# Hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes: a systematic review and economic modelling

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## Scientific summary

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# Scientific summary

This summary contains reference to confidential information provided as part of the National Institute for Health and Care Excellence (NICE) appraisal process. This information has been removed from the summary and the results discussions and conclusions of the summary do not include the confidential information. These sections are clearly marked in the summary.

## Background

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

## Objectives

The overall objectives of this project are to examine the clinical effectiveness and cost-effectiveness of HCL systems for managing glucose levels in people who have type 1 diabetes.

1. What is the clinical effectiveness of HCL systems in managing glucose in people who have type 1 diabetes and are having difficulty managing their condition despite prior use of at least one of the following technologies: CSII, real-time continuous glucose monitoring (rtCGM), flash glucose monitoring [intermittently scanned continuous glucose monitoring (isCGM)]?
2. What is the cost-effectiveness of HCL for managing glucose in people who have type 1 diabetes and are having difficulty managing their condition despite prior use of at least one of the following technologies: CSII, rt-CGM, isCGM?

## Methods

Systematic review methods followed the principles outlined in the Cochrane Handbook.

A comprehensive search was developed iteratively and undertaken in a range of relevant bibliographic databases and other source. Date limits were used to identify records added to the databases since the

searches for Diagnostic Guidance 2021 (run in 2014). Two reviewers screened titles and abstracts and assessed the eligibility of studies. Studies that satisfied the following criteria were included.

### *Populations*

People (of any age) who have type 1 diabetes and are having difficulty managing their condition despite prior use of at least one of the following technologies: CSII, rtCGM, isCGM.

### *Intervention*

Hybrid closed loop.

### *Comparator*

Real-time continuous glucose monitoring with CSII (non-integrated).

Intermittently scanned continuous glucose monitoring with CSII.

### *Outcomes*

#### Intermediate

- Per cent time in target range (percentage of time a person spends with blood glucose level in the target range of 3.9–10 mmol/l).
- Per cent time below and above target range.
- Change in glycated haemoglobin (HbA1c).
- Rate of glycaemic variability.
- Fear of hypoglycaemia.
- Rate of severe hypoglycaemic events (events recorded/unit time).
- Rate of severe hyperglycaemic events (events recorded/unit time).
- Episodes of diabetic ketoacidosis (events recorded/unit time).
- Rate of ambulance call-outs (events recorded/unit time).
- Rate of hospital outpatient visits (events recorded/unit time).
- Measures of weight gain.

#### Clinical

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

#### 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 birthweight).
- Respiratory distress syndrome in the newborn.

#### Device-related

- Adverse events related to the use of devices.

### Patient-reported

- Heath-related quality of life.
- Psychological well-being.
- Impact on patient.
- Anxiety about experiencing hypoglycaemia.
- Acceptability of testing and method of insulin administration.

### Carer-reported

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

#### *Study design*
Hybrid closed-loop systems studies included randomised controlled trials (RCTs) with a parallel-group or crossover design in which HCL or advanced HCL (AHCL) intervention was compared with a relevant comparator; observational studies (single-arm studies) of various designs: audit, retrospective and prospective cohort; and studies reporting outcomes after HCL or AHCL treatment.

#### *Healthcare setting*
Self-use supervised by primary or secondary care.

#### *Publication type*
Peer-reviewed papers.

#### *Language*
English.

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

## Results

#### *Clinical systematic review*
The clinical evidence identified 12 RCTs that compared HCL with CSII + CGM or sensor-augmented pump therapy. Studies were heterogeneous in terms of population, age groups, gender, RCT design, numbers of participants and variable adjustment methods. Studies did not consistently describe comparators. Overall, the HCL arm of RCTs achieved improvement in HbA1c% {HCL decreased HbA1c% by 0.28 [95% confidence interval (CI) −0.34 to −0.21], increased % time in range (TIR) (between 3.9 and 10.0 mmol/l) with a mean difference of 8.6 (95% CI 7.03 to 10.22), significantly decreased TIR (% above 10.0 mmol/l), with a mean difference of −7.2 (95% CI −8.89 to −5.51), but did not significantly affect % time below range (< 3.9 mmol/l)}. Comparator arms also showed improvements, but these were smaller than those observed in the HCL arm. Available evidence from the RCTs suggests that these gains in glycaemic management reported with HCL were not accompanied by a greater risk of hypoglycaemia; however, the power to detect small event sizes was limited because of the small study groups and the relatively short treatment duration.

### *External submissions*

National Health Service England submitted two observational audit studies: the first audit was conducted in adults and the second was conducted in children and young people. The audit included adult participants who had worse glycaemic management in terms of HbA1c and hyperglycaemia at baseline than in published observational studies. The studies were non-randomised with no control group and had a before-and-after design. This limits the scientific value of the evidence as there is a greater risk of bias due to lack of randomisation, lack of a true control and selection bias.

The improvement in HbA1c % and % time in range (between 3.9 and 10 mmol/L) were much greater in the NHS adult study in comparison to published evidence. The baseline level of the audit was considerably above than in all included observational studies, therefore there was a greater scope for improvement. In the NHS audit of children and young people baseline HbA1c was lower (~7.8%) and benefit was more modest (-0.61%) than in adults. For % time in range < 3.9 mmol/L the NHS audit adult study reported a change of -0.5% and an associated P value of <0.001. The CYP Pilot also reported a statistically significant improvement.

### *Economics*

#### Systematic review of cost-effectiveness

The literature search identified six studies, which were included. Five of the studies were economic evaluations of HCL systems, whereas one was a budget impact analysis. The structure of the models used in the cost-effectiveness studies was judged to be of good quality. The studies' authors clearly stated their research question, the viewpoint of their analyses and their modelling objectives. Studies that used the iQVIA model described the model as one with a complex semi-Markov model structure with interdependent sub-models, so more thorough, easier access to its reported features would be of benefit to the intended audience. All cost-effectiveness studies noted that HCL was cost-effective over the lifetime versus comparator interventions.

### *Company submission*

The Evidence Assessment Group (EAG) received economic submissions from Medtronic, Dexcom and CamDiab. The Tandem submission referenced the economics of the Dexcom submission.

The Medtronic treatment costs applied the anticipated April 2023 commercial-in-confidence prices rather than the current list prices. Using the iQVIA CORE Diabetes Model (CDM), it estimated that compared with the 640G system with rtCGM the 780G HCL system improved HbA1c by 0.8%, which resulted in a saving of £5816, patient gains of 0.21 QALYs and dominance of HCL. For the comparison with CSII + isCGM, the same HbA1c improvement was applied alongside an annual reduction of 0.9 severe hypoglycaemia events. This resulted in a net cost of £13,057, a patient gain of 0.70 QALYs and cost-effectiveness of £18,672 per QALY.

(Confidential information has been removed.)

### *Independent economic assessment*

Owing to the complexity of modelling type 1 diabetes, the EAG does not build a de novo model. In common with the NICE's guideline NG17 and its diagnostics guidance DG21 and most of the company submissions, the EAG uses the iQVIA CDM to model cost-effectiveness. The published model validation papers suggest that an earlier version of the iQVIA CDM tended to overestimate the incidences of the complications of diabetes. Medium-term modelling of overall survival appeared good, but there was uncertainty about its longer-term modelling. It is not known whether these issues persist in the current iQVIA CDM. The EAG assesses the cost-effectiveness of HCL and CSII + CGM.

Direct treatment costs are supplied by the NHS supply chain using current list prices. The EAG provides a confidential patient access scheme appendix that applies the confidential possible future prices.

Current prices suggest that HCL is around an annual average of £1500 more expensive than CSII + CGM, although this may increase by around a further £500 for some systems. CSII + CGM is cheaper than HCL in large part due to 90% or more of adult patients using isCGM sensors rather than rtCMG sensors.

Patient baseline characteristics in the EAG base case are drawn from the National Diabetes Audit subgroup of type 1 diabetes patients on pumps.

The EAG base case applies the EAG RCT network meta-analysis estimate of −0.29% HbA1c for HCL relative to CSII + CGM. Because there is no direct evidence of an effect on symptomatic or severe hypoglycaemia events, the EAG does not include these in its base case.

The change in HbA1c results in a gain in undiscounted life expectancy of 0.458 years and a gain of 0.160 QALYs. Net lifetime treatment costs are £31,185, with reduced complications leading to a net total cost of £28,628. The cost-effectiveness estimate is £179,000 per QALY.

The EAG provides scenario analyses that estimate symptomatic and severe hypoglycaemia events based on the differences in the time < 3.0 mmol/l for HCL and CSII + CGM. These improve the cost-effectiveness of HCL to £163,000 per QALY if it is valued using the EAG preferred source, to £121,000 if it is valued using the same source as NG17 and to £109,000 if it is valued using other credible sources.

If the NHS adult pilot change between baseline and 6 months of −1.5% HbA1c is assumed to be the net effect of HCL compared with CSII + CGM, the undiscounted gain in life expectancy more than doubles to 1.004 years, and the patient gain increases to 3.103 QALYs. Net lifetime treatment costs increase to £35,912 due to the greater life expectancy, but considerable cost savings from reduced eye complications of £16,442 and reduced renal complications of £6731 lead to a net total cost of £12,447 and a cost-effectiveness of £12,398 per QALY. Reducing the modelled complication costs by their possible overestimation worsens the cost-effectiveness to £21,583 per QALY. This does not take into account any quality-of-life effects and survival effects from the possible overestimation of complication rates.

The key model inputs are:

- the net effect on HbA1c
- the duration of the net effect on HbA1c
- the model time horizon
- treatment costs.

The EAG has some concerns about using the iQVIA T1DM to model a paediatric population. Exploratory modelling of a paediatric population broadly mirrors that of the adult population, although the NHS paediatric pilot reported a smaller −0.70 HbA1c change between baseline and 6 months, with a corresponding worsening in the cost-effectiveness estimate for this scenario. The EAG does not formally consider the cost-effectiveness of HCL compared with CSII + CGM for pregnant women due to a lack of evidence. It only notes the relationship between HbA1c and birth defects.

## Conclusions

Randomised controlled trials of HCL interventions in comparison with CSII + CGM achieved a statistically significant improvement in HbA1c%, in TIR between 3.9 and 10 mmol/l, and in hyperglycaemic levels. The outcome estimates reported for observational studies were quantitatively broadly in line with those from the RCTs. There is a research need for well-designed studies because the

studies were heterogeneous. Future research should clearly describe comparators because these are not clear in the current literature.

## Study registration

This study is registered as PROSPERO CRD42021248512.

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## This article


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