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Invited Review

Is an artificial pancreas (closed-loop system) for Type 1 diabetes effective?

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Abstract

The artificial pancreas is now a viable treatment option for people with Type 1 diabetes and has demonstrated improved glycaemic outcomes while also reducing the onus of self-management of Type 1 diabetes. Closed-loop glucose-responsive insulin delivery guided by real-time sensor glucose readings can accommodate highly variable day-to-day insulin requirements and reduce the hypoglycaemia risk observed with tight glycaemic control in Type 1 diabetes. In 2011, the James Lind Alliance research priorities for Type 1 diabetes were produced and priority 3 was to establish whether an artificial pancreas (closed-loop system) for Type 1 diabetes is effective. This review focuses on the progress that has been made in the evolution of closed-loop systems as an effective treatment option for Type 1 diabetes. Development of closed-loop systems has advanced from feasibility evaluations in highly supervised settings over short periods, to clinical studies in free-living, unsupervised conditions lasting several months. The approval in the USA of the first hybrid closed-loop system (MiniMed® 670G pump, Medtronic, Northridge, CA, USA) in 2016 for use in Type 1 diabetes reflects these advancements. We discuss the evidence from clinical studies that closed-loop systems are effective with improved glycaemic outcomes, reduced hypoglycaemia and had positive end-user acceptance in children, adolescents, adults and pregnant women with Type 1 diabetes. We also present the outlook for future closed-loop systems in the treatment of Type 1 diabetes and identify the challenges facing the wide-spread clinical adoption of this technology.

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Introduction

This review outlines progress in the development of the artificial pancreas as a treatment for Type 1 diabetes. We reflect on the status of artificial pancreas technology in 2011, at the time the James Lind Alliance research priorities for Type 1 diabetes were set, current efficacy and safety data, and future challenges for widespread adoption of closed-loop systems.

Attainment of near normoglycaemia for people with Type 1 diabetes is difficult without hypoglycaemia and a high burden of diabetes self-care. The Diabetes Control and Complications Trial demonstrated benefits of intensive insulin therapy and led to increased uptake of insulin pumps (continuous subcutaneous insulin infusion, CSII) to achieve improved glycaemic outcomes, reduce hypoglycaemia risk and improve the quality of life for people with Type 1 diabetes [1,2].

Insulin pumps can be used in association with continuous glucose monitoring (CGM) systems, allowing users to manually adjust insulin delivery rates according to the CGM values (sensor augmented pump therapy). CGM systems, which measure real-time interstitial glucose concentration, have demonstrated steady improvements in reliability and accuracy. Use of CGM has demonstrated improvements in glucose control and reduced hypoglycaemia [3,4].

Closed-loop insulin delivery (the artificial pancreas) is more sophisticated, combining insulin pump and CGM with a control algorithm, delivering insulin in a glucose-responsive fashion by automatically modifying the insulin infusion rate based on the sensor glucose levels (single-hormone closed-loop systems). Glucagon or other hormones can also be delivered in a similar glucose-responsive manner within dual-hormone closed-loop systems.

The control algorithm is the key component of a closed-loop system, directing insulin delivery in response to sensor glucose levels while also accommodating variability between and within individual users, glucose sensor and insulin delivery limitations, and kinetic delays [5]. The control algorithm can be incorporated into the pump or located in a separate device, such as a smartphone (Fig. 1) and the components communicate wirelessly.

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What's new?

- Attainment of near normoglycaemia in Type 1 diabetes is challenging with currently available treatment options.
- The artificial pancreas (closed-loop) is an efficacious and safe approach for management of Type 1 diabetes in children and adults.
- For widespread clinical adoption of artificial pancreas systems, challenges of cost-effectiveness, user acceptance, and user and healthcare professional training need to be addressed.

The artificial pancreas in 2011: where were we?

The concept of closed-loop glucose control was initially introduced in the 1960s [6] with the first commercial artificial pancreas system produced in 1977 (the Biostator, Miles Laboratories, Elkhart, IN, USA) [7]. This device combined glucose monitoring from whole blood each minute with intravenous insulin and dextrose infusions. Limitations were related to algorithm simplicity, the size of the individual closed-loop system components, the need for intravenous access and wastage of venous blood. Focus turned to alternative access routes.

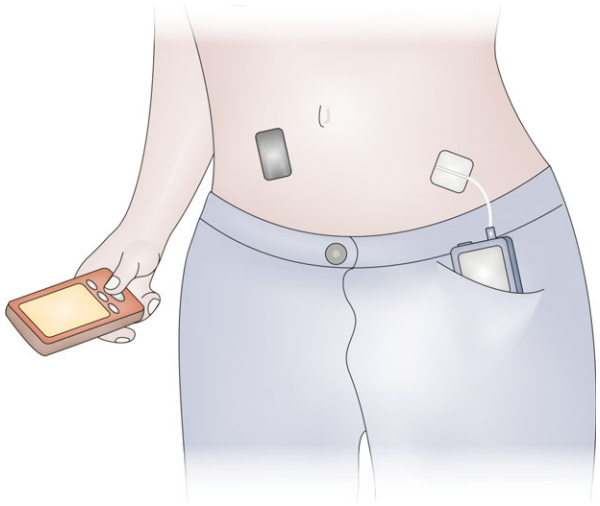

FIGURE 1 Artificial pancreas (single hormone). A sensor (black rectangle) transmits information about interstitial glucose levels to a mobile-phone-sized controller (red box located in the hand), which runs a control algorithm and interacts with the user. An insulin pump (blue box) delivers a rapid-acting insulin analogue subcutaneously. Insulin delivery is modulated in real-time by the control algorithm. The communication among system components is wireless. Reproduced with permission from Hovorka [5]. The control algorithm can be embedded in the pump (not shown).

Insulin pumps that deliver subcutaneous rapid-acting insulin were initially developed in the late 1970s [8], but increased utilization over the past 20 years is the result of improvements in the reliability of pump technology, reduced pump size and evidence of clinical benefit [9]. Early development of closed-loop systems was hampered by the limited precision and reliability of CGM systems, relatively slow absorption of rapid-acting insulin when delivered subcutaneously, and inadequate control algorithms to accommodate these issues and for inter- and intrasubject variability.

Significant improvements in closed-loop system components, particularly CGM accuracy and reliability, wireless connectivity and algorithm refinement, led to several different closed-loop research prototypes being developed using subcutaneous measurement of interstitial glucose and subcutaneous insulin delivery [5]. Delivery of insulin intraperitoneally has been shown to be feasible, but more attention has been given to the subcutaneous route [10]. Closed-loop prototypes include hybrid and fully closed-loop approaches, single- and dual-hormonal (glucagon) systems, and different closed-loop algorithms (Box 1).

Interest in the application of closed-loop technology for the management of Type 1 diabetes was supported by several international initiatives. The Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Project in 2005 aimed to expedite regulatory approvals, secure health insurance coverage, and facilitate clinician adoption of CGM and

Box 1 Closed-loop approaches and control algorithms

Closed loop approaches

Hybrid vs. fully closed loop systems
Hybrid closed-loop systems require meal announcements, whereas fully closed-loop systems are entirely automated

Single vs. dual-hormone closed-loop systems
Dual-hormone systems add glucagon to counteract the relatively long duration of action of subcutaneous insulin but increase system complexity and cost. The potential role of glucagon is further reduction in hypoglycaemia risk and addition of glucagon may achieve tighter glycaemic control by permitting more aggressive insulin delivery.

Algorithms

- **Model predictive control (MPC)** predicts glucose excursions using an individualized mathematical model of glucose regulation based on inputs such as insulin delivery. The model-predicted glucose concentration is compared with the measured glucose level, and the model is updated, calculating future insulin delivery rates to minimize the difference between the model-predicted glucose concentration and target glucose levels.
- **Proportional-integral-derivative (PID)** control adjusts the insulin delivery rate continuously by determining glucose excursions from three perspectives: deviation from target glucose (proportional component), area-under-the-curve between measured and target glucose (integral component), and the rate of change in the measured glucose levels (derivative component).
- **Fuzzy logic control** adjusts insulin delivery using approximate rules to reflect the knowledge of diabetes practitioners.

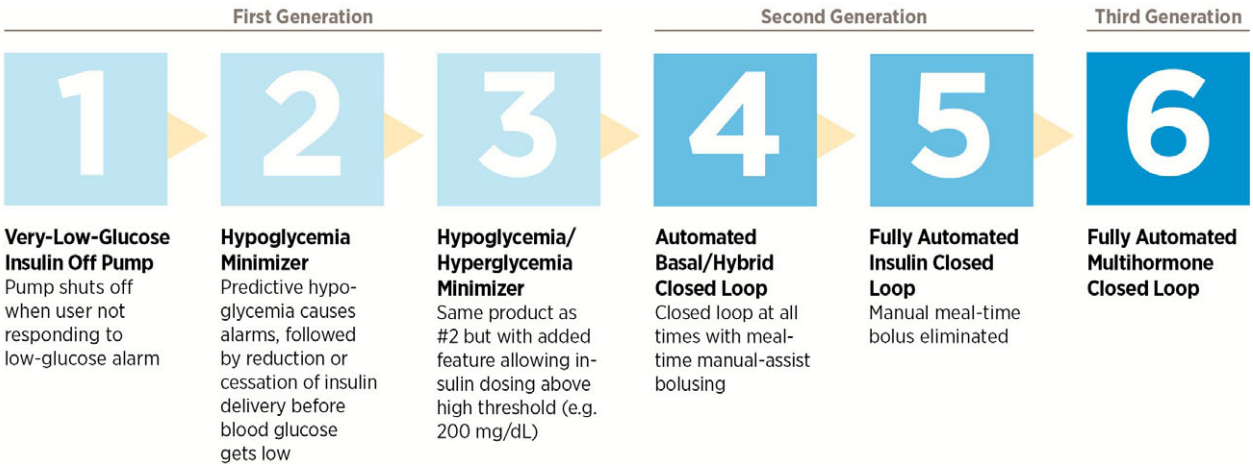

FIGURE 2 JDRF Roadmap to the Artificial Pancreas. The six developmental stages of artificial pancreas device systems. Reproduced with permission from JDRF.

artificial pancreas technologies. In 2006, the Food and Drug Administration (FDA) added the artificial pancreas to the Critical Path Initiative for the paediatric population to address regulatory challenges and promote translation of this unique medical product into clinical practice. The collaborative European AP@home Consortium, initiated in 2010, aimed to compare closed-loop insulin delivery with conventional insulin therapy in real-world settings by way of multinational controlled trials.

In 2009, the simplest form of automated insulin delivery (Fig. 2) became commercially available; an insulin pump with an integrated CGM system that suspends insulin delivery automatically for up to 2 h when hypoglycaemia is detected, and the hypoglycaemia alarm is not acknowledged. Post-marketing studies with low-glucose suspend pumps in children and adults with Type 1 diabetes showed reduced frequency and duration of nocturnal hypoglycaemia [11] and also reduced frequency of severe hypoglycaemia [12]. Predictive low-glucose suspend allows for automatic insulin infusion suspension when sensor glucose is predicted to cross the pre-programmed CGM threshold value. These systems were the first approved non-adjunct use of CGM data for decisions regarding insulin administration. Approval of these devices was very significant from a regulatory perspective for more advanced automated insulin delivery systems.

By 2011, at the time the James Lind Alliance priorities for Type 1 diabetes were published [13], closed-loop prototypes were being evaluated in closely supervised clinical research facility settings over short periods for feasibility assessments. Initial closed-loop studies were conducted during the night when most severe hypoglycaemic events occur, and glucose control is not so affected by meals and physical activity, which was assumed to ease regulatory approvals. Closed-loop insulin delivery, with the aim of reducing nocturnal hypoglycaemia, was assessed as a potential solution to this important clinical problem, particularly in young children. Randomized cross-over studies in young people and adults showed that closed-loop insulin delivery overnight was able to significantly increase the percentage of time spent within the target glucose range and reduce time in hypoglycaemia [14–17]. This was a significant step in demonstrating the potential of closed-loop systems in clinical practice.

Daytime closed-loop glucose control presents additional challenges such as variable dietary intake and exercise. Postprandial glucose control is particularly challenging with delayed absorption following subcutaneous insulin delivery and the unpredictable appearance of glucose from the meal. A pragmatic solution is to combine user-initiated prandial boluses with closed-loop operation (hybrid closed-loop systems). Although fully closed-loop systems are entirely automated offering the advantage of reduced user intervention, postprandial hyperglycaemic excursions and late postprandial hypoglycaemia are significant limitations with this approach and glucose control is significantly compromised compared with hybrid closed-loop at present [18].

A feasibility study in adults with Type 1 diabetes demonstrated that addition of glucagon to closed-loop systems (dual-hormone) at times of impending hypoglycaemia led to reduced time in hypoglycaemia [19]. Issues regarding glucagon stability after reconstitution still needed to be addressed.

Although inpatient studies demonstrated good evidence of efficacy and safety of closed-loop insulin delivery, evidence for closed-loop systems in the management of Type 1 diabetes under free-living conditions had not yet been demonstrated. User acceptance of closed-loop systems needed to be explored with potential barriers of perceived trust in automated insulin delivery and burden of device size and weight. Future success and speed of development of the artificial pancreas would depend on collaboration with regulatory bodies, the medical device industry, and healthcare insurance providers to ensure the availability and

affordability of this technology and reimbursement. Establishment of appropriate infrastructure, including patient and healthcare professional training would also need to be considered.

The artificial pancreas: where we are in 2018?

Since 2011, clinical studies have transitioned to lasting several months in unsupervised, free-living conditions using portable wireless closed-loop systems. Closed-loop insulin delivery has demonstrated efficacy and safety in the outpatient setting in children and adolescents, adults and pregnant women with Type 1 diabetes, and in hospitalized inpatients with hyperglycaemia. These studies have shown that closed-loop systems, compared with sensor augmented pump therapy or CSII, improve glycaemic control and reduce hypoglycaemia.

Efficacy of the artificial pancreas in adults and children with Type 1 diabetes

Two recent meta-analyses have evaluated the safety and efficacy of closed-loop therapy in non-pregnant people with Type 1 diabetes [20,21]. The larger of these included 41 studies (1042 participants). However, comparisons of clinical studies of closed-loop systems are limited by inconsistencies in outcome reporting and study design, short follow-up duration and small sample sizes. The JDRF Artificial Pancreas Project Consortium advocate the use of CGM glucose metrics (time in target glucose range, time in hypo- and hyperglycaemia, measures of CGM glucose variability) in addition to HbA_{1c}, safety and technical metrics as outcome measures in artificial pancreas clinical trials [22]. It is important that the hypoglycaemia threshold (< 3.0 mmol/l) recommended by the International Hypoglycaemia Study Group is reported in future trials [23].

Time in range

Meta-analysis data from 32 studies have shown that closed-loop systems increase time spent in near normoglycaemia (3.9–10.0 mmol/l) throughout 24 h by 9.6% compared with controls (140 additional min per 24 h period). The beneficial effect of closed-loop systems is most pronounced on the percentage of time spent in the target glucose range overnight, which is 15.2% greater than in controls [21]. Increased time in range with closed-loop systems is due to reduced time in hyperglycaemia (> 10 mmol/l) compared with controls.

Although dual-hormone systems have demonstrated greater improvements in time in target glucose range compared with single-hormone systems, almost all dual-hormone system studies have been relatively short and have been compared with pump therapy alone, whereas almost all single-hormone systems have been compared with sensor augmented pump therapy [20,21]. Few studies have directly compared single- and dual-hormone closed-loop systems and have been under supervised conditions and of short duration, but observed no difference in the time in target glucose range over 24 h [24].

Hypoglycaemia

Closed-loop systems reduce time spent in hypoglycaemia (< 3.9 mmol/l) by 1.5% (~ 20 min per 24 h period) compared with control [21]. Incidence of severe hypoglycaemia is very low in clinical studies comparing closed-loop with control so there is insufficient evidence to determine any benefit of closed-loop insulin delivery on severe hypoglycaemia. However, use of closed-loop systems was associated with a decrease in low blood glucose index overnight compared with controls, a measure of the risk of severe hypoglycaemia.

Clinical studies contrasting dual-hormone with single-hormone systems report 1.3% less time spent in hypoglycaemia (< 3.5 mmol/l) and eight fewer hypoglycaemic events with dual-hormone systems over 60 h [25]. The reduction in hypoglycaemia is observed with comparable mean glucose levels.

Mean glucose and HbA_{1c}

Compared with the control, use of closed-loop systems has a beneficial effect on the mean sensor glucose level over 24 h, which is reduced by 0.48 mmol/l in meta-analysis data [21]. These findings are consistent with a 3 mmol/mol (0.3%) reduction in HbA_{1c} observed with closed-loop systems compared with control in studies with a duration per intervention of > 8 weeks [21].

Glycaemic variability

In almost all closed-loop studies, glucose variability measures (standard deviation of the sensor glucose level between days) are lower with closed-loop systems than with controls [26].

Insulin requirements

Individual studies have conflicting results regarding the effect of closed-loop systems on total daily insulin dose. Meta-analysis data suggest there is no difference between closed-loop and control systems in the mean daily insulin requirement [20,21].

Efficacy of the artificial pancreas in pregnant women with Type 1 diabetes

Closed-loop insulin delivery has been shown to be effective and safe in women with Type 1 diabetes during pregnancy. In a randomized, cross-over study in pregnant women with Type 1 diabetes, overnight closed-loop therapy for 4 weeks resulted in increased time in target glucose range (3.5–7.8 mmol/l) by 15.2 percentage points (74.7% vs. 59.5%)

compared with sensor augmented pump therapy [27]. There was no difference between closed-loop and sensor augmented pump therapy in the percentage of spent time in hypoglycaemia. During a continuation phase of day and night closed-loop until delivery (up to 14.6 additional weeks which included antenatal hospitalizations, labour, and delivery), sensor glucose levels were in the target range 68.7% of the time. The impact of closed-loop insulin delivery on perinatal outcomes has not been established.

Efficacy of the artificial pancreas during physical activity

Glucose control during physical activity can be particularly challenging for individuals with Type 1 diabetes because of complex interactions between exercise-induced effects on glucose metabolism and exogenous insulin therapy. The risk of exercise-induced dysglycaemia deters many people with Type 1 diabetes from participating in and gaining benefits from physical activity. Closed-loop systems with autonomous modulation of insulin delivery in a glucose-responsive manner offer the potential to reduce the risks and burdens of exercise management in Type 1 diabetes.

Performance of closed-loop systems during physical activity has been evaluated, although most studies have been relatively small (~ 20 people). Closed-loop insulin delivery in adolescents with Type 1 diabetes improved glycaemic control and reduced time in hypoglycaemia (< 3.9 mmol/l) by 1.4% compared with remotely monitored sensor augmented pump therapy during winter sport activities at a ski camp [28]. Dual-hormone closed-loop systems have been shown to provide additional benefit over single-hormone closed-loop systems in reducing time in hypoglycaemia during announced exercise in adults with Type 1 diabetes [29,30].

Closed-loop insulin delivery has also been shown to be safe during and after unannounced exercise in the clinical research facility setting, with glucose values largely maintained within target range without increased risk of hypoglycaemia [31]. Diversity of physical activity (duration, intensity, and timing relative to food and insulin administration) remains challenging for fully automated closed-loop insulin delivery. Integration of additional signals from wearable technology, e.g. heart rate monitoring and accelerometery may lead to improved closed-loop performance during physical activity.

Psychosocial considerations of artificial pancreas technology

Long-term use of closed-loop technology will likely be influenced by user expectations and experience. Expectations include stability of glucose control, reduced requirement for glucose self-monitoring, reduced daily concerns and time-saving; however, trust in automated insulin delivery is perceived as a potential barrier [32].

Reported benefits of the artificial pancreas, aside from improved glycaemic control, include reduced fear of hypoglycaemia, reduced anxiety, 'time off' from the demands of diabetes, reassurance for both users and family members, improved sleep, increased confidence, excitement and empowerment, and more freedom to participate in exercise and unplanned activity. Burdens reported by users include the intrusiveness of alarms and associated sleep interruptions, size and appearance of the devices, greater time thinking about diabetes, technical difficulties, exercise limitations, and perceptions around deskilling and obsession with data. Individuals using the artificial pancreas for longer periods and more often, experienced greater benefits than those using the system for shorter periods and less frequently.

Individual users have variable degrees of engagement (a 'hands-off' approach with minimal input to high levels of engagement and adjustment of the control algorithm to their individual needs) and differing preferences with potential implications for effective long-term usage, associated glycaemic outcomes and training needs. Clinician attitudes to closed-loop systems have yet to be considered.

OpenAPS and LOOP communities suggest high user and parental interests in the technology [33]. The OpenAPS community comprises over 650 individuals globally who have built their own hybrid closed-loop systems, pairing open-source software (OpenAPS), small computing hardware, and currently available diabetes devices (older insulin pumps and CGM). This community has used these closed-loop systems in real-world settings for over 4.5 million hours. In this highly selective population, user self-reporting suggests OpenAPS is much safer than standard pump with CGM therapy, measured by time spent in hypo- and hyperglycaemia, with no self-reports of severe hypo- or hyperglycaemic events [34].

Current commercially available artificial pancreas systems

The MiniMed® 670G pump (Medtronic, Northridge, CA, USA), approved in 2016 by the U.S. FDA for use by people with Type 1 diabetes over 14 years of age, is a single-hormone hybrid closed-loop system with the control algorithm embedded in the insulin pump (Fig. 3). The pump basal rate is automated based on a proportional–integral–derivative algorithm with insulin on board feedback. Clinical trial evaluation to assess safety was non-randomized and lacked a control arm, therefore evidence regarding its efficacy is limited [35]. Some 94 adults and 30 adolescents used the closed loop system day and night for 3 months. There were no episodes of severe hypoglycaemia or ketoacidosis observed. Several other hybrid closed-loop systems are being developed for commercial use. Post-marketing studies are ongoing.

What does the future of the artificial pancreas look like?

Future closed-loop systems will utilize improved system components. Recent approval of non-adjunctive use of CGM

FIGURE 3 Hybrid closed-loop system comprising fourth generation Enlite 3 glucose sensor, MiniMed® 670G insulin pump, with an embedded proportional-integral-derivative algorithm with insulin feedback (Medtronic, Northridge, CA, USA. Reproduced with permission from Medtronic.

in the European Union (G5™ Mobile CGM) reflects improved accuracy and reliability of CGM, and is important for improved performance and acceptability of closed-loop systems. Factory calibration of CGM systems excludes an important source of user-introduced error and improves usability. CGM systems that require no calibration are now available (Dexcom G6). The Eversense CGM system (Eversense™; Senseonics Inc., Germantown, MD, USA) is a commercially available long-term fully implantable sensor and allows easy removal of the transmitter without the need for sensor replacement. However, the requirement for implantation and removal with minor surgery causes some discomfort for the patient and requires additional training for clinicians.

At present, meal announcement with accurate carbohydrate counting is recommended to achieve optimal glucose control. Ultra-rapid insulin analogues or use of adjuncts (pramlintide, glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors) to manage postprandial glucose control may further improve closed-loop system performance or even enable efficacious and safe fully automated closed-loop systems.

Addition of glucagon to closed-loop systems is limited at present by the need to exchange the glucagon depot every 24 h and side-effects including nausea. Novel glucagon analogues are under development but the full pharmacokinetic and safety profile is yet to be established.

Algorithms capable of integrating multiple signals may more accurately reflect the rapidly changing insulin requirements of a person with diabetes than CGM alone.

The speed of appearance of artificial pancreas systems into routine clinical practice will largely be dependent upon regulatory approvals. The FDA recently approved the first integrated CGM (iCGM) system (Dexcom G6) which can be combined with other medical devices as part of an integrated system including closed-loop systems. This device has been classified in class II enabling developers of iCGM systems the least burdensome pathway to bring products to market in the future. Whereas the FDA has taken positive steps to expedite similar products through regulatory procedures, the new European Medical Devices Regulation is likely to cause delays in development and approvals, and therefore appearance of artificial pancreas systems in clinical practice.

Increased flexibility to choose different combinations of devices for closed-loop systems is likely to improve both performance and user experience. JDRF recently launched an initiative to expedite the development of 'open protocol' devices (insulin pumps and CGM) for automated insulin delivery. This initiative aims to encourage manufacturers of pump and CGM systems to provide standardized and secure communication with other devices and smartphone apps to allow interoperability.

Data from CGM and pumps are uploaded to the Cloud and diabetes data management platforms such as Diasend/Glooko® (Glooko, Palo Alto, CA, USA), making data from a broad range of compatible diabetes devices available to users and healthcare providers through universal portals and smartphone applications. The way in which closed-loop data are integrated and visualized on such platforms needs consideration to support optimal usability by both users and healthcare professionals.

Remote monitoring capabilities, such as the Dexcom Share feature, which allows sharing of glucose data with up to five iOS or Android followers is likely to further increase appeal and acceptability particularly for parents of children with Type 1 diabetes.

Application of the artificial pancreas in particular cohorts (individuals newly diagnosed with Type 1 diabetes to prolong endogenous insulin secretion and people with impaired awareness of hypoglycaemia), will be useful to determine those who can benefit most from closed-loop technology.

Conclusions

Since the James Lind Alliance research priorities for Type 1 diabetes were formulated, studies have demonstrated that artificial pancreas systems are a safe and efficacious approach for treating people with Type 1 diabetes. Further questions remain regarding adoption of closed-loop systems into clinical practice. How much more effective and acceptable can closed-loop systems be with improved system components? Will current closed-loop systems be widely adopted by users with the current challenges of device connectivity, user-

friendliness of interfaces and wearability? Are closed-loop systems cost-effective for healthcare systems to provide? What training and infrastructure will be required to ensure successful implementation and reimbursement of this technology? The future will tell.

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Competing interests

RH reports having received speaker honoraria from Eli Lilly and Novo Nordisk, serving on advisory panel for Eli Lilly and Novo Nordisk, receiving license fees from B. Braun and Medtronic; having served as a consultant to B. Braun, and patents and patent applications related to closed-loop. CB declares no duality of interest associated with this manuscript.

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