be prioritised over shorter-term studies. For non-comparative studies, larger studies (100 participants or more) will be prioritised over smaller studies. We will also consult our clinical advisors in terms of relevance to current UK practice. Studies will be deprioritised if they are not clinically relevant to current practice.

We will extract the following study characteristics:

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

4.2 Extraction and study quality

4.2.1 Data extraction strategy

Two reviewers will extract data independently, using a piloted data extraction form. Disagreements will be resolved through consensus, with the inclusion of a third reviewer if required.

4.2.2 Assessment of study risk of bias

The risk of bias of randomised trials will be assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).¹⁷ Risk of bias in controlled trials, non-randomised trials, and cohort studies will be assessed using the Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I) tool.¹⁸ Risk of bias for case control studies and controlled before-and-after studies will be assessed using Effective Practice and Organisation of Care (EPOC) RoB Tool.¹⁹ Risk of bias for cross-sectional studies will be assessed using the Joanna Briggs institute checklist.²⁰ Two reviewers will independently assess risks of bias. Disagreements will be resolved through consensus, with the inclusion of a third reviewer if required. The results of each risk of bias item will be presented in tables.

4.2.3 Dealing with missing data

Where possible, we will calculate missing standard deviations using available data from the studies, such as confidence intervals based on methods outlined in the Cochrane Handbook for Systematic Reviews of interventions.²¹

4.3 Methods of analysis/synthesis

We will synthesise the evidence statistically if the number of studies permits (five or more studies) and where it is meaningful to pool the data in a meta-analysis or indirect treatment comparison. If particular studies or outcomes cannot be included in a statistical synthesis, we will provide a narrative synthesis of these studies. If all included studies do not permit a statistical synthesis, we will narratively synthesise the evidence and produce tabulated data to summarise included studies. If we include non-comparative studies, then they will be narratively synthesised. If possible, subgroup analyses will be undertaken for the different combinations of interventions that study participants have previously used to manage their blood glucose (i.e., flash glucose monitor and multiple daily insulin injections, flash glucose monitor and CSII, rtCGM and multiple daily insulin injections, rtCGM and CSII, self-blood glucose monitoring and CSII).

4.3.2 Pairwise and network meta-analysis

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

If suitable data are available on the outcomes of interest and meet our meta-analysis assumptions,²² then we will use pair-wise meta-analysis to pool data from multiple studies/RCTs which test the effectiveness of one intervention relative to another or a control intervention. Pooling data from multiple studies this way would allow us to assess the effectiveness of technologies based on a large patient/study sample. This increases likelihood of detecting the benefit of the technologies in a way that minimises the risk of finding an effect by chance.

Next, and again if the evidence allows it, we will conduct a network meta-analysis (NMA) to compare multiple interventions with one another including interventions that have not been directly compared in a single study.^{23, 24} An NMA is an extension of pairwise meta-analysis. It produces indirect estimates of effects when RCTs of two interventions share a common comparator such as placebo. The network enables an estimate of the comparative effectiveness between the two interventions if there is no available direct evidence. However, if there is direct evidence available, the network will still pool the indirect evidence, then add the direct evidence to the indirect evidence.

Using evidence this way necessarily requires assumptions to be made. Decisions about what information to include in the NMA will be informed by its relevance to the decision problem and sufficient similarity across studies (e.g., patient characteristics and study design) to reduce the risk of violating the underlying assumptions of transitivity/coherence when pooling direct and indirect evidence across studies. We will use an iterative process and refer to the Cochrane handbook²⁴ to define the extent of the treatment network and identify studies for inclusion. This would involve first, defining an initial *core set* of interventions that meet the criteria set out in the projects' scope and include trials (and or non-randomised studies) of such interventions in T1DM populations. Interventions not meeting the criteria for the core set will be considered for inclusion in a *supplementary set* of interventions.²⁵ Only if necessary, and scientifically robust, will we extend the network to include supplementary interventions. We will derive an internally consistent set of treatment effects from this evidence base by fitting a generalised linear model NMA.²⁶

We will fit both fixed and random effects models and select the best fitting model based on model fit assessments and magnitude of the between-study variation in the treatment effect. Statistical heterogeneity will be quantified using the between-study standard deviation and I^2 -statistic.¹⁹ The between-study standard deviation gives a direct measure of variance in the treatment effect across studies,^{26, 27} whilst the I^2 -statistic measures the proportion of variance across studies that is due to differences in population characteristics.^{27, 28} Where we find evidence of substantial heterogeneity in the data, we will use network meta-regression to identify the characteristics of the study population that could explain this heterogeneity and identify subgroups of patients mostly likely to benefit from

treatment. We will also test for consistency in the evidence and explore the impact of effect modifiers using subgroup analysis and network meta-regression.^{29, 30}

4.4 Assessment of bias in conducting the review

We will conduct the review according to the registered protocol. Any deviations from this protocol will be reported in a “Differences between protocol and review” section in the final report.

5. Methods for assessing cost-effectiveness

5.1 Identification and selection of studies

5.1.1 Search strategy

A comprehensive search of the literature for published economic evaluations, cost studies and health-related quality of life studies (HRQoL) relevant to the decision problem will be performed. The search will be informed by the strategy developed for the clinical effectiveness review, and filters designed to identify economic, cost and HRQoL studies will be added to the search strategies in resources that are not specific to the area of health economics. Strategies may be further refined, and other appropriate limits may be added. Databases will include:

MEDLINE All (Ovid), Embase (Ovid), International HTA database (INAHTA), Science Citation Index and Conference Proceedings Science (Web of Science), Cost-Effectiveness Analysis (CEA) registry, EconPapers (Research Papers in Economics (RePEc)), and School of Health and Related Research Health Utilities Database (SchARRHUD).

The reference lists of included studies will be checked. The search will be developed in MEDLINE (Ovid) and adapted as appropriate for other databases. Records will be exported to EndNote X9, where duplicates will be systematically identified and removed. Additional searches will be performed where necessary to identify other relevant inputs, for example to support building the economic model.

5.1.2. Review strategy

All records retrieved will be screened independently by two reviewers at title/abstract stage, of which potentially relevant records will be further examined at full text. Any disagreements between the reviewers will be resolved by a discussion, or recourse to a third reviewer if an agreement cannot be reached.

5.2 Extraction and study quality

5.2.1 Data extraction strategy

Information will be extracted by two reviewers independently, using a pre-piloted data extraction form for the full economic evaluation studies. The data extraction form will be developed to summarise the main characteristics of the studies and to capture useful information for the economic model. From each paper included in the systematic review, we will extract information about study details (title, author and year of study), baseline characteristics (population, intervention, comparator and outcomes), methods (study perspective, time horizon, discount rate, measure of effectiveness current, assumptions and analytical methods including the modelling strategy/type of model used), results (study parameters, base-case and sensitivity analysis results), discussion (study findings, limitations of the models and generalisability), other (source of funding and conflicts of interests), overall reviewer comments and conclusion (author's and reviewer's). Each reviewer will cross-check the other's extractions, with any discrepancies resolved by discussion, or recourse to a third reviewer if an agreement cannot be reached.

5.2.2 Assessment of study methodological quality

The quality of any full economic evaluation studies will be assessed using the consolidated health economic evaluation reporting standards (CHEERS) checklist.³¹ Any studies using an economic model will be further assessed against the framework for the quality assessment of decision analytic modelling developed by Philips and colleagues.³²

5.3 Methods of analysis/synthesis

Due to the nature of economic analyses (different aims/objectives, study designs, populations, and methods) these findings from individual studies will be compared narratively, and recommendations for future economic analyses will be discussed.

5.3.1 Model structure

T1DM is a chronic metabolic disorder associated with many long-term health complications. This requires a modelling approach which can capture the costs and outcomes of disease progression over the lifetime horizon whilst incorporating a large and complex set of health sequelae.

Multiple T1DM models are published within the literature, 13 of which were identified as unique by Henriksson (2016)³³ in a systematic review of T1DM economic models. More recently, authors presenting their own novel T1DM identified 4 further economic models in the published literature, in addition to their own³⁴. The majority of models identified use a Markov approach embedded within a patient-level micro-simulation models to simulate disease progress and complications of T1DM over-time³³, and consequently the vast majority of cost-effectiveness analyses (28, 93) conducted on health technologies in adults with T1DM also utilise Markov models.³⁵

A series of key attributes for best-practice in modelling T1DM were identified by Henriksson and colleagues³³ which included; Markov simulation at patient-level, ability to perform probabilistic sensitivity analysis, extensive microvascular and macrovascular health states modelled individually over a lifetime horizon, hypoglycaemia (ideally delineated by severity levels) and ketoacidosis modelled as key adverse events, direct costs broken down by intervention and health state, and quality-adjusted life-years (QALY) as an outcome measure.

The IQVIA CORE diabetes model (IQVIA CDM) possesses the best-practice key attributes and has been used widely among academics and industry. Two-thirds (20/30) cost-effectiveness studies of T1DM health technologies have been conducted using the CORE model.³⁵ Similarly, 40/61 studies categorised as secondary papers in a T1DM model systematic review³³ (i.e. studies using one of the 13 unique models identified) used the CORE model. Modelling for the previous DG21¹⁰ was also performed using CORE. However, this used version 8.5 which has since been decommissioned and is no longer accessible for the current EAG to consult for this update.

The EAG will therefore use the updated IQVIA CDM version 9.5 in its modelling of automated insulin delivery systems for managing blood glucose levels in T1DM (update of DG21). Figure 2 outlines the IQVIA Core Diabetes model structure (IQVIA Core Diabetes Model, provided via personal communication, [Mafalda Ramos], IQVIA, [23rd March 2021]).

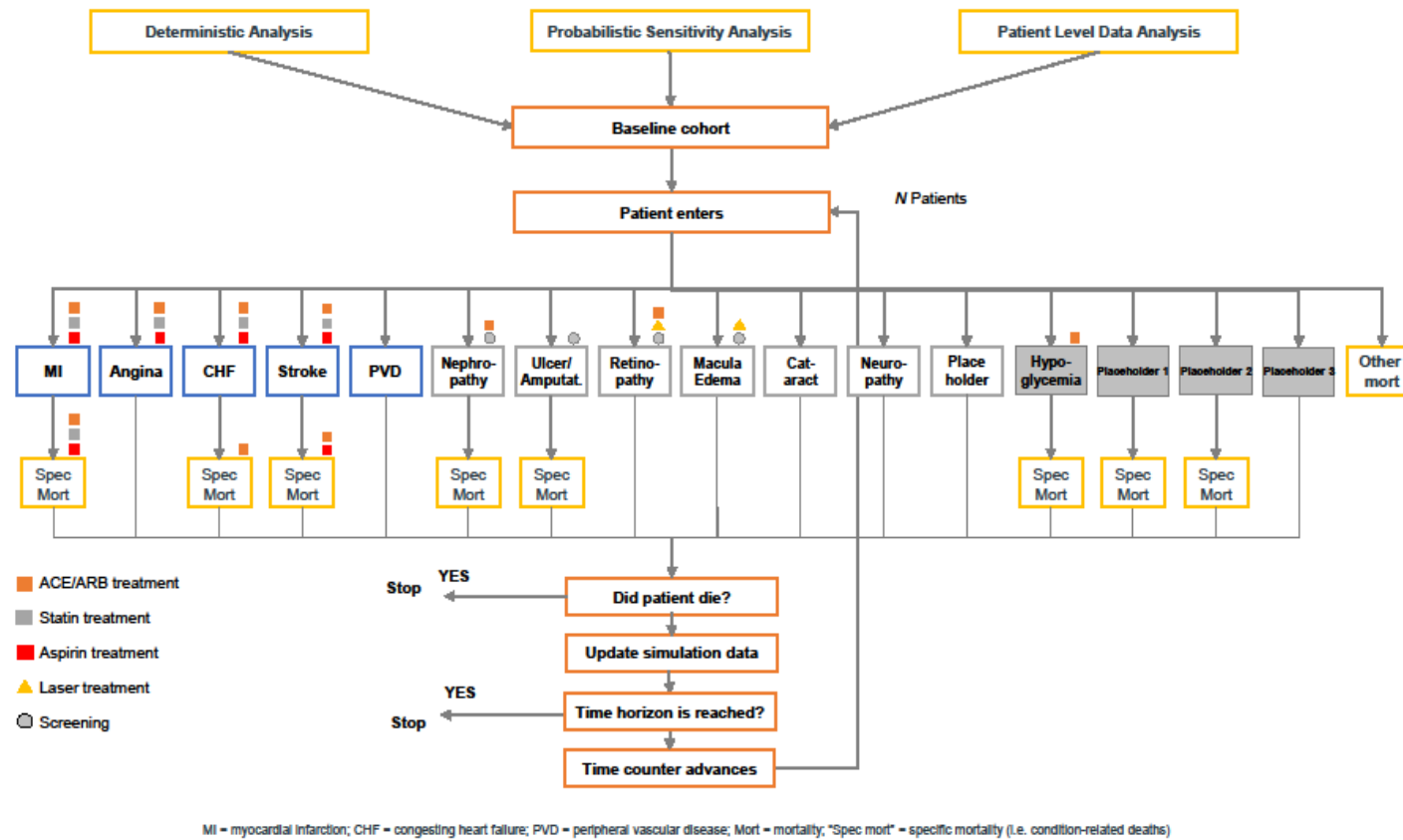


Figure 2. The IQVIA Core Diabetes Model structure

The model uses a Markov approach with tracker variables running in annual cycles across 17 inter-dependent sub-models representing health related complications of interest. The time horizon can be varied to a maximum of eighty years.³⁶

We anticipate that parameterisation will be driven by the findings from the clinical effectiveness systematic review and supported by clinical expert opinion.

Time in range (TIR) is increasingly being used as an outcome measure for glycaemic control in studies assessing technologies related to this appraisal. However, TIR is a relatively new outcome measure in T1DM, hence, current models are based on HbA1c to model the long-term complications associated with T1DM. Therefore, our base-case will use HbA1c as measure of treatment benefit. The EAG is aware that the developers of the IQVIA CDM have formulated a conversion algorithm to map TIR values to HbA1c within the model. We will use this approach to investigate the impact of using TIR as outcome measure on cost-effectiveness pre-specified sensitivity analyses.

5.3.2 Resource use and costs

As part of the framework to undertake the economic analysis, information will be required about the resource use and costs associated with the technologies used to manage blood glucose levels in T1DM. Additionally, resource use and costs will be required for the ongoing management and surveillance of people with T1DM, including severe hypoglycaemic/hyperglycaemic events and diabetic ketoacidosis, in addition to costs associated with long-term health complications due to diabetes such as retinopathy, neuropathy, cognitive impairment, end-stage renal disease and increased risk of cardiovascular disease.

5.3.3 Health outcomes

Two outcome measures will be used in the economic analysis, life-years (LY) and QALYs gained. LY and QALYs gained will be calculated from survival information, including incidence and survival of short-term complications (severe glycaemic events) and long-term complications (microvascular and macrovascular disease), and utility values obtained from the literature and other sources (e.g., elicited from experts). QALYs accrued will be derived based on the utility payoff assigned to the health states occupied along the management pathway. For each technology approach, the expected mean benefits yielded will be summed over the model time horizon and discounted at a 3.5% per annum rate.

5.3.4 Cost-effectiveness analysis

The cost-effectiveness analysis will consider the ratio between the costs incurred and benefits accrued for each testing strategy from the NHS and personal social services perspective. The results of the

analysis will be presented in terms of an incremental cost-effectiveness analysis, where each glucose management intervention will be ranked, excluding options that were dominated or extendedly dominated, with results expressed as cost per QALY. We will use univariate one-way sensitivity analysis to explore the impact of varying one parameter at a time, whilst keeping all other inputs constant to assess the robustness of the model, with results presented in the form of a tornado diagram. We anticipate undertaking scenario analyses around TIR as an outcome measure. Other scenario analyses will be undertaken as required through model development. Subgroup analysis where evidence permits will be undertaken for:

- Women with type 1 diabetes who are pregnant and those planning pregnancy (not including gestational diabetes)
- Children with type 1 diabetes. If possible, evidence will 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.

Probabilistic sensitivity analysis will be used to determine the impact of joint parameter uncertainty. In probabilistic sensitivity analysis, model parameters are assigned a distribution reflecting the amount and pattern of its variation, and cost-effectiveness results are calculated by simultaneously selecting random values from each distribution. This process is repeated several times, with the simulations plotted on an incremental cost-effectiveness plane; each point representing uncertainty in the incremental mean costs and QALYs between the strategies being compared. The results from these simulations will be used to obtain cost-effectiveness acceptability curves, which illustrate the effect of sampling uncertainty, and presents the probability that an intervention is optimal at a range of willingness-to-pay threshold values.³⁷

6. Patient and public involvement and engagement

Patient and public involvement and engagement (PPIE) is an important part of the review process. PPIE is commonly described as being consultation based (seeking views on key aspects of the research), collaborative (on-going partnership) or 'publicly led' (the public designs and undertakes the research).³⁸ A collaborative consultation approach was considered most suitable for this review. One service user is participating as a consultant. His input was valuable in refining the scope of the review and writing the Plain English Summary of this protocol. His involvement will be 'continuous', where

he will be consulted at several points of the review process. These will include identifying the literature, interpreting the results, and considering implications of the findings from the perspective of patients/service users.³⁹ The PPIE member will be a co-author on reports and publications arising from the review. Ongoing engagement with and involvement of the consultant will add value to the review, improving the quality and its relevance to patients, whilst also creating an opportunity for learning from one another.⁴⁰

7. Handling of information from manufacturers

All data submitted by the companies/sponsors will be considered if received by the External Assessment Group no later than 24th June 2022. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in line with the methods outlined in this protocol. Any economic evaluations included in the company submissions, provided they comply with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. Any information provided on technologies, costs and health related quality of life may be used for the description of the technologies under assessment and as potential model inputs.

According to NICE requirements, any 'commercial in confidence' data taken from a company submission, and specified as confidential in the checklist, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any 'academic in confidence' data will be highlighted in yellow and underlined. Where comparator Patient Access Scheme information is available, results will be presented in a confidential appendix, commercial in confidence results will be highlighted in green and underlined.

8. Competing interests of authors and advisors

None of the authors have any competing interests.

9. Timetable/milestones

Assessment report submission 27th September 2022

Economic model submission 30th September 2022

10. Team members' contributions

Warwick Evidence is an External Assessment Group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling.

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