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# Horizon Scanning Technology Prioritising Summary

# Closed-loop insulin delivery system ('artificial pancreas') for management of hypoglycaemia in type 1 diabetics

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AHTA

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# PRIORITISING SUMMARY

**REGISTER ID:** **000476**

**NAME OF TECHNOLOGY:** **CLOSED-LOOP INSULIN DELIVERY SYSTEM ('ARTIFICIAL PANCREAS')**

**PURPOSE AND TARGET GROUP:** **MANAGEMENT OF HYPOGLYCAEMIA IN TYPE 1 DIABETICS**

**STAGE OF DEVELOPMENT (IN AUSTRALIA):**

| | | | |
|---|---|---|---|
| ☐ | Yet to emerge | ☒ | Established |
| ☐ | Experimental | ☐ | Established *but* changed indication or modification of technique |
| ☐ | Investigational | ☐ | Should be taken out of use |
| ☐ | Nearly established | | |

**AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL**

| | | | |
|---|---|---|---|
| ☒ | Yes | ARTG number | 95763 |
| ☐ | No | | |
| ☐ | Not applicable | | |

**INTERNATIONAL UTILISATION:**

| COUNTRY | LEVEL OF USE | | |
|---|---|---|---|
| | Trials Underway or Completed | Limited Use | Widely Diffused |
| Australia | | ✓ | |
| United States | ✓ | | |
| UK | ✓ | ✓ | |
| France | ✓ | ✓ | |

**IMPACT SUMMARY:**

Closed-loop insulin delivery is a system that acts as an 'artificial pancreas'. The system utilises coupled technologies – real-time continuous glucose monitoring and insulin pumps – for improved glucose control among type 1 diabetes patients. Various companies make commercially available glucose monitors and pumps, however, only recently have devices been manufactured to function jointly. These closed-loop devices mimic non-diabetic insulin delivery via real-time control algorithms, rather than by pre-programmed rates that govern insulin pumps alone. Medtronic

(Northridge, CA) offers fully integrated systems[1] with the MiniLink® transmitter for wireless data input to a pump with LCD display.

## BACKGROUND

Diabetes mellitus is characterised by a total or near total insulin deficiency, resulting in an acute elevation of blood glucose levels (hyperglycaemia), rapid acidification of the blood (ketoacidosis), and death, unless treated with insulin. Onset may occur at any age but usually in childhood or adolescence. Type 1 diabetes is often referred to as an auto-immune disease as in most cases it is caused by the immune system attacking and destroying the pancreatic beta-cells, which produce insulin. Although there is a basal release of insulin from the β-cells, insulin synthesis and secretion is mainly controlled by the concentration of glucose in the blood, i.e. a high blood glucose level leads to insulin secretion. Insulin is inhibited by a feedback mechanism controlled by the sympathetic nervous system. Insulin affects every tissue in the body but particularly liver, muscle and fat cells. The overall function of insulin is to facilitate the uptake, utilisation and storage of glucose, amino acids and fats after a meal; a fall in insulin causes a reduced uptake of these substances and an increase in the mobilisation of fuel stores. WHO criteria recommend that diagnosis of diabetes should be based on a fasting plasma glucose level in excess of 126 mg/dL (7mmol/L)[2] and/or a 2-hour plasma glucose level in excess of 200 mg/dL (11 mmol/L) following an oral glucose tolerance test (Richter et al 2007).

Despite the importance of overall management of blood glucose, including the avoidance of hyperglycaemia, this summary draws specific attention to the control of hypoglycaemia, which can pose the most immediate adverse and life-threatening effects among type 1 diabetics. Since the danger of hypoglycaemia can limit the application of intensive therapy for type 1 diabetes, there have been initiatives to develop insulin delivery devices that respond to glucose concentrations and automatically regulate blood glucose to the non-diabetic range (El-Khatib et al 2010). This forms the basis for the control of hypoglycaemia using closed-loop insulin delivery systems. The algorithms used in these systems are varied, but primarily work by initialising an individual's insulin sensitivity from basal insulin requirements, then adapting the estimate in real-time on the basis of administered insulin and resulting sensor glucose concentrations (Hovorka et al 2010). In short, the closed-loop system comprises a pump which continuously infuses rapid-acting insulin at a basal level, whilst at the same time the glucose sensor continuously monitors glucose levels, with the infused insulin dose being adjusted according to the glucose levels obtained.

[1] The Paradigm Veo™ Insulin Pump and Continuous Glucose Monitoring System is marketed in Australia.

[2] To convert mg/dL of glucose to mmol/l, divide by 18 or multiply by 0.055To convert mmol/l of glucose to mg/dL, multiply by 18.

## CLINICAL NEED AND BURDEN OF DISEASE

In Australia during the period 2000-2006, the annual age-adjusted incidence rate of type 1 diabetes among children aged 0-14 years was 22.4 new cases per 100,000 population. There has been a slight increase in the incidence in this age group from 19.2 in 2000 to 22.6 in 2006, with the greatest increase occurring in 10-14 year olds (Catanzariti et al 2008). In comparison to other OECD countries, the incidence of type 1 diabetes in Australia is high, with only Norway, Sweden and Finland having a higher annual incidence. Amongst people aged 15-years and over at first insulin use, there were an average of 1,260 new cases per year. The rate of new cases amongst people aged over 15-years decreases dramatically with age and plateaus at age 45-years. The peak annual incidence rate of type 1 diabetes occurs at age 15-years (Pieris-Caldwell et al 2008).

There is little information available on the quality of life of people with type 1 diabetes in Australia. A Melbourne study of children and young people with type 1 diabetes found that their general health and quality of life were poorer than their population peers. Lower quality of life was found to be related to poor blood glucose control in children aged 5–11 years, but not in adolescents aged 12–18 year-olds, however the presence of diabetes-related symptoms and concerns was associated with poorer psychosocial functioning for both age groups (Pieris-Caldwell et al 2008).

In New Zealand the incidence of type 1 diabetes appears to be increasing and in the year 2000 it was estimated that the number of people with type 1 diabetes was 10,564[3] (Health Funding Authority 2000). The estimated incidence of type 1 juvenile diabetes in New Zealand was 25.8 cases per 100,000 persons aged up to 19 years in 2001.

## DIFFUSION

The Paradigm Veo™ System (Figure 1) is currently marketed to private patients in Australia by Medtronic Australasia Pty Ltd. Models MMT-554 and MMT-754 are listed under billing codes MC839 and MC840 on the Commonwealth Prostheses List. Under provision of the Private Health Insurance Act 2007, private health insurers are obliged to pay a benefit towards listed prostheses provided as part of an episode of hospital or hospital substitute treatment for which a patient has cover and for which a Medicare benefit is payable for the associated professional service (Department of Health and Ageing 2010).

[3] Estimated population of New Zealand in 2000 was 3,857,800 (Statistics New Zealand 2008).

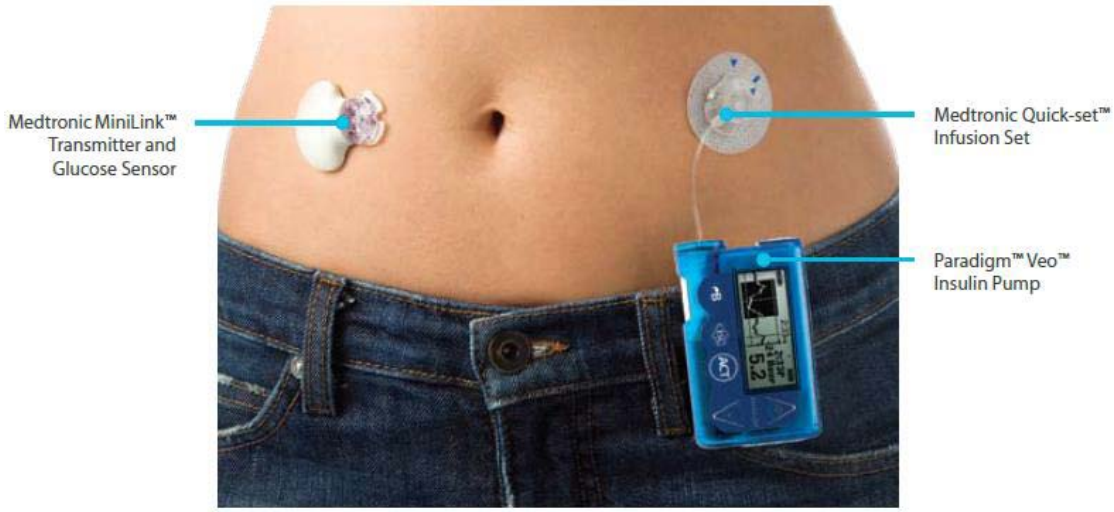


Figure 1 The Medtronic Paradigm Veo™ System (Medtronic Australasia 2010).

## COMPARATORS

Type 1 diabetics are frequently treated with multiple daily injections of slow-acting insulin or insulin analogues (Cohen et al 2007). Injection regimes are usually informed by self-monitoring of blood glucose by capillary finger-prick test, or continuous subcutaneous monitoring may be employed. Standard pumps without the use of CGM data may be used in regimes based on capillary blood glucose measurements (Jacobsen et al 2009).

## SAFETY AND EFFECTIVENESS ISSUES

Continuous glucose monitoring has previously been assessed for use in Type-I diabetes and for women with gestational diabetes.

Literature detailing the use of closed-loop insulin delivery is extensive and many small studies were identified. Therefore, this summary only considers larger studies and Australian research in determining whether closed-loop systems offer safe and improved management of hypoglycaemia, relative to the appropriate comparators.

The RealTrend study in France randomised 132 adults and children[4] to receive standard insulin pump or closed-loop therapy across eight centres, and followed outcomes for six months (Raccah et al 2009) (level III-1 intervention evidence). All subjects had uncontrolled type 1 diabetes (glycated haemoglobin ≥ 8%)[5] and were being treated with multiple daily injections. Patients assigned to closed-loop therapy were fitted with the Medtronic MiniMed Paradigm Real-Time system (PRT group) and agreed to wear the sensor component for at least 70 per cent of the study period. Outcomes of interest, obtained for 115 patients, included HbA1C levels and glycaemic variability. A difference of ≥ 0.5 per cent between treatment groups was

[4] 81 adults and 51 children aged 2to 65 years.
[5] Glycated haemoglobin (HbA1C) is an index of mean blood glucose concentration. The internationally recommended target is HbA1C < 7% American Diabetes Association (2009). 'Standards of medical care in diabetes--2009', *Diabetes Care*, 32, S13 - S61..

taken as clinically meaningful. It is critical to note that because HbA1C levels are measured and sometimes reported as a per cent, a change of ≥ 0 5 per cent in fact represents an absolute change.

Screening was performed to determine HbA1C levels at study commencement (visit 1), three and six months.[6] Two weeks after screening, biochemical hyper- and hypoglycaemic parameters were collected using a blinded continuous glucose monitoring (CGM) device over three days[7]. Blinded CGM data were retrieved at the end of this period (visit 2), and PRT patients were then asked to start using the unblinded sensor component of their closed-loop equipment while continuing multiple injection treatment for nine days. During this period, PRT patients were free to use CGM information as desired. At visit 3, insulin pump therapy began in both groups – patients in the PRT started using the pump function of their device, while subjects in the standard continuous subcutaneous insulin infusion (CSII) group were fitted with the Medtronic MiniMed Paradigm 512/712 (no CGM). Subjects in both groups continued use of their usual blood glucose meters to obtain a minimum of three daily readings, which served as reference for therapeutic decisions. The PRT group were advised on appropriate pump programming in response to CGM information.

One month after pump therapy commencement (visit 4), data from both groups devices were downloaded and patients discussed treatment with a study physician. Sensor alarm settings for hypo- and hyperglycaemia were adjusted as necessary. At the conclusion of three months pump therapy (visit 5), data were again downloaded, blood samples were taken for HbA1C determination, and treatment guidelines adjusted as required. Three days before the final study visit, following six months of pump therapy, all subjects again wore a blinded CGM device. Blinded CGM, PRT and CSII data were downloaded at study conclusion.

Although analysis was possible for 115 patients, only 91 out of this full set of patients were protocol compliant. Consequently, analysis was conducted for the full set and then separately for the 91 compliant patients. Of the 55 PRT patients, 23 failed to comply with the study protocol, i.e. did not use the sensor component of their device at least 70 per cent of the time, whereas 59 of the 60 CSII patients met the protocol requirements (one failed screening).

In the full set analysis, HbA1C levels between baseline and study end were significantly reduced in both groups (PRT -0.81 ± 1.09%, $p < 0.01$; CSII -0.57 ± 0.94%, $p < 0.001$), but the difference in favour of the PRT was not statistically significant ($p=0.087$). For patients who were fully compliant with the protocol, HbA1C was significantly more reduced among PRT subjects (PRT -0.96 ± 0.93%, $p < 0.001$; CSII -0.55 ± 0.93%, $p < 0.001$; intergroup comparison, $p=0.004$) (Table 1).

[6] Study physicians and patients were blinded to the centralised HbA1C data.
[7] This process was required to initialise the closed-loop algorithm.

The initial decline in HbA1C between screening and baseline could indicate an immediate benefit of exposure to CGM data and possibly explain blunting of the difference seen between baseline and study end. The authors suggest a more meaningful comparison of HbA1C data between screening and study end, however such an analysis falls outside the scope of this summary which is limited to appraisal of CGM and insulin pump therapy in tandem, not the benefits of CGM alone.

Analysis of glycaemic control for the full set of 115 subjects showed a decrease in mean glucose concentration among both groups between baseline and study end. This reduction was significantly greater in the PRT group (-30.6 ± 54.0) than in the CSII group (-10.8 ± 39.6, p=0.005). Significant differences favouring the PRT group were also observed with respect to hyperglycaemia, mean amplitude of glycaemic excursions and overall standard deviation of blood glucose values. Similarly, trends of improved glycaemic variation were observed among protocol compliant patients (n = 91), although it is thought that the small sample size meant that some trends did not reach statistical significance. Measures of hypoglycaemia remained constant and comparable in both groups. Results for changes in the glycaemic profiles of the patient groups are summarised in (Table 1).

Table 1 Changes in measures of glycaemic variability from baseline to end of study

| | Full patient set analysis | | Protocol compliant analysis | |
|---|---|---|---|---|
| | PRT | CSII | PRT | CSII |
| n | 46# | 54# | 30# | 53# |
| **Absolute per cent Δ HbA1C** | -0.81 ± 1.09 | -0.57 ± 0.94 | -0.96 ± 0.93† | -0.55 ± 0.93 |
| **Δ Blood glucose (mg/dL)** | -30.6 ± 54.0* | -10.8 ± 39.6 | -39.6 ± 55.8* | -9.0 ± 39.6 |
| **Δ Hyperglycaemia > 190mg/dL** (hrs/day) | -3.5 ± 4.8* | -0.7 ± 3.8 | -4.1 ± 5.1* | -0.6 ± 3.8 |
| **Δ Hyperg**lycaemia AUC‡ (mg/dL/day) | -17.1 ± 31.7† | -5.8 ± 26.7 | -19.1 ± 35.5† | -5.2 ± 26.5 |
| **Δ Hyperglycaemia (episodes/day)** | -0.2 ± 0.7 | -0.2 ± 0.7 | -0.2 ± 0.7 | -0.2 ± 0.7 |
| **Δ Hypoglycaemia < 70mg/dL** (hrs/day) | 0.3 ± 1.4 | 0.0 ± 1.2 | 0.6 ± 1.3 | 0.0 ± 1.2 |
| **Δ Hypoglcaemia** AUC (mg/dL/day) | 0.4 ± 1.3 | 0.0 ± 1.8 | 0.7 ± 1.3 | 0.0 ± 1.8 |
| **Δ Hypoglycaemia (episodes/day)** | 0.1 ± 0.9 | 0.1 ± 0.7 | 0.2 ± 1.0 | 0.1 ± 0.7 |
| **Δ MAGE**§ (mg/dL) | -27.5* | -16.2 | -20.4 | -16.2 |
| **Δ Standard deviation** | -15.8* | -5.7 | -11.3 | -5.7 |
| **Δ Daily insulin dose (units/day)** | 6.8 ± 17.3† | 1.5 ± 1.91 | 6.2 ± 14.8 | 1.1 ± 8.4 |

Data are means ± standard deviation or means. *p ≤ 0.005 vs. CSII group. †p ≤ 0.05 vs. CSII group. ‡ area under curve. § mean amplitude of glycaemic excursions. #Discrepancies in n for various patient groups due to problems ascertaining loss-to-follow up. Adapted from Raccah et al 2009.

Tabulated patient numbers for the various groups do not appear to match with the in text data and there were problems ascertaining where patients may have been lost. The authors were contacted regarding this but no response was obtained. It is also uncertain whether the results for change in hyperglycaemia episodes per day are reliable.

The large standard deviations observed are a cause for concern as this indicates a large degree of variability within each group. The authors duly acknowledge the high attrition rate as a major limitation, and propose that a more comprehensive run-in period could have selected for the most motivated patients. Additionally they conclude that the short duration does not provide information on the long-term impact of the treatments. Their results suggest patients who incorporate pump therapy with at least 70 per cent sensor component use can expect some additional benefit in glycaemic control. However, benefits in hypoglycaemic profiles were not statistically or clinically different between patients receiving CGM guided treatment (closed-loop) or those with stand-alone pump therapy (Raccah et al 2009).

A UK study described three randomised crossover trials investigating closed-loop and standard continuous subcutaneous insulin infusion. Nineteen type 1 diabetes patients aged 5 to 18 years were recruited of whom 17 were studied overnight for 33 closed-loop and 21 continuous infusion sessions, following. The aim was to determine whether closed-loop insulin delivery could control overnight blood glucose in young people (Hovorka et al 2010) (level II intervention evidence). Main outcomes were time for which plasma glucose was in target range (3.91 to 8.00 mmol/L) or in the hypoglycaemic range ($\leq$ 3.90mmol/L). Secondary outcomes were mean glucose concentration, time for which glucose concentration was higher than 8.0mmol/L, mean rate of insulin infusion and mean plasma insulin concentration. Figure 2 shows the randomised crossover design of the three studies.

On all study occasions, plasma glucose was obtained via sampling cannula at regular intervals to validate the accuracy of sensors used for continuous glucose monitoring. Blood glucose data were not used to calculate or change insulin doses in any groups during any of the protocols. APCam01 used the Guardian Real-Time (Medtronic, Northridge, CA) during closed-loop control and the non-real-time CGMS Gold (Medtronic) during CSII for sensor glucose data. The relative absolute difference between sensor and blood glucose data was 9.2 (4.3-16.7) per cent for the Guardian Real-Time and 7.6 (3.8-14.1) per cent for CGMS. In APCam02 and APCam03, sensor glucose data were obtained using the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA), for which the relative absolute difference from blood glucose data was 12.7 (5.6-21.9) per cent. The study pump employed in both closed-loop and CSII was the Deltec Cozmo (Smiths Medical, St Paul, MN), which replaced the patients' regular pumps for the duration of the study periods. The closed-loop system used an adaptive algorithm based on model-predictive control. Real-time glucose sensor data

were entered every 15 minutes and the algorithm calculated infusion rates for the insulin pump which was adjusted manually by a nurse (Figure 3). The algorithm was initialised using data on patient weight, total daily insulin dose and basal insulin requirements.

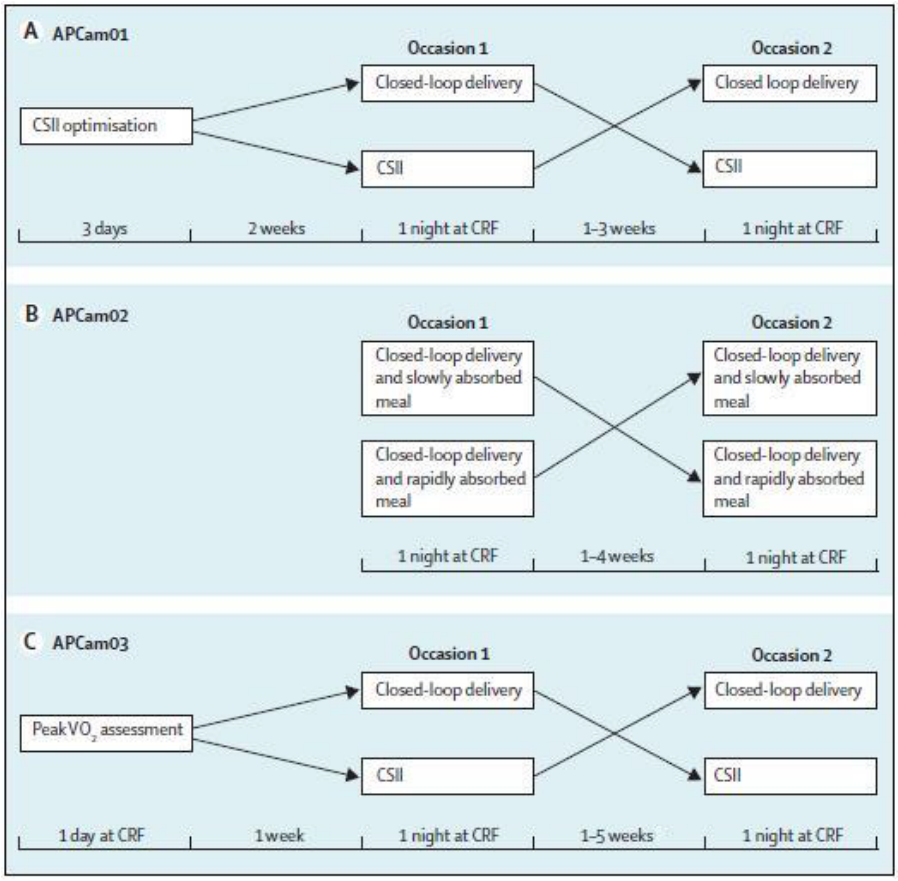


Figure 2 Randomised crossover design of the APCam studies. (A) 12 nights per treatment. (B) Six nights per treatment (C) Nine nights per treatment. APCam = Artificial Pancreas Project at Cambridge. CSII = continuous subcutaneous insulin infusion. CRF = clinical research facility. Peak $VO_2$ = maximum oxygen uptake (Hovorka et al 2010).

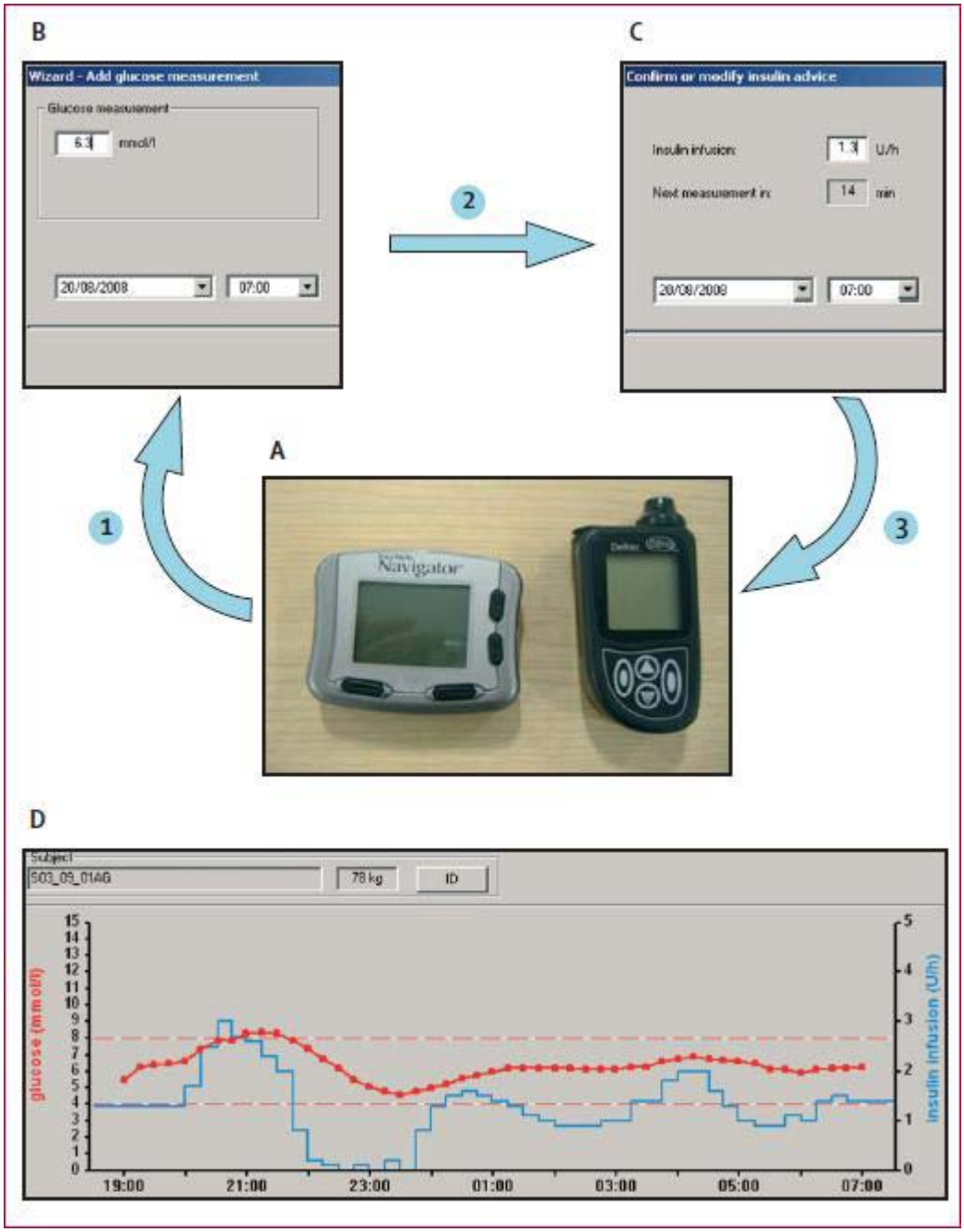


Figure 3 Closed-loop algorithm. Manual operation consists of three steps repeated in 15 min cycles. 1: Research nurse reads sensor glucose from CGM display (A) and enters glucose concentration in workflow wizard running on a laptop (B). 2: Wizard calls the control algorithm, which calculates the rate of insulin infusion, subsequently displayed by the workflow wizard (C). 3: Research nurse manually set infusion rate on insulin pump (A). FreeStyle Navigator CGM and Deltec Cozmo pump are shown (A). Graphical user interface shown at (D). Red circle indicates sensor glucose while blue line show insulin infusion obtained during a sample study. Dashed red lines designate target glucose range (Hovorka et al 2010).

In APCam01, 13 patients aged 5 to 18 years were randomly assigned treatment with overnight closed-loop delivery or standard treatment on two occasions with a one to three week interval. Two weeks prior to study commencement, insulin pump delivery was optimised by analysis of non-real time sensor glucose over 72 hours. On both occasions, patients ate a meal of choice (mean carbohydrates = 87 ± 23g) at 18.00 and

were administered 9U (nine units) of prandial insulin calculated in accordance with their insulin-to-carbohydrate ratio and capillary finger-stick glucose value. Closed-loop delivery or standard CSII was between 20.00 and 8.00. On CSII nights, standard insulin pump settings were applied. Results for APCam01 showed that more time was spent in the plasma glucose target range during closed-loop delivery than during CSII, though the difference was not significant. It is necessary to note that for the results of the primary analysis (which used re-sampling) significance was corrected at 0.0125 using a non-parametric permutation test. Results for APCam02 are not reported, since this trial assessed two closed-loop control scenarios, not closed-loop control against an appropriate comparator. In APCam03, ten patients (aged 12 to 18 years) were assigned for two study occasions. The patients exercised on a treadmill for 45 minutes (18.00 – 18.45) at 55 per cent of peak $VO_2$ with a five minute break at the half-way point. Closed-loop or CSII was from 20.00 to 8.00. On CSII nights, patients' standard pump settings were applied. Results are summarised in Table 2

Table 2 Outcomes of APCam01 and APCam03

| | APCam01 (n = 12) | | | APCam03 (n = 9) | | | APCam01 and 03 combined (n = 21) | | |
|---|---|---|---|---|---|---|---|---|---|
| | CL | CSII | p | CL | CSII | p | CL | CSII | p |
| Proportion of time for plasma glucose in target range (%) | 52 (43-83) | 39 (15-51) | 0.06 | 78 (60-92) | 43 (25-65) | 0.025 | 60 (51-88) | 40 (18-61) | 0.002 |
| Proportion of time for plasma glucose ≤ 3.90mmol/L (%) | 1.0 (0.0-7.1) | 2.0 (0.0-41) | 0.13 | 10 (2.0-15) | 6.1 (0.0-44) | 0.27 | 2.1 (0.0-10) | 4.1 (0.0-42) | 0.03 |

Data are median (interquartile range). Target range = 3.91 to 8.00mmol/L. CL = closed-loop delivery. CSII = continuous subcutaneous insulin infusion. Adapted from Hovorka et al 2010.

Secondary outcomes[8] were derived from analysis of pooled APCam01 and APCam03 data and suggested[9] that closed-loop delivery increased time in the plasma glucose target range and reduced time in the hypoglycaemic range (< 3.90mmol/L). Time in the target range was more apparent after midnight, when the authors suggest closed-loop control became fully effective. Closed-loop delivery performed consistently better than CSII at low and high plasma glucose concentrations (Figure 4).

[8] Mean glucose concentration, time for which glucose concentration was higher than 8.0mmol/L, mean rate of insulin infusion and mean plasma insulin concentration.
[9] The authors note that in the secondary analysis, no formal adjustment was performed as in the primary analysis. Results are therefore recommended as hypothesis-generating rather than conclusive.

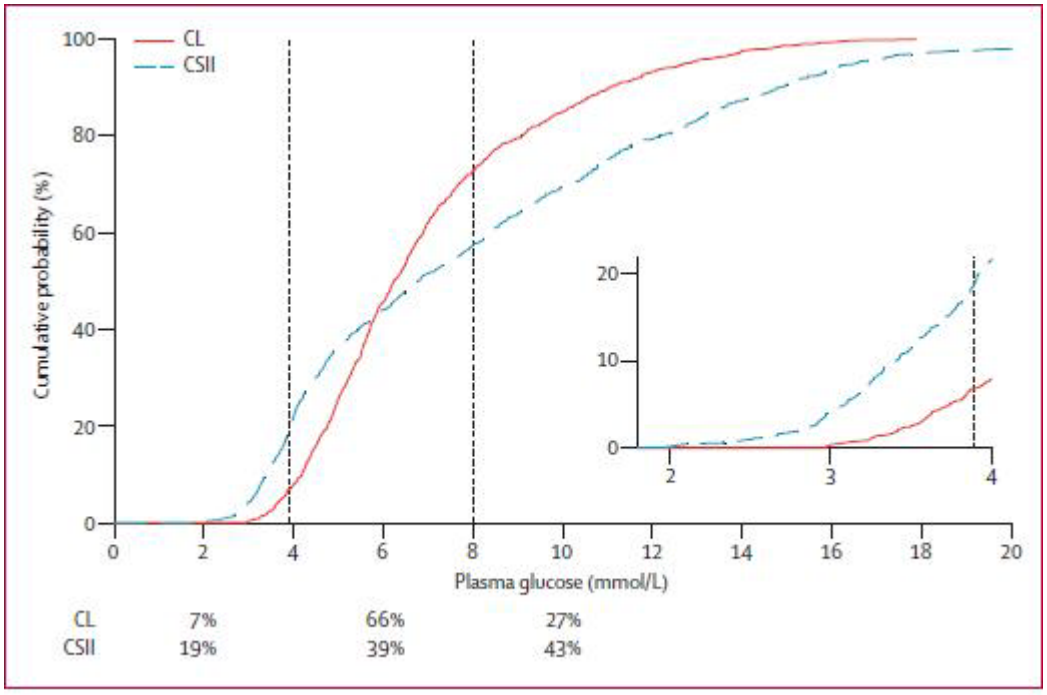


Figure 4 Cumulative probability of plasma glucose during closed-loop delivery and CSII (APCam01 and03). Vertical dashes indicate plasma glucose target range (3.91-8.00mmol/L). Inset shows detail for low glucose concentrations. Numbers below are the total percentage of time spent less than, within, or higher than target range from closed-loop commencement until 8.00 the following day (Hovorka et al 2010).

Importantly, the devices used in this study required manual control by nurses and did not incorporate a wireless data transmission feature that characterises fully automated closed-loop systems, such as those manufactured by Medtronic. The authors indicated that the logical advancement toward such systems could improve closed-loop systems in the future. This logical progression to fully automated systems has in fact occurred, but appears to have been contemporaneous with recent publications detailing work in this area conducted in the preceding years. Though the distinction between fully automated and manually controlled systems in an institutional setting should not differ in terms of basic performance, the advantage of the former is the accessibility for regular use in home and every-day settings. Overall, the primary analysis provided the most relevant and promising data in this study, establishing some elementary evidence for the benefit of closed-loop insulin delivery to control nocturnal hypoglycaemia in children and adolescents.

A randomised multicenter study enrolled 146 type 1 diabetics (aged 12 to 72 years) to compare clinical effectiveness and safety of a closed-loop system[10] with a standard pump and blood glucose monitoring[11] (Hirsch et al 2008) (level III-1 intervention evidence). All patients had an initial HbA1C level ≥ 7.5 per cent. The six month study

[10] Medtronic Paradigm 722 System, incorporating continuous subcutaneous glucose monitoring.
[11] Medtronic Paradigm 715 Insulin Pump used in accordance with blood glucose measurements.

was conducted with a therapy goal to achieve HbA1C of 7.0 in adolescent subjects (without excessive hypoglycaemia[12]) and less than 7.0 in adults.

Subsequent to initial screening, subjects in both groups wore blinded CGM sensors (Medtronic, Northridge, CA) for 10 days to obtain baseline data. At the first visit, subjects underwent randomisation in a 1:1 ratio to either the sensor group using the Paradigm 722 System, or the control group using self-obtained blood glucose measurements and the Paradigm 715 Insulin Pump.[13] Subjects in the sensor group used real-time sensor features in addition to the Bolus Wizard™.[14] The Bolus Wizard™ was also available to the control group. Both groups received training in intensive management of diabetes, with the sensor group receiving additional training in the use of CGM data. Midway through the study (week 13) and at study conclusion (week 26) control subjects wore two subcutaneous blinded CGM sensors consecutively (two 3-day periods). HbA1C values were collected on each occasion and insulin pump data were downloaded. The primary end-point was average change in HbA1C measured from baseline to study end. Predetermined secondary end-points included percentage of subjects achieving HbA1C level of 7.0, area under the curve (AUC) for hypo- and hyperglycaemia, incidence/frequency of hypo- and hyperglycaemic events, and safety. Data were obtained for 138 subjects who completed the study. Results for change in HbA1C are summarised in Table 3.

Change in HbA1C levels from baseline was significant for both groups ($p < 0.001$), however, the difference between groups was not statistically significant ($p=0.371$). It has been reported elsewhere (Raccah et al 2009) that an absolute difference in HbA1C of $\geq 0.5$, the magnitude of difference noted in this study, can be considered as clinically important. This was independently substantiated by personal communication with a diabetes specialist (University of Adelaide). It should be noted that the effect of sensor use compliance was marginally significant ($p=0.046$) for HbA1C outcomes. Each 10 per cent increase in compliance was associated with a 41 per cent increase in the probability of an absolute HbA1C reduction of 0.5.

Twenty (30.8%) of sensor subjects achieved HbA1C levels of seven per cent by midway through the study, while eight (11.1%) controls achieved this target ($p=0.007$). However, subjects remaining within target at study end did not show a statistically significant difference between groups; 16 (24.2%) in the sensor group versus 12 (19.4%) in the control group. The number of sensor subjects who reached seven per cent HbA1C at either midway or study end was greater ($p=0.003$) than the number of controls.

[12] A severe hypoglycaemic event was defined as a clinical episode of hypoglycaemia resulting in seizure or coma, requiring hospital admission or intravenous glucose/glucagon, or any hypoglycaemia requiring another person's assistance.
[13] Apart from the Paradigm 722–glucose sensor communication, functionality of pumps is identical.
[14] Bolus Wizard™ generates information enabling patients to modify insulin infusion as necessary.

Table 3 Change in HbA1C from baseline in all per protocol, adult and adolescent subjects

| | Mean (SD) | LS mean difference (SE) | p |
|---|---|---|---|
| CG (n=72) | | | |
| Baseline | 8.39 (0.64) | | |
| End of study | 7.84 (0.81) | NA | |
| Change | -0.55 (0.72) | | p < 0.001 |
| SG (n=66) | | | |
| Baseline | 8.49 (0.76) | | |
| End of study | 7.77 (0.92) | NA | |
| Change | -0.72 (0.71) | | p < 0.001 |
| Total subjects (n=138) | | | |
| Baseline | 8.44 (0.70) | | |
| End of study | 7.80 (0.86) | NA | |
| Change | -0.64 (0.71) | | p < 0.001 |
| Between group difference | NA | 0.112 (0.125) | 0.371 |

LS mean = least square mean from ANCOVA model. p-value for between group difference is from ANCOVA model. Adapted from Hirsch et al 2008.

For hyperglycaemia (> 180mg/dL) area under curve analysis, both study groups experienced a significant decrease in mean values at study end (control group, -9.7 ± 16.5mg/dL/min; sensor group, -11.3 ± 19.3mg/dL/min, p < 0.0001). However, the difference in change from baseline between groups was not significant (2.8mg/dL/min, p=0.291). Mean hyperglycaemic events per patient per day at baseline for control and sensor subjects were 2.667 ± 0.649 and 2.635 ± 0.635, respectively. Comparison within groups showed small changes in the number of hyperglycaemic events at study end (controls, 2.657 ± 0.805, p=0.77; sensor group 2.869 ± 0.913, p=0.03). Change between groups was not significant. For hypoglycaemia (< 70mg/dL) area under curve, there was no mean change among the sensor group, but mean values in the control group increased significantly (p=0.001). Change from baseline between the groups was statistically significant (least square mean ± SE = 0.465 ± 0.121mg/dL/min, p < 0.0002). Mean hypoglycaemic events per patient per day at baseline for control and sensor subjects were 0.835 ± 0.728 and 0.838 ± 0.725, respectively. Hypoglycaemic events in control subjects increased significantly to 1.166 ± 0.744 (p=0.0008) at study end compared to sensor subjects (0.883 ± 0.756, p=0.62). There was no significant difference between groups.

Fourteen severe hypoglycaemic events occurred; 11 were in the sensor group, six of which occurred while the sensor was not being worn/used. For the remaining five events, a Safety Review Board established that subjects ignored alerts associated with low sensor readings, tended to inject multiple insulin boluses without using the Bolus Wizard (causing insulin-stacking), or 'blind bolused' (based treatment decisions on sensor readings only, without confirmatory blood glucose test). In terms of other

safety considerations, one patient twice experienced skin abscess at the insulin infusion site and one patient (sensor group) developed diabetic ketoacidosis.

Overall, these data suggest that improved glycaemic control is possible with the use of a closed-loop system, without increasing time spent in hypoglycaemia. However, compliance is highlighted as a major factor in the success or failure of closed-loop systems, and the authors rightly conclude that patient selection for CGM guided pump therapy needs to carefully assess willingness and ability to use the technology appropriately.

Conflict of interest issues were identified in this study, a number of the authors having received honoraria and grant support from several manufacturers (including Medtronic) and pharmaceuticals companies (Hirsh et al 2008).

The majority of studies identified have included clinician-led review and adjustments to insulin delivery when using closed-loop systems. Since such protocols may impact on accrued glycaemic improvements, an Australian study (n=62) investigated whether type 1 diabetics can adapt to and employ real-time CGM to increase their own glycaemic control (O'Connell et al 2009) (level II intervention evidence). The effect of patient-led closed-loop control was compared with standard insulin pump therapy.

The RCT was conducted across five Australian centres, and recruited diabetics aged 13 to 40 years in age- and sex-matched pairs. When an individual consented to participate, the next suitable age- and sex-matched person was approached to complete the pair. Recruited pairs were then randomised by computer-generated schedule to either self-led closed-loop (intervention) or open-loop (standard pump) therapy and studied over three months. All pump and sensor equipment was supplied by Medtronic Australia. Time spent in the target glycaemic range of 4.0 to 10mmol/L was the primary outcome. Secondarily, differences in HbA1C, proportion of time spent in hypoglycaemia ($\leq$ 3.9mmol/L) and hyperglycaemia ($\geq$ 10.1 mmol/L), and glycaemic variability were assessed.

At baseline and end-of-study, all participants underwent six days of blinded CGM, using the CGMS Gold (Medtronic), and HbA1C measurements. Participants in the intervention group received standard instruction on using CGM enabled pumps from the same instructor across all sites. Systems were calibrated using capillary blood glucose and alarm features were set to alert the user at sensor glucose levels less than 4.5 and greater than 12.0mmol/L. Subjects were finally instructed to perform confirmatory blood glucose measurements if real-time data suggested administration of therapeutic action (e.g. correction bolus of insulin).

Seven participants withdrew from the study; five from the intervention group and two controls. End-of-study data were therefore available for 26 out of 31 participants in the intervention arm and for 29 out of 31 controls. Median time spent using the sensor component in the intervention group was 62.5 per cent (range 17.7% to 93.8%) during

the three-month study period. Eleven out of 25 participants were compliant with the protocol requirement of ≥ 70 per cent sensor use. Glycaemic outcomes for both groups (compliant and non-compliant patients) are summarised in Table 4.

Table 4 Glycaemic outcomes

| | Baseline | | End-of-study | | | |
|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Difference [95% CI]* | p-value |
| HbA1C (%) | 7.3 ± 0.6 | 7.5 ± 0.7 | 7.1 ± 0.8 | 7.8 ± 0.9 | -0.43 [-0.19 to -0.75] | 0.009 |
| Time spent (%): | | | | | | |
| 4-10mmol/L | 62.1±12.5 | 58.0±9.4 | 57.2±11.3 | 53.9±15.0 | 1.72 [-5.7, 8.81] | 0.63 |
| **≤3.9mmol/L** | 9.3±5.9 | 10.3±7.6 | 9.2±8.7 | 9.1±6.9 | 0.54 [-3.48, 4.55] | 0.79 |
| **≥10.1mmol/L** | 28.6±13.5 | 31.7±13.0 | 33.6±12.7 | 37.0±17.3 | -2.18 [-10.0, 5.69] | 0.58 |

Adapted from O'Connell et al 2009. Data are mean ± SD. *Difference between end-of-study means, adjusted for baseline values.

Overall, HbA1C reduction was achieved by 16 out of 26 (64%) participants who used closed-loop management, compared with only five out of 29 (17%) participants who used standard pumps. At study-end HbA1C levels below 7.0 per cent were achieved more often among the intervention group compared to controls (56% versus 17%, respectively; p=0.004). End-of-study HbA1C levels were lower (6.7%) among patients with sensor use of 70 per cent or more, while those not compliant with this level of usage had significantly worse outcomes (HbA1C = 7.4%), p=0.04. No episodes of severe hypoglycaemia or diabetic ketoacidosis occurred.

The authors note that the nature of the intervention in their study precluded participant blinding and this is a potential source of ascertainment bias. Individuals with suboptimal diabetes control were excluded; therefore the findings may only be applicable within patient groups who are already well controlled on insulin pump therapy. Even among these motivated groups, this study has revealed that compliance may remain an obstacle in the uptake of patient-led closed-loop devices. Nonetheless, it is anticipated that continued technological developments, particularly in relation to better algorithms will overcome limitations related to current behavioural responses still required for optimal effectiveness of closed-loop devices. No differences in time spent in hypoglycaemia were observed between the study groups, showing that although blood glucose was better overall due to closed-loop management, neither treatment was more effective in avoiding hypoglycaemia.

Conflicts of interest were noted for a number of the authors, having variously obtained honoraria and education, research and/or travel support (O'Connell et al 2009).

Results of a US study showed positive effects for closed-loop model predictive control, but due to small sample size (n = 8), these are not discussed in detail. The study indicated closed-loop control was at least as effective as patient-led open-loop control in the management of post-prandial rises in blood glucose. Of more interest,

closed-loop demonstrated a clear advantage over open-loop in the prevention of overnight hypoglycaemia (Clarke et al 2009).

### COST IMPACT

In Australia, for the year 2004-05, diabetes accounted for 1.9 per cent of the year's total allocated recurrent health expenditure with a direct health-care expenditure of $989 million. It is estimated that expenditure on Type 1 diabetes accounted for 14% of this expenditure, at $139 million and $22 million related to diabetes prevention services. The greatest proportion of diabetes expenditure was on hospital services, $371 million (37.5%) followed by out-of-hospital medical services, $288 million (29.1%), diabetes-related pharmaceuticals, $275 million (27.8%), and research, $55 million (5.6%).

The National Diabetes Services Scheme (NDSS) provides access to products and services including syringes, insulin infusion pump consumables and blood and urine glucose testing reagents that are required for self-management of diabetes at prices subsidised by the Australian Government. The state and territory governments contribute co-payments for needles and syringes. In 2006–07, there were 844,062 people registered with the NDSS and the Australian government expenditure on the NDSS in that financial year was approximately $114 million (Pieris-Caldwell et al 2008).

Medtronic Australasia Pty Ltd markets the Paradigm Veo™ System for A$8,000; however the transmitter[15] costs an additional A$1,250. Cost of sensors is also extra; A$725 for a box of 10 or A$310 for a box of four. Each sensor typically lasts for six days of normal use, after which a replacement is recommended (Medtronic personal communication).

### ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

### OTHER ISSUES

There is evidence to suggest that sensor-guided subcutaneous insulin delivery via an external pump can experience delays and variability in absorption (Hovorka 2006). This has led some investigators to consider the use of implantable intraperitoneal closed-loop devices. To some extent, these have demonstrated fast insulin action and low basal plasma insulin levels. The claimed benefit is tight glucose control and low incidence of hypoglycaemic events (Renard et al 2010).

A case-series in the US has reported the results of experiments with a bi-hormonal closed-loop system at an early stage of development (El-Khatib et al 2010). Bi-hormonal systems differ from other closed-loop equipment in the ability to deliver

[15] The transmitter does not attract a private health insurance rebate.

glucagon in addition to insulin, thus potentiating a broader scope for glycaemic control via processes not dissimilar to the bi-hormonal secretions of a normal pancreas. The appeal in using the two hormones is the ability of glucagon to counteract the effects of insulin and increase glucose production by the liver, thereby stabilising post-prandial glucose concentrations and preventing hypoglycaemia. It is re-emphasised, however, that the equipment used in these experiments appeared to be at prototype level. The protocol required two intravenous catheters for sampling of blood glucose, an insulin analogue and glucagon. Additionally, three pumps were connected to each patient; one for glucagon infusion, one for low resolution insulin dosing, and one for high resolution insulin dosing (insulin diluted to achieve increments of 0.005U, below the pump's minimum bolus size of 0.05U). Since these requirements are cumbersome even in an institutional setting, considerable development of bi-hormonal closed-loop systems will be necessary if such therapy is to reduce the risk of hypoglycaemia in every-day settings (El-Khatib et al 2010).

### SUMMARY OF FINDINGS

Most of the identified sources have shown at least some improvement in overall management of blood glucose associated with closed-loop insulin delivery. However, outcomes in terms of hypoglycaemia were not consistent. One study provided relatively tenuous evidence for improved hypoglycaemic control with closed-loop (Hovorka et al 2010), one indicated a marked statistical difference between groups for hypoglycaemia despite small sample size (Clarke et al 2009), and the remaining studies did not show differences in hypoglycaemia outcomes.

### HEALTHPACT ASSESSMENT:

The modest levels of evidence demonstrate the potential for further development and accessibility of closed-loop insulin delivery. However, HealthPACT have concerns about the reliability of the sensor components and therefore wish to monitor the technology, which will be reviewed in 24 months time.

### NUMBER OF INCLUDED STUDIES

| | |
|---|---|
| Total number of studies | 5 |
| Level II intervention evidence | 2 |
| Level III-1 intervention evidence | 2 |
| Level III-3 intervention evidence | 1 |

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**SEARCH CRITERIA TO BE USED:**

Diabetes mellitus, type 1/blood glucose

Closed loop insulin delivery
Artificial pancreas
Continuous glucose monitoring, subcutaneous
Blood glucose/metabolism