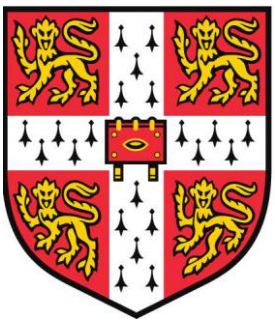
The Artificial Pancreas in Children and Adolescents with Type 1 Diabetes: Bringing Closed-Loop Home



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Summary/ Abstract

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Martin Tauschmann

Type 1 diabetes is one of the most common chronic conditions in childhood and adolescence. Despite ongoing development of more physiological insulin preparations, recent advancements in insulin pump technology and more accurate blood glucose monitoring, in clinical practice it remains challenging to achieve normoglycaemia whilst reducing the risk of hypoglycaemia, particularly in young people with type 1 diabetes.

Closed-loop insulin delivery (the artificial pancreas) is an emerging technology gradually progressing from bench to clinical practice. Closed-loop systems combine glucose sensing with computer-based algorithm informed insulin delivery to provide real-time glucose-responsive insulin administration.

The key objective of my thesis is to evaluate the safety, efficacy and utility of closed-loop insulin delivery in children and adolescents with type 1 diabetes outside of the research facility setting. Results of five clinical trials are presented in the main chapters of this thesis.

In a mechanistic study, the impact of glucose sensor operation duration on efficacy of overnight closed-loop was investigated comparing closed-loop performance on day 1 of sensor insertion to day 3 to 4 of sensor. Twelve adolescents with type 1 diabetes attended the research facility for two overnight visits. The sequence of the interventions was random. In spite of differences in sensor accuracy, overnight CL glucose control informed by sensor glucose on day 1 or day 3-4 after sensor insertion was comparable. The model predictive controller appears to mitigate against sensor inaccuracies.

In home settings, overnight closed-loop application was evaluated over three months in 25 children and adolescents with type 1 diabetes aged six to 18 years. The study was

conducted at three centres in the UK and adopted a randomised cross-over design. Compared to sensor-augmented pump therapy, overnight home use of closed-loop increased the proportion of time sensor glucose was in target and reduced mean glucose and hypoglycaemia.

Two randomised crossover studies evaluated the safety and efficacy of day-and-night hybrid closed-loop insulin delivery in young people with type 1 diabetes aged 10 to 18 years over seven days, and 21 days, respectively. A total of 24 subjects were enrolled in this single centre trial. Free-living home use of day-and-night closed-loop in suboptimally controlled adolescents with type 1 diabetes was safe, and improved glucose control without increasing the risk of hypoglycaemia.

Finally, closed-loop technology was assessed in five very young children (aged one to seven years) with type 1 diabetes in a two-period, crossover study. Closed-loop was used during both 3-week intervention periods, either with standard strength insulin (U100), or with diluted insulin (U20). The order of intervention was random. Free-living home use of day-and-night hybrid closed-loop in very young children with type 1 diabetes was feasible and safe. Glucose control was comparable during both intervention periods. Thus, use of diluted insulin during closed-loop insulin delivery might not be of additional benefit in this population.

In conclusion, studies conducted as part of my thesis demonstrate that use of hybrid closed-loop insulin delivery systems in children and adolescents aged one to 18 years in free daily living without remote monitoring or supervision is feasible, safe and effective. My work supports the progression of this technology from research to mainstream clinical practice.

Declaration

This dissertation is the result of my work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text. Any errors in this dissertation are mine alone. No part of this work has been submitted for any other qualification. The length of this dissertation lies within the word limit set by the Degree Committee for Clinical Medicine and Veterinary Medicine.

Acknowledgement

The work presented in my thesis would not have been possible without contributions from a large number of people.

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Table of Contents

List of figures

List of tables

List of abbreviations

ADA	American Diabetes Association
BC	Bolus Calculator
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CL	Closed-loop
CRF	Clinical Research Facilty or Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complication Trial
HbA1c	Glycosylated haemoglobin
IDF	International Diabetes Federation
ISPAD	International Society for Pediatric and Adolescent Diabetes
JDRF	Juvenile Diabetes Research Foundation
LGS	Low Glucose Suspend
MARD	Mean/Median Absolute Relative Difference
MDI	Multiple Daily Injections
MPC	Model Predictive Control
PID	Proportional-Integral-Derivative
PLGS	Predicted Low Glucose Suspend
SAP	Sensor-Augmented Pump
SMBG	Self-monitoring of Blood Glucose
T1D	Type 1 diabetes mellitus
WHO	World Health Organisation

1 Introduction

1.1 RATIONALE

Type 1 diabetes represents 5-10% of diabetes cases worldwide and is characterised by increasing incidence and no immediate prospect of cure. Despite advances in insulin replacement therapy with more physiological insulin preparations, ongoing developments in insulin pump therapy and glucose monitoring, it remains challenging to achieve normoglycaemia whilst reducing the risk of hypoglycaemia in daily living, particularly for children and adolescents with type 1 diabetes.

Closed-loop insulin delivery (the artificial pancreas) is an emerging technology gradually progressing from bench to clinical practice. Closed-loop systems combine glucose sensing with computer-based algorithm informed insulin delivery to provide real-time glucose-responsive insulin administration. First evaluations of closed-loop insulin delivery in controlled laboratory settings have demonstrated the great potential of this novel therapeutic approach to ameliorate shortcomings of the current management practice. Homes studies of closed-loop use in free daily living represent the ultimate test-bed for a true assessment of the merits of closed-loop treatment.

1.2 AIM

The aim of my thesis was to evaluate the safety and efficacy of closed-loop insulin delivery in children and adolescents with type 1 diabetes focussing on closed-loop applications in real-life conditions.

1.3 STRUCTURE AND OUTLINE

Chapter 2 is dedicated to childhood type 1 diabetes per se to set the framework and context of this thesis. Disease-related complications and challenges in the management of type 1 diabetes in children are listed and current treatment modalities and their limitations are described. In the second part of this chapter, I introduce the concept of closed-loop insulin delivery and review results of clinical evaluations in

paediatric populations in various settings, including laboratory conditions and first outpatient studies.

In the main body of my thesis (Chapters 3 to 6), clinical studies and related journal articles (Chapters 3, 4 and 5) or manuscripts in preparation for publication (Chapter 6) are featured. These chapters are similarly structured, each with a brief introductory section, and separate 'methods', 'results' and 'discussion' sections.

Clinical trials included in my thesis were all conducted from December 2013 to December 2017. The majority of the work presented in this thesis was undertaken by myself. For all the included studies, I was majorly involved in the design and planning of the clinical studies, the actual study conduct and data collection, and the analyses and dissemination of study findings. My responsibilities included preparation of study protocols and documents for regulatory approvals, attending the Research Ethics Committee (REC) meetings and follow up with the REC, recruitment and training of participants and families, planning and conduct of study visits and contacts, study device management, data management and adverse event reporting. After completion of the studies, I was responsible for data preparation and statistical analyses, and I wrote up and submitted manuscripts to peer reviewed journals. Additionally, I presented results at diverse national and international conferences. A more detailed description of my study specific responsibilities, as well as any collaboration and assistance are included in the appendix (*Appendix B: Assistance, collaboration and funding).* Achievements related to the work presented in my thesis (including peer-reviewed publications and presentations at scientific meetings) are summarised in *Appendix C: Achievements.*

In Chapter 3, I present results from a clinical research facility- based overnight trial in adolescents evaluating the impact of glucose sensor operation duration after subcutaneous insertion and associated variability in sensor accuracy on the efficacy and safety of a closed-loop system.

Chapter 4 describes the feasibility and efficacy of prolonged overnight closed-loop application during free daily living over a 3-month period in children and adolescents

with type 1 diabetes aged six to 18 years, representing the longest randomised home study of closed-loop use in this population up until then. In a randomised controlled crossover multicentre study, we compared closed-loop to state-of-the-art sensor-augmented pump therapy.

In Chapter 5, outcomes of two clinical trials are presented evaluating day-and-night application of closed-loop in pre-adolescent children and adolescents aged 10 to 18 years, a 1-week trial, and a 3-week trial. Both trials adopted a single centre, randomised cross-over design and were conducted at home under free-living conditions without supervision or remote monitoring. The control intervention in both studies was sensor-augmented pump therapy.

In Chapter 6, I present preliminary results of a multicentre, multinational trial evaluating the use of closed-loop insulin delivery in very young children (aged one to seven years) with type 1 diabetes. It is the first home study in free daily living without supervision in this population. In a randomised two-period cross-over design study, we evaluated the use of closed-loop insulin delivery with diluted insulin (U20) compared to that of closed-loop with standard strength insulin (U100) with both intervention periods lasting 3 weeks.

Chapter 7 comprises a summary of the results and conclusions from the evidence collated in my thesis, along with an outlook on currently ongoing and future studies in the set-up and conduction of which I have been majorly involved. Finally, current challenges to closed-loop technologies and possible future directions are outlined.

2 Background

2.1 CHILDHOOD ONSET TYPE 1 DIABETES

2.1.1 Definition, classification and epidemiology

Diabetes mellitus is a chronic metabolic condition caused by either the lack of insulin secretion or insulin action, or both. The current World Health Organisation (WHO) diagnostic criteria for diabetes are fasting plasma glucose ≥ 7.0 mmol/l or two-hour plasma glucose ≥ 11.1 mmol/l[1]. The condition is clinically classified, according to aetiologies, into type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types of diabetes[2]. Type 1 and type 2 diabetes are the two main subtypes, with the latter accounting for more than 95% of all cases. Type 2 diabetes is a heterogeneous condition, ranging from predominantly insulin resistant states with relative insulin deficiency to predominantly secretory defect states with or without insulin resistance[2].

Type 1 diabetes is characterised by a cell-mediated autoimmune destruction of the pancreatic beta-cells triggered by a complex interaction between environmental and genetic factors leading to absolute insulin deficiency and hyperglycaemia[3]. Markers of immune destruction include islet cell autoantibodies (ICA), autoantibodies to glutamic acid decarboxylase (65 K GAD isoform), insulin autoantibodies (IAA), autoantibodies to the tyrosine phosphatases IA-2 and IA-2β, and beta-cell-specific zinc transporter 8 autoantibodies (ZnT8)[4].

The incidence of type 2 diabetes in children and adolescents is increasing in parallel with the rising incidence of childhood overweight and obesity[5-7]. However, type 1 diabetes remains the predominant aetiological type in childhood diabetes in most regions of the world. Type 1 diabetes is one of the most common chronic conditions in childhood and adolescence. It is estimated that around 490,000 children under the age of 15 are affected by type 1 diabetes, approximately 76,000 children are diagnosed each year[8]. Despite different geographical trends (see Figure 2.1), its incidence is increasing worldwide[9], with an estimated overall annual rate of up to 3%[2], particularly in the youngest age group[10].

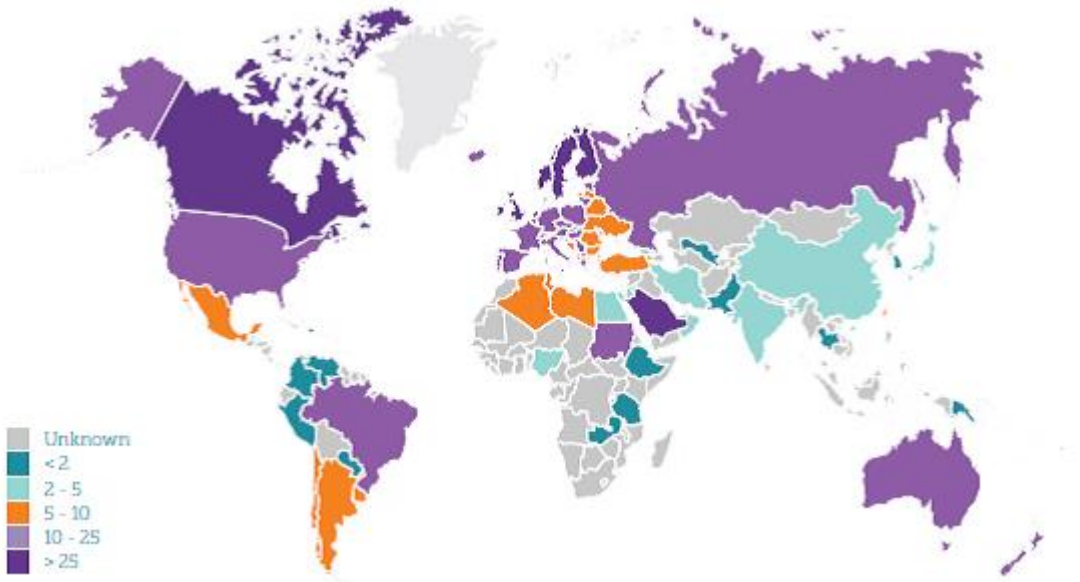

Figure 2.1. Estimated geographical incidence of type 1 diabetes in children <15 years of age. Incidence is reported as number of cases per 100,000 per year. Data adapted from the International Diabetes Federation (IDF) diabetes atlas – 7th edition, 2015[8].

2.1.2 Complications

Type 1 diabetes is characterised by life-long dependency on insulin administration due to absolute insulin deficiency. It is associated with significant morbidity and decreased life expectancy due to acute and long-term complications[11].

2.1.2.1 Acute complications

Acute complications include hyperglycaemia and hypoglycaemia. Acute hyperglycaemia is caused by insufficient insulin supply, and might lead to diabetic ketoacidosis (DKA). Hypoglycaemia is based on a mismatch between insulin administration with glucose appearance and glucose disposal potentially leading to unconsciousness or seizures if not remedied. Both hyperglycaemia and hypoglycaemia go along with significant symptoms affecting cognitive and physical functioning, and negatively impact on the quality of life of children and adolescents with type 1 diabetes and their caregivers. DKA and severe hypoglycaemia are associated with significant morbidity, and occasionally, mortality[12,13].

2.1.2.1.1 Hypoglycaemia and severe hypoglycaemia

Hypoglycaemia is the most common acute complication of type 1 diabetes[14,15]. Every aspect of the lives of both children and their carers can be affected, such as performance and concentration at school, sport, during play activities or sleep. Symptoms include signs of autonomic (adrenergic) activation (e.g. shakiness, weakness, hunger, sweating) and/or neurological dysfunction (neuroglycopenia) resulting from brain glucose deprivation (e.g. headache, difficulty concentrating, blurred vision, difficulty hearing, slurred speech, confusion)[16], or may result from a combination of neuroglycopenic and autonomic responses (e.g. behavioural changes, particularly seen in children, including irritability, agitation, quietness, stubbornness)[17]. Hypoglycaemic episodes might also be asymptomatic. The risk of hypoglycaemia causes significant anxiety and emotional morbidity for patients with type 1 diabetes and their families, and is a barrier to achieving optimal glycaemic control[18].

There is no consistent numerical definition of hypoglycaemia as regards children with diabetes. Glycaemic thresholds for symptoms, central nervous system dysfunction and hormonal counter-regulation might vary between individuals and in the same individual over time[19,20]. However, blood glucose levels of <3.3-3.9 mmol/l are generally used as threshold values for identifying and treating of hypoglycaemia in children and adolescents with diabetes. Severe hypoglycaemia in the paediatric population is generally defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy (i.e. glucagon or intravenous glucose)[21,22]. Recently, the International Society for Pediatric and Adolescent Diabetes (ISPAD) hypoglycaemia guidelines working group have suggested three levels for children and adolescents[23] in alignment with recommendations by the European Association for the Study of Diabetes (EASD) and the International Hypoglycaemia Study Group (IHSG)[24]: these included an “alert” value of less than 3.9 mmol/L, a biochemically defined glucose level that may be considered clinically important or serious of <3.0 mmol/L, and a clinically defined level of severe hypoglycaemia with severe cognitive impairment (including coma or convulsion) requiring external assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.

The incidence of mild to moderate hypoglycaemia in individuals with type 1 diabetes remains unknown. Mild episodes do occur frequently amongst patients treated with insulin, and are often underreported or unrecognised, particularly overnight[22]. The prevalence of prolonged, nocturnal hypoglycaemia is high in children and adolescents (up to 40% on any given night)[25-27], and almost 50% of these episodes are undetected by individuals affected or carers[28].

Severe hypoglycaemia is more likely to be recognised, and thus easier to track. There is emerging evidence that rates of severe hypoglycaemia may be declining, potentially due to changes in clinical practice including more widespread use of new insulin analogues, better understanding of insulin dose adjustments[21,29], new insulin regimen, more intensive glucose monitoring or improved management guidelines. Data from the T1D Exchange Registry, a registry of >25 000 individuals with type 1 diabetes at 67 centres in the USA, described a 12-month frequency of 6.2% of one or more severe hypoglycaemia events in their cohort of 2 to 26-year olds[30]. Severe hypoglycaemia is accounting for an estimated 4-10% of disease related mortality in children and adolescents[31-33]

2.1.2.1.2 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) results from insulin deficiency and increased levels of counterregulatory hormones such as catecholamines, glucagon, cortisol and growth hormone, and leads to an accelerated catabolic state with increased glucose production by the liver and kidney via gluconeogenesis and glycogenolysis, simultaneously impaired peripheral glucose utilisation, and increased lipolysis and ketogenesis[34-36]. This results in hyperglycaemia, hyperosmolarity, ketonaemia and metabolic acidosis, requiring complex management and hospitalisation. Biochemical criteria for the diagnosis of DKA are (A) hyperglycaemia (blood glucose>11 mmol/l), (B) venous pH<7.3 or bicarbonate <15mmol/l, and (C) ketonaemia and ketonuria[36]. The risk of DKA in established type 1 diabetes is 1-10% per patient per year[30,37-39]. The mortality rate from DKA in children is 0.15-0.30%[40-42] and may be decreasing[42].

2.1.2.2 Long-term complications

The relationship between chronic hyperglycaemia and vascular damage has been established by the Diabetes Control and Complications Trial (DCCT)[43]. Microvascular and macrovascular changes are the cause of diabetes-related long-term complications such as retinopathy, nephropathy, neuropathy (all microvascular), and cardio-vascular diseases (macrovascular), all leading to increased morbidity and mortality amongst people affected by diabetes.

Long-term complications usually start to develop years or decades after diabetes onset, initially being asymptomatic, or showing very subtle clinical manifestation during their early stages[44]. Hence, clinically evident complications are rarely seen among children and young people with type 1 diabetes. Notwithstanding, childhood and adolescence seem to be particularly vulnerable periods for onset and priming of microvascular complications[45,46]. Thus, early identification of complications is important[47]. Good metabolic control facilitated by intensive education and treatment is essential to prevent or delay the onset or progression of complications[48]. Lower glycated haemoglobin A1c (HbA1c) levels are associated with fewer and delayed micro- and macrovascular complications[43,48,49].

2.1.3 Management and treatment

2.1.3.1 Treatment goals

The ultimate goal of diabetes care in childhood diabetes is to reduce the risk of acute and long-term complications while ensuring a good quality of life, normal growth and development. The care of children and young people with diabetes should take into account the specific needs of these age groups. Ideally, a multidisciplinary team including a paediatric diabetologist, a diabetes specialist nurse educator, a dietician, a social worker and /or psychologist/psychiatrist should take care of children with diabetes and their families[50]. Recent consensus guidelines by both the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) suggest overall target HbA1c levels of below 7.5% (58 mmol/mol) across all paediatric age groups[49,51]. Treatment goals might be individualised to achieve HbA1c levels as close to normal as possible while avoiding hypoglycaemia.

Despite advances in therapy, data from big western diabetes registries suggests that the majority of people with type 1 diabetes still fail to achieve recommended glycaemic targets[52-54]. This is particularly evident in paediatric age groups. Above all, adolescents and young adults seem to struggle most (see Figure 2.2.)

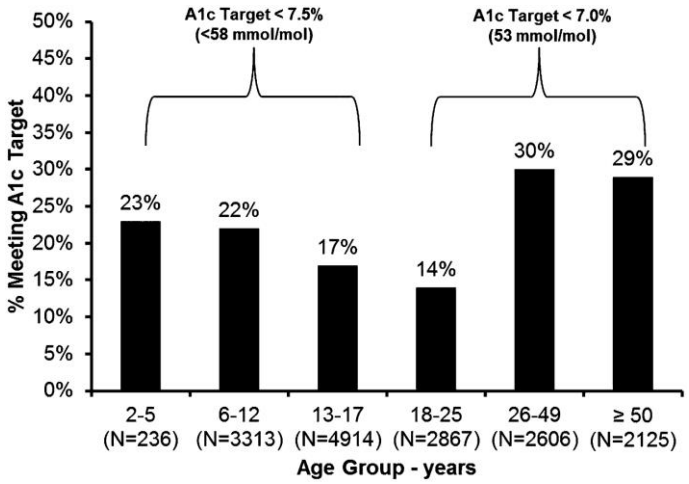

Figure 2.2. Percent of patients achieving HbA1c ADA targets by age-group (T1D Exchange registry). HbA1c target for those aged <18 years is <7.5% (<58 mmol/mol). HbA1c target for those aged ≥18 years is <7.0% (<53 mmol/mol). Adapted from Millter et al[54].

2.1.3.2 Insulin replacement therapy

Insulin therapy regimen should mimic non-diabetic insulin secretion profiles in response to dietary intake, exercise levels, and the underlying metabolic state, keeping plasma concentrations in the euglycaemic range[55]. Physiological patterns include (A) a continuous basal insulin secretion that regulates lipolysis and restrains hepatic gluconeogenesis to keep blood glucose levels at equilibrium with basal glucose utilisation by the brain and other tissues that are obligate glucose consumers, and (B) a prandial insulin release to control meal-related glucose excursion by stimulating glucose utilisation and storage, while inhibiting hepatic glucose output (see Figure 2.3)[56].

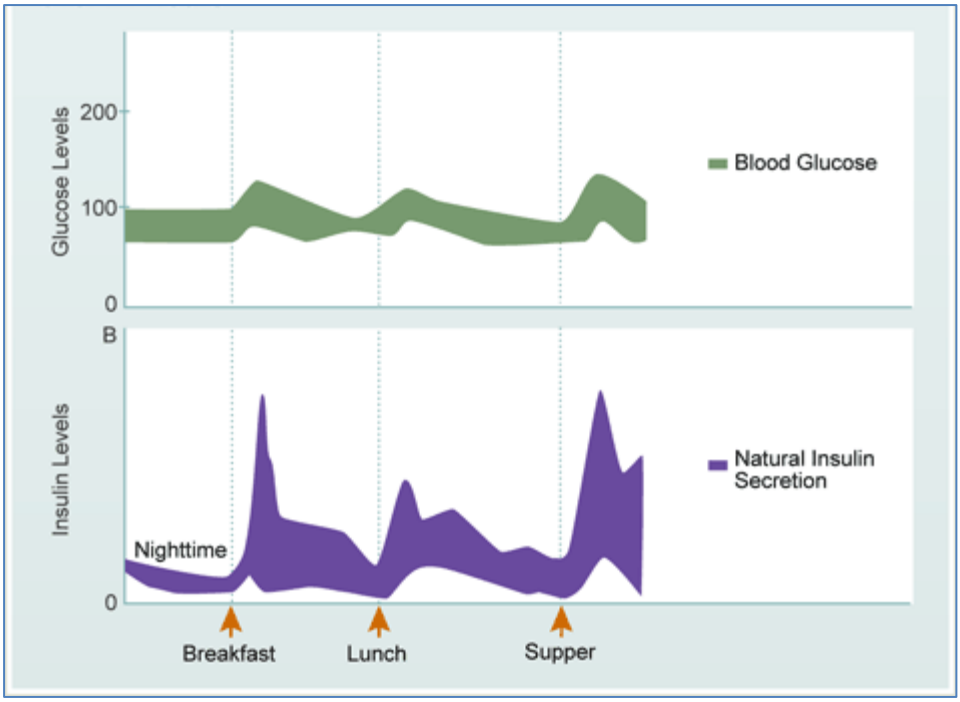

Figure 2.3. Normal (non-diabetic) blood glucose (top panel) and insulin levels (bottom panel) over 24 hours. Adapted from Jacobs et al[57].

Following results from Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, there has been a paradigm shift towards intensive insulin therapies such as multiple daily injection therapy (MDI) or insulin pump therapy[43,58]. Intensive management comprises frequent blood glucose monitoring, meal planning, attention to exercise and flexible multiple daily insulin administrations, either using an insulin pen as in MDI therapy, or using an insulin pump as in continuous subcutaneous insulin infusion therapy (CSII).

2.1.3.2.1 Multiple daily injections

In MDI therapy, different insulin formulations are used, each characterised by a specific profile of action. The basal secretion of insulin by the healthy pancreas is replaced by once or twice daily injections of intermediate-acting or long-acting insulins or insulin analogues. Short-acting or rapid-acting insulins or insulin analogue formulations are used to mimic higher-rate secretion of insulin with meals. Various combination of short or- rapid-acting insulin with intermediate- or long-acting insulin can be employed. MDI

usually involves three to five (or more) injections per day. A clinical superiority of a specific insulin regimen for glycaemic control has not yet been clearly established[59].

2.1.3.2.1.1 Insulin pens

Insulin pens contain insulin in a cartridge and incorporate a fine replaceable needle. Introduced in 1981 as convenient, easy to use injection devices[60], pens are widely used as a part of multiple daily injection (MDI) therapy and are continuously evolving. Pens with memory functions (e.g. HumaPen® Memoir, Ely Lilly, Indianapolis, IN, USA; NovoPen Echo®, Novo Nordisk, Bagsværd, Denmark) or pen caps that track past doses (e.g. Timesulin®, Patients Pending Ltd, London, UK; GoCap®, Common Sensing, Cambridge, MA, USA) are available. Recently, pens with built-in Bluetooth connectivity have received regulatory approvals (e.g. InPen®, Companion Medical, San Diego, CA, USA; Esysta® pen, Emperra Digital Diabetes Care, Potsdam, Germany). These smart pens allow users to track doses, and automatically transfer data via Bluetooth to diabetes management apps on smartphones for convenience and automatic cloud upload for sharing data with health care professionals. However, no studies have been reported on superiority of smart pens over conventional pens.

2.1.3.2.2 Continuous subcutaneous insulin pump therapy

Insulin pumps date back to 1970s[61], but it took another 20 years for insulin pump therapy to become widely available. The increasing utilisation of insulin pump therapy over the last 20 years has resulted from improvements and increased, albeit still imperfect, reliability of pump technology documented health benefits, and availability of rapid acting insulin analogues, and has been further amplified through coverage by private insurance and public health care systems. Uptake and availability of insulin pump therapy varies considerably between and within countries[62], with pump users representing 40 to 60% of the type 1 diabetes population in countries most adept to pump use[53,63].

2.1.3.2.2.1 Types of insulin pumps

Insulin pumps deliver short- or rapid acting insulin into the subcutaneous tissue at pre-programmed rates, normally half-hourly to hourly adjustable, with user-activated boosts/boluses at mealtimes via self-inserted Teflon or steel catheters. In conventional

or tethered pumps, the pump's insulin reservoir and the transcutaneously placed cannula are connected via tubes with a length of 18-42 inches. Patch pumps comprise a very short insulin infusion set typically embedded inside the pump housing or within the base part of the modular designed pump[64]. While tethered pumps are usually tucked into pockets or carried in pump pouches, patch pumps are directly attached to the user's skin. A recent retrospective observational study did not demonstrate any differences in HbA1c when comparing patch pumps vs. traditional tethered pumps[65].

2.1.3.2.2.2 Adjunctive technologies

Modern insulin pumps usually come with adjunctive features such as bolus calculators to ease calculation of meal and correction boluses, bolus profiles including immediate and/or extended delivery of calculated bolus dose to meet postprandial insulin requirements, and temporary basal rates to accommodate physical activity resulting in acutely lower insulin needs, or stress or illness resulting in acutely higher insulin needs. Use of these advanced features may improve glycaemic outcomes including HbA1c[66], and postprandial glycaemic excursions[67,68].

2.1.3.2.2.3 Efficacy of insulin pump therapy

In adults with type 1 diabetes, the use of insulin pump is associated with a modest 0.3 to 0.6% reduction in HbA1c compared to MDI therapy[69-73], with those most poorly controlled on MDI experiencing the greatest, and often a substantial and clinically valuable improvement in HbA1c[69]. A comparable to lower risk of severe hypoglycaemia has been documented, while quality of life in pump users is higher compared to MDI[69-73]. Despite the high appeal for children and adolescents due to more flexible and subtly customisable insulin delivery essential to paediatric needs, meta-analyses and systematic reviews of RCTs including paediatric populations[69-72,74] are not as conclusive as in adults. Similar to adults, slightly lower HbA1c levels and apparently no difference in severe hypoglycaemia risk were reported in meta-analyses of paediatric pump users compared to MDI therapy.

With respect to severe hypoglycaemia, however, these meta-analyses should be interpreted with caution due to several issues, for example, clinical trials were too short for severe hypoglycaemia to occur or participation was limited intentionally or

unintentionally to those with a very low rate of baseline hypoglycaemia. Severe hypoglycaemia or hypoglycaemia unawareness might have been listed as specific exclusion criteria in these trials, or early generation pumps and pump insulins were used. In a meta-regression analysis, Pickup et al. demonstrated that there is significant hypoglycaemia reduction even in children and adolescents on pump therapy compared to MDI, though to a lesser degree than in adults[69]. Greatest reductions in severe hypoglycaemia occurred in those with highest baseline hypoglycaemia and in elderly.

Insulin requirements are usually lower on pump, while rates of DKA do not differ between pump and MDI therapy. Lifestyle flexibility and reduced blood glucose variability is also regarded an advantage of insulin pump therapy[75]. Improved quality of life and reduced fear of hypoglycaemia in both parents and children were documented when switching from MDI to insulin pump therapy[76].

While on the whole, the above mentioned meta-analyses of RCTs in paediatric and adult type 1 diabetes are cautiously favouring insulin pump therapy compared to MDI therapy, recent observational studies more optimistically documented sustained benefit over prolonged periods of pump use across different populations including reductions in DKA and severe hypoglycaemia[13,77-81]. This may reflect that non-minority and less social deprived users more frequently adopt insulin pump therapy[53,82].

Systematic reviews and meta-analyses documented improved HbA1c levels and reduced risk of severe hypoglycaemia compared to MDI[69,83,84].

Disadvantages of insulin pump therapy include skin infection and dermatological changes at the site of infusion. Despite standard clinical practise involves changing the infusion set and site, usually every 2-3 days, as well as a no-touch-technique for insertion, local skin infections still occur but are rarely serious[85]. The pump is more complex to set up and liable to malfunctions than the pens, syringes, and needles. Though current pumps are robust and reliable, malfunctions still occur frequently. Problems with blocked, kinked or leaking cannulas, and priming failures are common[86]. Given the smaller subcutaneous depot of insulin during insulin pump therapy, stopped delivery of insulin may lead to rapid metabolic disturbances. Yet available evidence

suggests that insulin pump therapy poses a risk of diabetic ketoacidosis (DKA) similar to or smaller than that associated with MDI in children and adolescents[74].

2.1.3.3 Glucose monitoring

Blood glucose monitoring is an essential tool in optimal diabetes management in childhood and adolescence, as it facilitates detection of hypo- or hyperglycaemia, insulin dose adjustments, and optimisation of treatment.

2.1.3.3.1 Self-monitoring of blood glucose

Handheld, portable meters measuring capillary blood glucose are used by patients at home for the purpose of self-monitoring of blood glucose (SMBG). The frequency of SMBG measurements has been associated with improved HbA1c levels and reduced acute complications[87-89]. Successful implementation of intensified diabetes management usually requires four to six measurements per day (though the actual number should be individualised), and regular review of the results[49].

Similar to bolus calculators on insulin pumps, recently introduced expert meters comprise integrated bolus advisors to calculate insulin dosages. Recent randomised controlled trials have shown a significant increase in the number of people achieving HbA1c targets[90-92] in the bolus calculator group and a reduction in hypoglycaemia compared to controls[91,92].

Capillary blood glucose monitoring has its drawbacks as blood is sampled intermittently providing only snapshots of glucose concentrations even if performed frequently. Episodes of hyper- and hypoglycaemia may be missed and not factored into treatment decisions.

2.1.3.3.2 Continuous glucose monitoring

The emergence of continuous glucose monitoring (CGM) has been an important step in glucose monitoring. Currently available CGM devices measure interstitial glucose concentrations subcutaneously at one- to five-minute intervals utilizing enzyme-tipped electrodes or fluorescence technology. Readers - either in the form of stand-alone devices or integrated into insulin pumps or mobile phones - display transmitted interstitial glucose readings either in real-time (real-time CGM), or on demand when scanning (flash glucose monitoring), or simply collect data for retrospective read-out and analysis (professional, masked or blinded CGM).

Real-time CGM systems automatically display glucose readings at regular intervals and utilise real-time alarms when sensor glucose levels reach pre-defined thresholds regarding hypo- and hyperglycaemia, as well as rate of change alarms for rapid glycaemic excursion. Recently introduced flash glucose monitoring systems (FreeStyle Libre, Abbott Diabetes Care, Alameda, CA, USA) report glucose levels only when the user scans the sensor by holding a reader or a cell phone close to the sensor. Blinded CGMs are applied intermittently over a short period of time to provide more information about glycaemic excursions and patterns to the healthcare professional in order to facilitate changes in therapy and could serve as educational tools. Blinded CGM and flash glucose monitoring systems do not provide alarms.

While most CGMs still require calibration using capillary blood glucose readings, the Libre flash glucose monitoring system is factory calibrated and does not require re-calibration by the user[93]. Most CGM systems are minimally invasive and have a life time of 6 to 14 days. A longer-term sensor implantable up to 6 months (Eversense®, Senseonics Inc, Germantown, MD, USA) is available in Europe.[94]Unlike short term CGM systems, which are self-inserted by the user, sensor implantation and removal require a minor surgical procedure by a trained health care professional.

2.1.3.3.2.1 CGM uptake and use

A niche product in the recent past, CGM has now become the standard of care for people with type 1 diabetes in certain countries and clinics[95]. Recent data from the DPV

registry in Germany and Austria, and the T1D Exchange registry in the USA suggest that overall CGM use for all registry participants (DPV: n=20,938; T1D: n= 8,186) is 18.4% (DPV) and 21.7% (T1D), respectively[96]. Overall accuracy of the latest sensor generations measured as the mean relative absolute difference (MARD) versus a given laboratory standard is between 8% to14%[93,94,97-99] with lower accuracy in the hypoglycaemic range and at rapidly changing glucose levels[100,101]. The technology has reached the proposed mark sufficient to allow self-adjustment of insulin dosage without confirmatory capillary blood glucose measurements (*MARD* <10%)[102,103]. CGM systems have received approvals for non-adjunctive use in the USA (G5™ Mobile, Dexcom, San Diego, California, USA; Libre Flash Glucose Monitor, Abbott Diabetes Care, Alameda, CA) and in the EU (G5™ Mobile, Dexcom; Libre Flash Glucose Monitor and FreeStyle Navigator II, Abbott Diabetes Care, Alameda, CA). Confirmatory capillary glucose measurement is suggested at hypoglycaemia with Libre.

Data provided by CGM devices allow limitations of the traditional glucose metrics such HbA1c and capillary glucose measurements to be overcome. A recent consensus report defined measures of glycaemic control based on CGM highlighting the significance of CGM technology in modern diabetes care[104,105].

2.1.3.3.2.2 Efficacy of CGM

RCTs and meta-analyses using early generation devices were cautious with respect to the overall benefit of CGM systems, particularly in children and young people with type 1 diabetes[70,106-111]. More recent data more consistently report that use of CGM is associated with an improvement in HbA1c, reduction in mild to moderate hypoglycaemia, and reduced glucose variability[112-117]. While earlier analysis and guidelines were favouring CGM in combination with pump therapy[49,70,108,118], emerging evidence supports use of CGM as part of MDI[117,119-121]. As the technology is evolving fast, the older RTCs and meta-analyses have limited validity.

2.1.3.3.2.3 Flash glucose monitoring

With a 2-week sensor life, factory calibration, satisfactory accuracy with overall MARD of 11% to 14%, its small size and light weight, the recently introduced Libre flash glucose monitoring system is particularly appealing and convenient to assess glucose

levels[121,122]. However, evidence on its effectiveness is limited[121,123-125]. An RCT showed that flash glucose monitoring in adults with well controlled type 1 diabetes reduced time spent in hypoglycaemia, reduced glucose variability, and improved the percentage of time with glucose readings in the near-normoglycaemic range compared to self-monitoring of capillary blood glucose with median 15 scans per day[121]. Benefits were identical for users of insulin pump therapy and MDI. In a recent head-to-head comparison of flash glucose monitoring and conventional CGM in adults with type 1 diabetes and impaired awareness of hypoglycaemia, CGM more effectively reduced time spent in hypoglycaemia compared with flash glucose monitoring[126]. In the paediatric population, there is currently no evidence regarding effectiveness of flash glucose monitoring[122]. Observational data link frequent scanning to improved outcomes[127].

2.1.3.4 Sensor-augmented pump therapy

Sensor-augmented pump (SAP) therapy combines insulin pump and glucose sensor, the latter wirelessly transmitting data to a handheld receiver or insulin pump. Usually, the continuously measured readings can be viewed on the pump's screen or a separate monitor, and glucose trend arrows and warnings against pre-set parameters are provided. In standard SAP, insulin is delivered according to manually entered and pre-programmed infusion rates. More advanced approaches based on automated adaptive glucose responsive regulation of insulin delivery are extensively discussed in subsequent sub-chapters.

Following RCTs evaluating CGM alone use in children and adults with T1D on intensive[128] and insulin pump therapy[129], multicentre RCTs on SAP therapy including children and adolescents with intervention periods up to 12 months have been conducted, e.g. RealTrend[130], Star3[131], Onset[132] and SWITCH[116]. SAP therapy was investigated in participants with newly diagnosed T1D[132], when switching from MDI with insulin analogues[130,131], or in those already on insulin pump therapy[116]. SAP therapy was either compared to MDI and SMBG[131], or insulin pump therapy and SMBG[116,130,132]. Most trials were conducted in inadequately controlled

patients[116,130,131], and usually excluded those with recurrent severe hypoglycaemia and/or hypoglycaemia unawareness[116,131].

SAP therapy resulted in significant improvement in HbA1c compared to MDI and SMBG in the paediatric population[131]. SAP therapy, in particular in those participants with higher sensor use, was more likely to meet age-appropriate HbA1c targets[131]. However, studies investigating whether SAP therapy can further improve HbA1c in participants with T1D already using insulin pump therapy have yielded conflicting results ranging from no significant benefit[130,132] to significantly improved glycaemic control[116]. The beneficial effect of SAP therapy became more prominent with increasing sensor use[116,129-132], reaching significance in subgroup analysis in participants who wore CGM more than 60%[129] or 70%[130] of the time. A reduced effect of SAP therapy was seen in adolescents wearing the sensor less frequently[128,131] compared to children[131].

The rate of severe hypoglycaemia in the SAP group did not differ significantly from that in the MDI group[131] or in the insulin pump therapy only group[116,130,132]. This lack of significance might be due to very low baseline rates of severe hypoglycaemic episodes. SAP therapy was associated with decreased time spent in hypoglycaemia compared to MDI[131] or conventional insulin pump therapy[116].

The time spent in the hyperglycaemic range was significantly decreased with SAP therapy[116,131].Glucose variability favours SAP therapy[116,131,132] but a significant difference in children and adolescents was only reached when calculating the standard deviation (SD) of sensor glucose values[131] or 24h SD of mean glucose rather than the mean amplitude of glycaemic excursions (MAGE)[116,131].

Interestingly, results from the ONSET trial indicate that SAP therapy from the onset of diabetes may lead to better long-term glycaemic control and possibly preserve endogenous beta-cell function, if users comply with frequent sensor use[132,133]. Following data from the DCCT showing that assignment to the intensively managed group reduced the risk for loss of C-peptide[134], this approach aims to optimise metabolic control as soon as possible after diagnosis. In vitro data has shown that resting b -cells are less immunogenic and more resistant to autoimmune damage

compared to active b -cells[135]. In the biobreeding (BB) rats' model, tight glycaemic control at the onset of type 1 diabetes was shown to protect against insulitis[136,137]. In humans, b-cell rest induced by closed-loop therapy shortly after the diagnosis of type 1 diabetes was reported to preserve b-cell function as assessed by C-peptide levels 1 year after diagnosis[138]. However, Buckingham and colleagues did not observe beneficial effects on beta-cell preservation in youth at 12 months of diagnosis following a brief spell of inpatient hybrid closed-loop control shortly after the diagnosis of T1D followed by SAP therapy in both control and intervention groups[139].

In summary, SAP therapy has been demonstrated to improve glycaemic control in children and adolescents without increasing the risk of hypoglycaemia. Frequent sensor use is vital to the success.

2.1.3.5 Sensor-augmented pump therapy with hypoglycaemia protection feature

Automated suspension of insulin delivery at low glucose levels or when low glucose levels are predicted represent the early embodiments of technology-enabled glucose responsive regulation of insulin delivery to address the issue of hypoglycaemia. Closed-loop approaches are more complex and address both the issues of hypoglycaemia and hyperglycaemia

2.1.3.5.1 Threshold-based insulin suspend

Released in 2009, the Medtronic Paradigm Veo (Medtronic Diabetes, Northridge, CA, USA) implements threshold-based insulin suspension. A revised version was approved in the USA in 2013 (MiniMed 530G). The available systems suspend insulin delivery for up to 2 h or until the user responds to the hypoglycaemic alarm when a low-glucose threshold is reached.

Multicentre randomised controlled[140-142] and non-randomised studies[143-145] including in children and adolescents[140,141,143] in real life settings have demonstrated that automated insulin suspension is safe and reduces the frequency and duration of overall and nocturnal hypoglycaemic episodes compared to insulin pump therapy alone[140] or sensor augmented pump therapy[141,143] . Threshold-based suspend was shown to reduce the overall risk of severe and moderate hypoglycaemia in those with the highest

risk, impaired hypoglycaemia awareness and the highest frequency of severe hypoglycaemia.[140,144]

2.1.3.5.2 Predictive low glucose suspension

Predictive low glucose insulin suspend discontinues insulin delivery when hypoglycaemia is predicted by an algorithm to occur within a specified time limit, or horizon. Thus, insulin delivery is suspended before hypoglycaemia occurs. This feature was introduced in Europe and Australia in 2015 (MiniMed 640G pump; Medtronic Diabetes). A revised version of this pump was approved in the USA for those aged sixteen and older (MiniMed 630G pump).

In RCTs including adults[146], and children and adolescents[146-148], the use of predictive low glucose suspend technology was shown to reduce the exposure to nocturnal[146-148] and overall hypoglycaemia[148], including reduced frequency of nocturnal and diurnal episodes and a reduction of prolonged nocturnal events. These benefits were achieved at the expense of mildly elevated overnight and morning glucose[146,147] or increased time in moderate hyperglycaemia.[148]

2.2 CLOSED-LOOP INSULIN DELIVERY

2.2.1 Overview

The artificial pancreas or closed-loop systems refer to a range of applications which expand on the concept of sensor responsive insulin delivery using a control algorithm that automatically directs insulin delivery, and in some instances other hormones including glucagon, below and above pre-set insulin pump delivery based on real-time sensor glucose levels[149-152]. The degree of automation varies between different categories of closed-loop systems and according to treatment objectives (Table 2.1).

The concept of closed-loop insulin delivery was first proposed over five decades ago[153]. The Biostator was introduced in the late 1970s utilizing intravenous insulin infusion and intravenous glucose sampling. With advances in subcutaneous insulin pump and sensor technology, the focus moved to body worn and not implantable devices, combining insulin delivery and glucose sensing in the subcutaneous tissue. Current closed-loop systems consist of three main components: a real-time CGM, an insulin pump and a control algorithm (Figure 2.4) although the control algorithm could be incorporated in the insulin pump.

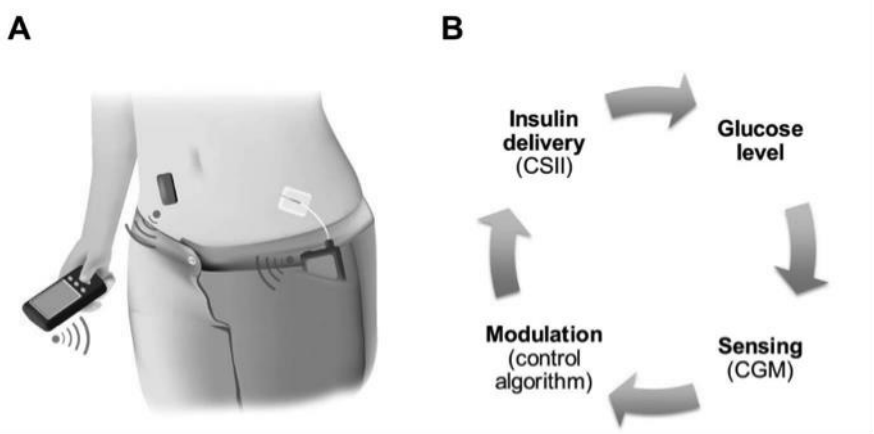

Figure 2.4. Closed-loop insulin delivery.A closed-loop system comprising a glucose sensor (black rectangle on the left-hand side of the abdomen), an insulin pump (device in the pocket), and a mobile-sized device containing the control algorithm (in patient's hand). Each component communicates with the other wirelessly (adapted from Hovorka[149]). (B) The closed-loop system mimics the physiological feedback normally provided by the β-cell.

Table 2.1. Closed-loop approaches according to treatment objective.

Objective	Modulation of insulin delivery
Reduction of severity and/or duration of hypoglycaemia	Suspension of insulin delivery at low glucose threshold
Hypoglycaemia prevention	Suspension/reduction of insulin delivery when hypoglycaemia is predicted
Control to range	Modulation of insulin delivery outside target range to reduce hypoglycaemic and hyperglycaemic excursions
Overnight glucose control	Modulation of insulin delivery for nocturnal glucose control
Closed-loop system with meal/exercise announcement, hybrid closed-loop systems	Modulation of insulin delivery when control algorithm is aware of exercises and meals as announced by user; meal boluses are administered by user; glucagon or other hormone may be co-administered
Fully closed-loop system	Modulation of insulin delivery when the control algorithm is unaware of meals, exercise, stress and other lifestyle disturbances that affect glucose control; glucagon or other hormone may be co-administered

2.2.2 Control algorithms

The control algorithm is the core of a closed-loop system and directs the delivery of insulin to mimic physiologic glucose homeostasis. Two main categories of control algorithms have been employed, the proportional-integral-derivative (PID) controller[154,155], a classic feedback control mechanism, and the model predictive controller (MPC)[156]. Other clinically evaluated approaches include controllers based on fuzzy logic[157] or a combination of MPC and PID for insulin and glucagon co-delivery[158].

2.2.2.1 Proportional-integral-derivative algorithm

A PID controller is a generic control loop feedback mechanism widely used in industrial control systems. It adjusts insulin delivery by assessing glucose excursions as deviations from a target glucose level (proportional component), the area under the curve between the measured and

the target glucose level (integral component) and the rate of change in the measured glucose levels (derivative component). Figure 2.5 provides a schematic description of the PID controller approach for insulin delivery. PID algorithms are considered to be reactive given that they respond to observed glucose levels[149].

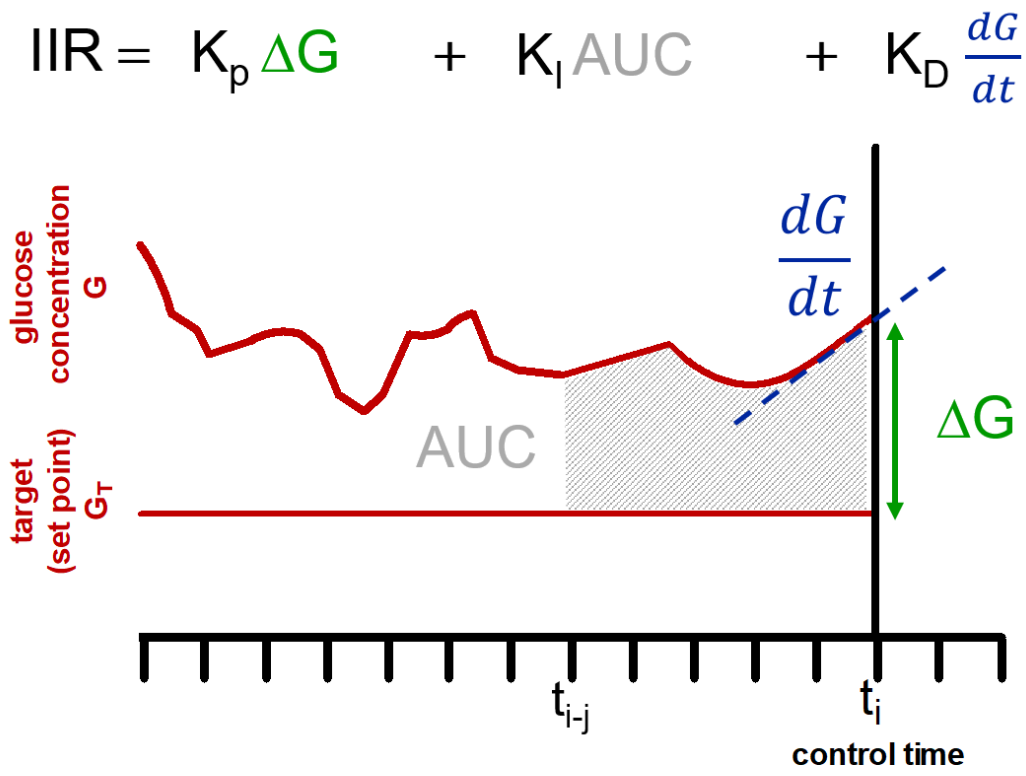

Figure 2.5. Schematic representation of the PID controller. The respective insulin infusion rate (IIR) at time point t_i is comprised of a component, K_p, that is proportional to the difference between sensor and target glucose (ΔG); an integral component, K_I, that increments a basal rate in proportion to the difference between sensor and target glucose (AUC); and a component, K_D, that adjusts insulin delivery in proportion to the rate of change of sensor glucose (dG/dt). Adapted from Steil et al.[154]

2.2.2.2 Model predictive control

Model predictive controllers (MPC) rely on dynamic models of the glucoregulatory process to forecast glucose excursions[159]. The MPC approach is the algorithm employed in the studies described in this thesis (Chapters 3 to 6). Insulin delivery is calculated based on previous information of glucose levels and insulin infusion rates. MPC controller work by optimising insulin delivery to minimize the difference between model predicted glucose levels and the target glucose trajectory over a prediction window. MPC algorithms can be regarded as

proactive and are suitable to handle delays associated with insulin absorption, and account for announced disturbances such as meal intake and physical activity[149].

The Cambridge MPC controller utilises a compartment model of glucose kinetics describing the effect of rapid-acting insulin and the carbohydrate content of meals on sensor glucose excursions[160]. The model facilitates simulation of 'what if' scenarios, particularly the prediction of future glucose excursions resulting from past and proposed insulin infusion delivery. These prediction capabilities enable the calculation of insulin infusion rates expecting to lead to predefined target glucose excursions. The insulin infusion rate is obtained by minimizing the difference between the model-predicted glucose concentration and the target glucose trajectory over, e.g. a two to four-hour prediction window that corresponds to the duration of action of rapid-acting insulin analogues. At each control step, normally every 10 minutes, the minimisation is carried out. Figure 2.6 provides a schematic description of the MPC controller approach used in the studies presented in this thesis.

Algorithms often include a safety layer or supervisor that constraints insulin delivery. This supervisory module may monitor and limit insulin 'on board' (i.e. insulin delivered but yet to exert its action) or a maximum insulin infusion rate or may stop insulin delivery at low glucose levels or when glucose is falling rapidly[149]. The Cambridge algorithm comprises two supervisory modules which may modify both the generation of the original advice and after the advice is generated. The algorithm aims to achieve glucose levels between 5.8 and 7.3mmol/l and adjusts the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. The maximum insulin infusion rate is limited, and safety rules suspend insulin delivery at sensor glucose at or below 4.3 mmol/l or when glucose is decreasing rapidly. The stepwise generation of the algorithm advice is shown in Figure 2.7.

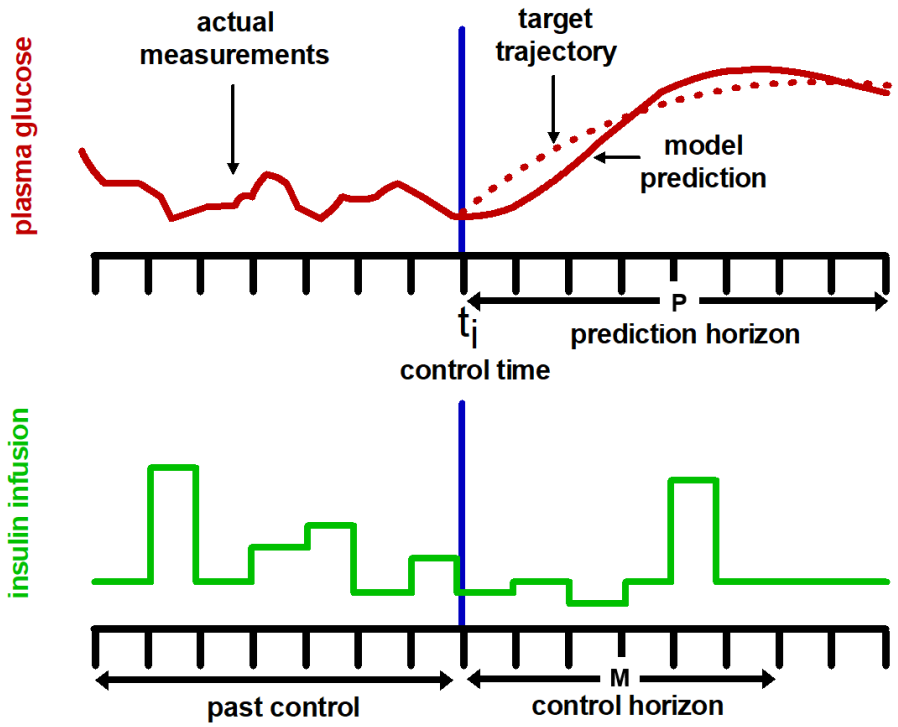

Figure 2.6. Schematic view of the Model Predictive Control (MPC) approach. The blue vertical line represents each time step t_i when previous glucose measurements (red curve) and insulin delivery (green curve) is known. The controller calculates a set of M current and future insulin delivery rates in order for the model to predict glucose levels to reach a desired target trajectory over a future horizon of P time steps. Adapted from Hovorka[161]

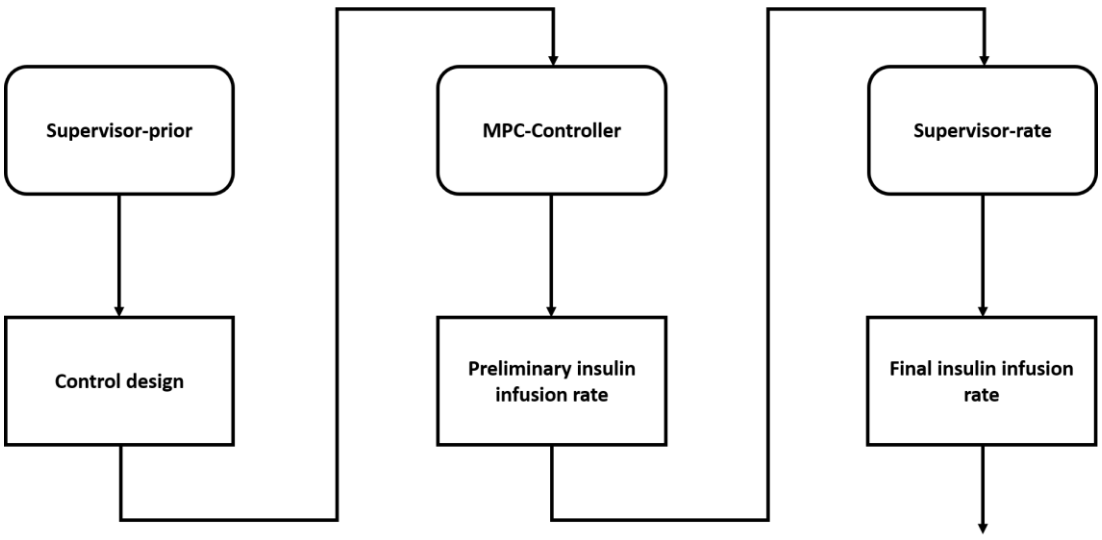

Figure 2.7. Generation of insulin delivery advice by the Cambridge MPC controller.

2.2.3 Bi-hormonal closed-loop

Bi-hormonal (also known as dual-hormone) closed-loop systems also deliver subcutaneous glucagon in addition to insulin when hypoglycaemia is observed or predicted and may provide additional benefit in terms of safety and further reduction of hypoglycaemia risk[150]. Two different approaches have been taken by scientists developing such systems. One aims to improve glucose control by tuning insulin delivery in a similar way to that of a single hormone artificial pancreas, adding glucagon as an additional safety layer only to further reduce hypoglycaemia. The other delivers insulin more aggressively to rapidly achieve lower insulin levels, and counteract it with glucagon, if necessary, to mitigate the risk of insulin overdosing[162].

2.2.4 Other adjunctive approaches with closed-loop insulin delivery

Closed-loop effectively maintains glucose overnight, but meals are still challenging. Adjunctive therapies including pramlitide and glucagon-like peptide-1 (GLP-1) to suppress post-prandial hyperglucagonaemia and associated hyperglycaemia were evaluated in combination with close-loop insulin delivery in adolescents and young adults in research facility settings[163-165].

2.2.5 Clinical evaluation of closed-loop insulin delivery

Studies of closed-loop insulin delivery have evolved from small pilots undertaken in laboratory settings over single night, to larger trials in outpatient settings such as diabetes camps and hotels for over up to 6 days, to medium-term multicentre unsupervised studies in home settings with a duration of up to 6 months.

Most prototypes of closed-loop systems follow a hybrid approach characterised by manual delivery of prandial insulin. In September 2016 the FDA approved the first hybrid closed-loop system (MiniMed 670G pump, Medtronic, Northridge, CA) based on safety outcomes of a non-randomised pivotal trial including 124 adolescents and adults[99,166].

Henceforth I discuss results of closed-loop applications in laboratory, inpatient environments, and transitional outpatient settings, as well as evaluations in home settings from a paediatric perspective. The focus is on randomised controlled trials. Evaluations of bi-hormonal systems, as well as other adjunctive approaches with closed-loop insulin delivery are discussed separately. Randomised controlled studies in transitional outpatient settings and home environments are summarised in Table 2.2.

2.2.5.1 Laboratory studies

Overnight closed-loop is not complicated by meals or physical activity. More than half of episodes of severe hypoglycaemia occur during sleep[167] with up to 75% of hypoglycaemic seizures occurring at night[14]. Hyperglycaemia, resulting from inadequate insulin delivery or parenteral fear of hypoglycaemia, is associated with structural brain alterations[168,169]. Overnight closed-loop may provide a solution to the important clinical problem of nocturnal glucose control, a major source of concern to parents and caregivers[170].

Evaluations of overnight closed-loop systems in laboratory settings documented a reduced risk of hypoglycaemia and improved glycaemic control[149,152]. RCTs in the young using an MPC algorithm[156] showed that overnight closed-loop increases the percentage of time during which plasma glucose levels are within a target range (between 3.9 and

8.0mmol/l) from 40% to 60%. Closed-loop resulted in a significantly reduced time spent with glucose below 3.9 mmol/l (from 4.1% to 2.1%). No nocturnal episodes of hypoglycaemia were documented.

Using a PID algorithm, O'Grady et al. demonstrated the efficacy and safety of a portable automated closed-loop system in adolescents and young adults[171]. The proportion of time during which overnight sensor glucose values were maintained between 3.9 and 8 mmol/l was greater during closed-loop and time spent below 3.3 mmol/l was reduced. An evaluation of a PID algorithm in adolescents and young adults by Sherr et al.[172] demonstrated the benefits of overnight closed-loop insulin delivery following antecedent afternoon exercise in inpatient settings. Closed-loop was effective in reducing nocturnal hypoglycaemia whilst increasing the percentage of time spent in the target range. This effect was observed regardless of activity level in the mid-afternoon. In a randomized multicentre multinational crossover trial, Nimri et al. showed the ability of a fuzzy logic-based algorithm to improve overnight glucose control without increasing hypoglycaemic risk in children and adolescents in laboratory settings[173].

Maintaining tight glucose control during waking hours, as opposed to overnight control, is complicated by meal intake and exercise activity. Early postprandial hyperglycaemia followed by a late post-meal hypoglycaemia is common and can be attributed to slow insulin absorption, insulin stacking, and overshooting hyperinsulinemia[154]. A practical approach is to combine closed-loop operation for determining insulin delivery between meals with manual delivery of partial or full prandial boluses. Such a hybrid closed-loop system using a PID algorithm has been shown to improve postprandial glucose levels compared to a fully closed-loop PID algorithm[155].

In a day and night study including regular meals and unannounced periods of exercise, Elleri et al. showed that closed-loop insulin delivery in adolescents using a hybrid MPC approach increased percentage time when glucose was in the target range with greatest benefit observed overnight, including significantly reduced mean plasma glucose without increasing the risk of hypoglycaemia[174].

Furthermore, day and night systems were evaluated in the very young age group (less than seven years) and in young people with recent onset T1D. Buckingham et al. demonstrated the efficacy and safety of an inpatient hybrid closed-loop system initiated within seven days of diagnosis of T1D in young people for up to 93 hours[175]. Dauber et al. investigated a PID approach in children younger than seven years and showed improved re-establishment of target glucose levels after meals compared to standard insulin therapy and a reduced overnight exposure to hyperglycaemia without increasing the incidence of hypoglycaemia[176].

2.2.5.2 Transitional phase closed-loop studies

Many transitional outpatient studies have been performed in camp settings with children and adolescents (Table 2.2). Whilst participants are studied in "real-world" surroundings, monitoring by medical and research personnel allows interventions to take place in case of safety concerns or system malfunctions. Hypoglycaemia is a well-recognised complication at diabetes camps often attributed to increased exercise and dietary alterations[177]. Thus, camp settings provide a challenging testbed for closed-loop systems. Given the higher hypoglycaemia burden, studies in camp environments are more likely to show benefits with respect to hypoglycaemia reduction.

In one of the first outpatient studies adopting a multicentre randomised design, an MD-logic control algorithm was evaluated over a single night in fifty-six children and adolescents in a diabetes camp and compared to sensor augmented pump therapy[178]. The number of hypoglycaemia events with sensor glucose values below 3.5mmol/l was significantly reduced during closed-loop use with comparable median glucose levels during the two interventions.

The use of a closed-loop system with an MPC control algorithm in a diabetes camp in children and adolescents in a diabetes camp for over five to six nights significantly reduced the time spent in hypoglycaemia overnight (<2.8mmol/l, <3.3mmol/l, and <3.9mmol/l) but did not improve time spent in the target range from 3.9 to 8.3 mmol/l nor mean glucose levels compared to sensor augmented pump therapy as per intention-to-treat analysis[179]. Using a similar system day-and-night in a diabetes camp

over five to six days in adolescents with type 1 diabetes, the percentage of time spent with sensor readings below 3.9mmol/l overnight was significantly reduced with the closed-loop system compared to sensor augmented pump therapy, as were mean overnight glucose and time spent in hyperglycaemic glucose ranges, while overnight time in target between 3.9 and 10.0mmol/l was increased[180].

Comparing the use of a closed-loop system utilising a modified PID controller[181] with sensor augmented pump therapy at a diabetes camp in 21 children and adolescents for up to six nights, nocturnal hypoglycaemia was reduced and overnight time spent in the target range 3.9 to 8.3mmol/l was greater with closed-loop[182]. Using the same algorithm in a fully integrated hybrid day-and-night closed-loop system in 21 adolescents and young adults over up to six days in a diabetes camp, there was no additional benefit with regards to nocturnal hypoglycaemia, time in target range and mean overnight glucose when compared with sensor augmented pump therapy combined with low glucose suspension[183].

Focusing on younger children, Del Favero et al. conducted a camp trial in children aged five to nine years[184]. A hybrid closed-loop system was compared against sensor augmented pump therapy over three days. Closed-loop use resulted in a significant reduction of nocturnal time spent with sensor glucose readings below 3.9mmol/l. Time in range overnight was similar between interventions, but mean overnight glucose was higher with closed-loop.

In a hotel setting, outpatient use of closed-loop in young children aged five to eight years was compared with standard SAP use at home over two 68-hours study periods[185]. Compared to home care, the closed-loop use resulted in increased time with blood glucose in the target range of 3.9 to 10.0 mmol/l (73% vs. 47%) and lower mean glucose (8.4 mmol/l vs. 10.6 mmol/l), both $P < 0.001$. Occurrence of hypoglycaemia was similar between sessions without differences in time <3.9mmol/l (1.1% ± 1.1% vs. 1.6% ± 1.2%, closed-loop vs. SAP).

2.2.5.3 Closed-loop home studies

At diabetes camps, hypoglycaemia is a well-recognised complication due to increased exercise and dietary changes impacting on glucose control[177], which certainly pose a challenge to closed-loop systems. On the other hand, given the higher exposure, studies in camp environments are more likely to show benefits with respect to hypoglycaemia reduction. Home studies, however, more accurately mimic anticipated use of closed-loop systems in clinical practice. Evaluations without supervision or close remote monitoring represent the ultimate challenge in providing unequivocal assessment of closed-loop performance under free-living conditions.

Overnight closed-loop insulin delivery with remote monitoring supervision was tested in 24 participants including adolescents for six weeks using the MD-logic algorithm applying sensor augmented pump therapy as comparator[186]. The use of overnight closed-loop showed significant reduction of time spent hypoglycaemic by nearly two-fold ($p=0.02$) while improving time spent within range by 14% ($p=0.003$). Similar results were observed in a multicentre, multinational study using the MD-logic system in 75 patients aged 10 to 54 years over four consecutive nights with sensor augmented pump therapy as a comparator[187]

Unsupervised free living overnight use of a MPC algorithm driven closed-loop in adolescents over a period of three weeks showed significant improvements in time spent within range by a median 15 percentage points ($p<0.001$), reduced mean glucose by a mean 0.8 mmol/l ($p<0.001$) and number of nights with glucose readings below 3.5 mmol/l ($p=0.01$) compared to sensor-augmented pump therapy[188].

Unsupervised free living overnight use of a MPC algorithm driven closed-loop in adolescents over a period of three weeks showed significant improvements in time spent within target range by a median 15 percentage points, reduced mean glucose by a mean 0.8 mmol/l, and reduced the number of nights with glucose readings below 3.5 mmol/l compared to sensor augmented pump therapy[188]. A slightly revised version of this closed-loop system was tested in the longest randomised home study in children and adolescents to date. Over a period of three months, the overnight closed-loop

application was compared to sensor augmented pump therapy during free-living conditions in 6 to 18 year youth[189]. Closed-loop improved the overnight time in target range between 3.9 and 8.0mmol/l by 25 percentage points and reduced overnight mean glucose by 1.6mmol/l. Extended benefits of overnight closed-loop use were seen over the full 24-hour period including greater percentage of time in target range, lower mean glucose, and significantly reduced burden of hypoglycaemia. Results of this trial are extensively discussed in Chapter 4 of this theses. In two recent day-and-night trials conducted in adolescents over one [190] and three week duration[191] we could demonstrate improved overnight time spent within target range compared to sensor augmented pump therapy and reduced mean overnight sensor glucose without increasing the risk of hypoglycaemia. More details regarding these trials are presented in Chapter 5 of this thesis.

The overnight application of a hybrid closed-loop system using a modified PID algorithm was compared to sensor augmented pump therapy with low-glucose suspend function over four consecutive nights in a study including 12 adolescents[192]. Closed-loop resulted in a reduced time spent with sensor readings below 3.9%; no difference in the percentage of time in the target range between 4.0 and 8.0 mmol/l was observed, but mean overnight glucose was slightly elevated during closed-loop use.

Recently, Spaic et al. compared predictive hyperglycaemia and hypoglycaemia minimization system with predictive low glucose suspend in the home setting in adolescents and adults over 42 nights[193]. The addition of the predictive hyperglycaemia minimisation component increased the time spent in the target range between 3.9 and 10.0 mmol/l, significantly reduced mean overnight and morning blood glucose levels, and performed equally well with respect to hypoglycaemia outcomes.

In adults, two multicentre trials of two- to three-month application of evening-and-overnight closed-loop [194], and day-and-night closed-loop [195], respectively, showed improved time spent in target range, reduced mean glucose and time spent hypoglycaemic, as well as statistical significant reduction in HbA1c levels.

These results of extended closed-loop use in home settings are promising and demonstrate the unique ability of such systems to reduce both mean glucose and the risk of hypoglycaemia, a feat almost unachievable with other therapeutic modalities so far.

2.2.5.4 Evaluations of bi-hormonal closed-loop systems

Day and night bi-hormonal insulin-aggressively-tuned closed-loop system was studied over five days in adolescent participants in a diabetes camp setting[196]. Conventional insulin pump therapy was the comparator. Overall, mean plasma glucose was significantly reduced during the closed-loop period (p=0.004), the percentage of time spent with low plasma glucose readings was similar during the two interventions (p=0.23), but the frequency of interventions for hypoglycaemia was lower during closed-loop (one per 1.6 days, vs. one per 0.8 days, p<0.001). Time spent hypoglycaemic in adults was significantly reduced compared to conventional insulin pump therapy (p=0.01). The bi-hormonal system delivered an average 0.7 mg of subcutaneous glucagon per day. In another outpatient diabetes camp bi-hormonal closed-loop was tested in preadolescent children aged 6-11 years for five days[197]. Compared to conventional insulin pump therapy, mean sensor glucose on days 2-5 were reduced by 1.7mmol/l (p=0.0037) and the time spent hypoglycaemia was also reduced (p<0.0001). The bi-hormonal system reduced the need for rescue carbohydrates (p=0·037). Mean plasma glucagon levels were projected to be above the normal fasting range.

Non-aggressive bi-hormonal, insulin-alone closed-loop systems and conventional pump therapy were compared in children and adolescents in a diabetes camp over three consecutive nights[198]. The nocturnal time spent in hypoglycaemia with the bi-hormonal system was significantly reduced compared to the insulin-alone system (p=0·032) and insulin pump therapy alone (p=0.005). The number of hypoglycaemic events overnight was reduced from 15 events during nights with conventional pump therapy to four events with the insulin-alone system and to none with the bi-hormonal system.

2.2.5.5 Evaluations of other adjunctive approaches with closed-loop insulin delivery

Weinzimer and colleagues compared closed-loop insulin delivery alone to closed-loop insulin delivery with subcutaneous pramlintide before meals during two 24-hour periods[163] . No pre-meal insulin boluses or meal announcement were provided during both visits. Compared to closed-loop alone, pramlintide co-delivery significantly reduced the postprandial time to peak plasma glucose ($p<0.0001$), plasma glucose excursion ($p=0.006$), and the meal-related area under the curve glucose excursion ($p=0.04$).

The use of either pramlintide or GLP-1 during closed-loop insulin delivery were compared to closed-loop insulin delivery alone in a 27-hour trial[164]. Co-administration of exenatide, but not pramlintide, led to significantly greater reduction of blood glucose after lunch and dinner ($p<0.03$ and $p>0.05$, respectively). Glucagon suppression compared to closed-loop insulin delivery alone was significantly greater with exenatide ($p<0.03$) but not pramlintide ($p>0.05$). The investigators reported no increase in hypoglycaemia episodes with either exenatide or pramlitide.

A different trial[165] showed that adjunctive pramlintide to closed-loop without meal announcement significantly delayed the time to peak plasma glucose ($p>0.001$) with concomitant blunting of peak postprandial increments ($p>0.001$) and reductions in postmeal incremental plasma glucose area under the curve. Similarly, adjunctive liraglutide led to reductions in postprandial glucose excursions ($p=0.005$) and incremental meal-related area under the curve glucose excursion ($p=0.004$) along with a 28% reduction in prandial insulin delivery.

2.2.6 Psychosocial aspects

Until recently, the use of closed-loop systems has been restricted to hospital-based trials. Elleri et al. evaluated parental attitudes towards closed-loop systems. The majority of parents of children and adolescents with T1D expressed trust and felt positive about these systems[170].With the emergence of home studies and more advanced closed-loop prototypes, the evaluation of closed-loop user feedback and

experience have become increasingly important as they may guide and inform future directions of closed-loop system development.

In a quantitative and qualitative psychosocial analysis of experiences of home trial participants, adolescent users of overnight closed-loop and their parents, widely reported benefits including reassurance/peace of mind, having "time-off" from managing their diabetes, improved overnight control leading to improved daily functioning and diabetes control, and improved sleep[199]. The key negative aspects mentioned related mainly to technical difficulties (e.g. device connectivity and sensor calibration), intrusiveness of alarms, and size of the devices. Overall, for adolescents benefits of a closed-loop system seemed to outweigh practical challenges[199].

This is in line with experiences from a study testing overnight predictive low glucose management systems at home where participants perceived the PLGM as a much deserved break from the daily burden of diabetes care[200]. In another overnight home trial, closed-loop application was found to have a positive impact on hypoglycaemia fear and other indices of health-related quality of life outcomes[201].

2.3 CAMBRIDGE CLOSED-LOOP SYSTEM PROTOTYPES

During my years of study in Cambridge, different closed-loop system prototypes were used which differed in terms of the computer algorithm hosting device, connectivity to the CGM receiver, and remote data upload, but which all used the same Cambridge control algorithm. Descriptions of the specific closed-loop system prototypes used in each trial are included in the respective chapters. The prototypes were all developed by the University of Cambridge and collaborators; components were modified as diabetes specific (e.g. CGM and pump technology) and non-specific technologies evolved (e.g. tablet, smartphones). Along with smaller device size, and better connectivity and portability, the focus has shifted from closed-loop applications overnight only to day-and-night use of portable, wireless systems. As the emphasis of this thesis is on clinical evaluations, the issue of prototype and algorithm development is not discussed in greater detail.

2.4 OUTCOME MEASURES

Efficacy and safety are important outcome measures for closed-loop trials. The main safety outcomes are diabetic ketoacidosis and severe hypoglycaemia. Efficacy equates with improved glycaemic control, a reduction in mean glucose, and/or reduction in hypo- or hyperglycaemia. Thus, HbA1c and CGM-derived metrics seem to be most suitable efficacy outcome measures for closed-loop trials.

Measurement of HbA1c has been the gold standard method for assessing glycaemic control. HbA1c reflects mean glycaemia over the previous 8 to 12 weeks. It can be measured with a high degree of precision in a central laboratory and is not dependent on the continuous use of a devices such as a blood glucose meter or CGM. Lower HbA1c levels are associated with lower risk of chronic diabetes complications as shown in the Diabetes Control and Complications Trial (DCCT)[43]. However, there are certain limitations using HbA1c as the primary outcome measure in closed-loop trials: The intervention duration of close loop trials might not be long enough to show meaningful changes in HbA1 levels. Secondly, HbA1c provides only an average of glucose levels over the previous past two to three months and does not provide information regarding intra- and inter-day glycaemic excursions, nor information regarding hypoglycaemia or hyperglycaemia frequency and patterns that might lead to hypo- or hyperglycaemia. Thirdly, it is an unreliable measure in patient with anaemia, haemoglobinopathies or iron deficiency and during pregnancy[202-204].

Data provided by CGM devices allow the limitations of traditional metrics of glycaemic control to be overcome. CGM provides the opportunity to measure actual glucose values during daily living and provides assessments of both hyperglycaemia and hypoglycaemia. Additionally, CGM can be used to separately analyse glycaemic control during the daytime and overnight. As such, it could be considered the optimal method for assessing outcomes in a closed-loop study. The value of CGM as a primary endpoint measure has been shown in long-term randomised trials assessing CGM as an intervention in participants with type 1 diabetes[115,205]. Indeed, a consensus report published in 2017 defined measures of glycaemic control based on CGM and highlighted the importance of CGM technology in modern diabetes care[104,105]. CGM

metrics used for outcome assessment should include metrics that provide a measure of overall control (mean glucose, time within a target range), hyperglycaemia, hypoglycaemia, and glucose variability[104,105,206].

Glycaemic variability as a clinically valuable marker of glucose control has greatly expanded the understanding of glucose control beyond HbA1c alone[207-210]. There are various metrics to assess glucose variability including standard deviation (SD), coefficient of variation (CV), interquartile range, mean amplitude of glycaemic excursion (MAGE), continuous overall net glycaemic action (CONGA), mean of daily differences (MODD), and others[211]. SD and MAGE typically increase with mean glucose, which makes it difficult to separate the effect of the intervention on glucose variability from the effect on the mean glucose itself. The CV, which is the SD divided by the mean glucose, has the advantage of being a metric relative to the mean, which makes it more descriptive of hypoglycaemic excursions than the SD alone[105].

Potential limitations using CGM glucose metrics as efficacy outcomes include sensor inaccuracies which might inflate or deflate closed-loop performance compared to actual glucose levels. However, overall accuracy of the latest sensor generations has tremendously improved compared to previous generations[93,94,97,98,212]. Additionally, potential sensor inaccuracy might be addressed in the study design by increasing sample size to account for greater variance of continuous outcome variables. Another issue is that outcome data might not be available for certain study participants due to sensor malfunction or limited sensor usage or in those who completely discontinue CGM. Redundant sensor technology using identical or differing sensing approach in study participants or additional blinded sensors in those who discontinue CGM might help mitigate these issues[213]. Alternatively, for short-duration inpatient trials, outcome measures based on frequent plasma or capillary glucose sampling might be an alternative. But this is not a feasible approach as far as home trials are concerned. Depending on the sampling frequency, a lot of information regarding glucose excursions might be lost. With respect to long-term studies, HbA1c could be used as an overall marker of metabolic control. Again, this is associated with a significant loss of information as regards actual glycaemic excursions.

Given the relatively short duration of the trials included in my thesis, and in line with above mentioned consensus statements and considerations, the time spent with glucose levels within the target range has been chosen as primary efficacy outcome in all studies. The target range was defined as glucose levels between 3.9 and 8.0mmol/l for overnight studies (Chapters 3 and 4), and 3.9 to 10.0mmol/l for day-and-night studies (Chapters 5 and 6). For the 12-week trial long enough to report meaningful results for HbA1c, changes in HbA1c levels were also analysed (Chapter 4). Other CGM-based secondary outcomes included the times below and above target ranges, using a few severity thresholds for each level. Additionally, the coefficient of variation (CV) as the recommended primary measure of variability, as well as the standard deviation of glucose as the key secondary glycaemic variability measure were reported[105]. Safety outcomes for all trials included the frequency of severe hypoglycaemia and diabetic ketoacidosis episodes as well as the nature and severity of all other adverse events.

Table 2.2. List of transitional and home closed-loop studies in the paediatric population.

Reference (year)	Study population *Age inclusion criterion* *Mean age* ± SD	N	Study design	Study setting	Closed-loop system	Comparator	Duration of intervention	Primary/co-primary outcome(s)
DeBoer et al.[185] (May 2017)	5–8 years Median age: 7	12	Randomised, two-period crossover	Research House/Hotel	Single hormone	SAP	Day-and-night 68 hours	% of time in target range (3.9-10.0 mmol/l): 73% vs. 47%, CL vs. SAP (p < 0.001)
Nimri et al.[187] (Apr 2017)	10-65 years 19.5±10.0	75	Randomised, two-period crossover	At home	Single hormone	SAP	Overnight 4 nights	% of time with sensor glucose <3.9 mmol/l: median 2.1 vs. 2.6%, CL vs. SAP (p=0.004); % of nights with a mean overnight glucose level in range (3.9 to 7.8 mmol/l): median 75% vs. 50%, CL vs. SAP (p = 0.008).
Spaic et al.[193] (Mar 2017)	15-45 years Median age: 31	30	Randomised each night	At home	Single hormone	PLGS	Overnight 42 nights	% of time in range (3.9-10.0 mmol/l): mean 78 vs. 71%, CL vs. PLGS (p<0.001)
Sharifi et al.[192] (Dec 2016)	> 14 years 15.2± 1.6	12	Randomised, two-period crossover	At home	Single hormone	SAP+TS	Overnight 4 nights	% of time in overnight target range (3.9-8.0 mmol/l):): 61.7 vs. 64.9%, CL vs. SAP+TS (p=0.62)
Tauschmann et al.[191] (Nov 2016)	10-18 years 14.6 ± 3.1	12	Randomised, two-period crossover	At home	Single hormone	SAP	Day-and-night 21 days	% of time in range (3.9 to 8.0 mmol/l): mean 54.4% vs. 33.4%, CL vs. SAP (p<0.001)
Ly et al.[180] (Aug 2016)	10-35 years 17.9 ± 5.5	33		Diabetes Camp	Single hormone	SAP	Day-and-night 5 days	% of time in target range (3.9 o 10.0 mmol/l): mean 90.3 vs. 67.2%, CL vs. SAP (p<0.001)
Tauschmann M et al.[190] (Jan 2016)	10-18 years 15.4±2.6 years	12	Randomised, two period crossover	Home without remote monitoring/supervision	Single hormone	SAP	Day-and-night 1 week	% of time in target range (3.9-10mmol/l): *mean 72% vs. 53%, CL vs. SAP (p< 0.001)*
Ly TT et al.[182] (Jun 2016)	10-35 years 15.9±2.5 years	21	Randomised, crossover	Diabetes camp	Single hormone	SAP	Overnight Up to 6 days	% of time in target range (3.9-8.3 mmol/l): median 66.4% vs. 50.6% (p=0.0004)
Del Favero et al.[184] (Jun 2016)	5-9 years 7.6±1.2 years	30	Randomised, two period crossover	Diabetes camp	Single hormone	SAP	Day-and-night 3 days	% of time sensor glucose <3.9mmol/l and % of time in target range (3.9-10mmol/l): median 2.0% vs. 6.7%, CL vs.

								SAP (*p<0.001)*, and mean 56.8% vs. 63.1%, CL vs. SAP (p=0.022)
Russell SJ et al.[197] (Mar 2016)	6-11 years 9.8±1.6 years	19	Randomised, two period crossover	Diabetes camp	Bi-hormonal	Insulin pump	Day-and-night 5 days	Mean glucose and % of time sensor glucose <3.3mmol/l: *mean 7.6 vs. 9.3mmol/l, CL vs. pump (p=0.00037) and mean 1.2% vs. 2.8% (p<0.0001)*
Thabit H et al.[195] (Sep 2015)	6-18 years 12.0±3.4 years	25	Randomised, two period crossover	Home without remote monitoring/supervision	Single hormone	SAP	Overnight 12 weeks	% of time in sensor target range (3.9-8mmol/l): *mean 59.7% vs. 34.4% CL vs. SAP (p=0.004)*
Haidar et al. (Aug 2015)	9-17 years 13.3±2.3 years	33	Randomised, three period crossover	Diabetes camp	Bi-hormonal	Single hormone, Insulin pump	Overnight 3 days	% of time sensor glucose <4.0mmol/l: *median 0% (bi-hormonal CL) vs. 3.1% (single hormone CL) (p=0.032) vs. 3.4% (conventional pump therapy) (p=0.005 compared with bi-hormonal CL; p=0.32 compared with single hormone CL)*
Ly TT et al.[183] (Jun 2015)	14-40 years 18.6±3.7 years	21	Randomised, two group parallel	Diabetes camp	Single hormone	SAP+LGS	Day-and-night 6 days	% of time in sensor target range (3.9-10mmol/l): *mean 69.9% vs. 73.1% vs., CL vs. SAP+LGS (p = 0.580)*
Nimri R et al.[186] (Nov 2014)	12-64 years 21.2±8.9 years	24	Randomised, two period crossover	Home with remote monitoring/supervision	Single hormone	SAP	Overnight 6 weeks	% of time below 3.9mmol/l: *median 2.5% vs. 5.2%, CL vs. SAP (p=0.02*)
Russell SJ et al.[196] (Jun 2014)	12-21 years 16±3 years	32	Randomised, two-period crossover	Diabetes camp	Bi-hormonal	Insulin pump	Day-and-night 5 days	Mean plasma glucose and % of time plasma glucose <3.9mmol/l: *mean 7.7 vs. 8.7 mmol/l, CL vs. pump (p=0.004) and mean 6.1% vs. 7.6% (p=0.23)*
Ly TT et al.[179] (May 2014)	10-35 years 15.3±2.9 years	20	Randomised, crossover	Diabetes camp	Single hormone	SAP	Overnight 5 – 6 days	% of time in sensor target range (3.9-8.3mmol/l*): median 62% vs. 55%, CL vs. SAP (p =0.233)*
Hovorka et al.[188] (May 2014)	12-18 years 15.6±2.1 years		Randomised, two-period crossover	Home without remote monitoring/supervision	Single hormone	SAP	Overnight 3 weeks	% of time in target range (3.9-8mmol/l): *median 68% vs. 46%, CL vs. SAP (p< 0.001)*
Phillip M et al.[178] (Feb 2013)	10-18 years, Mean age 13.8±1.8	56	Randomised, two-period crossover	Diabetes camp	Single hormone	SAP	One night	Number of hypoglycaemic events (sensor glucose <3.5mmol/l for ≥ 10 consecutive minutes*): median 7 vs. 22, CL vs. SAP (p=0.003)*

3 Sensor operation duration and closed-loop efficacy (APCam09)

3.1 BACKGROUND

Glucose control during closed-loop application to a large extend depends on the accuracy and reliability of CGM systems. CGM accuracy and reliability have improved due to advances in sensor technology, data processing and calibration algorithms [214,215]. However, consistent glucose sensor function over the full lifetime of a sensor may be unattainable and sensors are least accurate in the 24-hour period immediately post-insertion compared to half-way through sensor life (say days 3 to 4) [216,217]. This may relate to insertion trauma causing onset of an inflammatory response and tissue microhemorrhage which may resolve with time[218-220].

3.2 STUDY OBJECTIVES

The purpose of the present study was to evaluate the effect of sensor life on closed-loop performance comparing closed-loop efficacy and safety on day 1 of sensor insertion to day 3 to 4 of sensor insertion in young people with type 1 diabetes over an overnight period at a clinical research facility. We hypothesized that more accurate sensor performance as usually seen half-way through sensor life, could lead to better closed-loop performance as assessed by frequent plasma glucose measurements.

3.3 RESEARCH DESIGN AND METHODS

3.3.1 Study participants

The study was conducted at the Wellcome Trust Clinical Research Facility at Addenbrooke's Hospital, Cambridge, between May 2014 and April 2015. Children and adolescents aged 6-18 years were recruited from three paediatric diabetes clinics at Cambridge, London University College Hospital, and Peterborough. Eligibility criteria included type 1 diabetes (WHO criteria) for at least 12 months, insulin pump therapy for at least 3 months, glycated haemoglobin (HbA1c) below 97mmol/mol (11%) based on analysis from local laboratory within 3 months. Exclusion criteria included any physical or psychological disease likely to interfere with the normal conduct of the

study and data interpretation or current treatment with drugs likely to interfere with glucose metabolism.

3.3.2 Study design

An open label randomized two-period crossover study compared overnight closed-loop insulin delivery on day 1 of sensor insertion versus day 3 to 4 of sensor insertion (Figure 3.1) Prior to study initialization, approval was sought and received from the local independent research ethics committee and the UK regulatory authority (Medicines & Health products Regulatory Agency). Participants aged ≥16 years and parents or guardians of participants aged <16 years signed informed consent; written assent was obtained from minors.

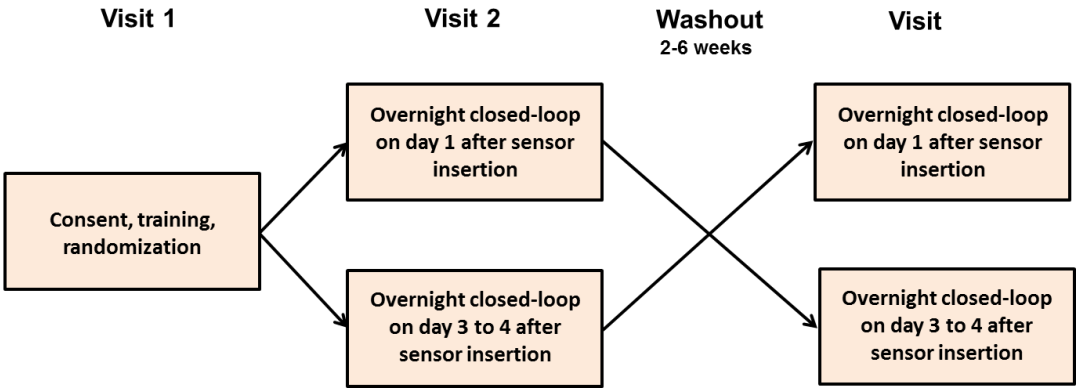

Figure 3.1. Study design

3.3.3 Study procedures

Medtronic MiniMed Paradigm® Veo™ insulin pumps (MMT-554 or MMT-754) with second generation Enlite™ CGM sensors (Medtronic Minimed, Northridge, CA, USA) were used as study pump and continuous glucose monitoring systems (CGM). At recruitment, participants received training on real-time CGM component of the Veo system, and participants' competency in using CGM was assessed and documented by the clinical investigators. No additional pump training was provided as all participants recruited for this trial had already been using Veo™ insulin pump prior to enrolment. CGM calibration followed manufacturer's instructions using finger-stick glucose

measurements taken every 12 h on CONTOUR XT Meter (Bayer, Leverkusen, Germany) which was checked for accuracy by calibration fluid.

Participants attended the clinical research facility for two overnight periods, 2 to 6 weeks apart, with the identical study protocol performed on both occasions. On one occasion, the closed-loop system was informed by a glucose sensor inserted in the morning of the study visit, and on the other occasion study participants had been fitted with a CGM sensor 3 to 4 days prior to the study visit. The order of the interventions was random according to a computer-generated allocation sequence with permuted blocks (Figure 3.1).

On each occasion, participants were admitted at 17:00 and stayed until 08:00 the following day (Figure 3.2). An intravenous cannula was placed for blood sampling starting at 18:00. Participants consumed an evening meal at 18:30 (74±27 g carbohydrates) and an optional bedtime snack at 21:00 (23±15 g carbohydrates). The meals and snacks were identical on the two occasions. Meals and carbohydrate content were chosen by the children and their families based on individual preferences and reflecting usual practice at home. Meals were accompanied by insulin boluses calculated using participants' standard insulin pump bolus calculator settings and pre-meal finger-stick glucose levels. Rapid acting insulin analogue aspart (Novo Nordisk, Bagsvaerd, Denmark) was used.

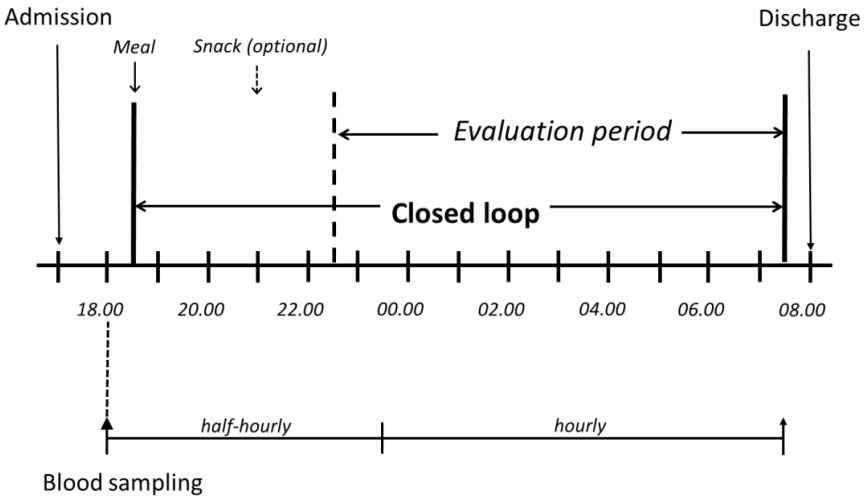

Figure 3.2. Schematic presentation of overnight study visits. Identical procedures were followed during both study visits.

3.3.4 Closed-loop system

The Amber system Android closed-loop platform employed an Android smartphone (Nexus 4, LG, South Korea) running a model predictive control algorithm (version 0.3.30, University of Cambridge) embedded in user interface module and communicating with a Bluetooth to radiofrequency translator module linked to Veo pump (all Medtronic Minimed; Figure 3.3). Every 15 min, the control algorithm automatically initiated a new insulin infusion rate based on sensor glucose through wireless communication. The calculations utilised a compartment model of glucose kinetics describing the effect of rapid-acting insulin analogues and the carbohydrate content of meals on glucose levels. The control algorithm was initialized by downloading preprogrammed basal insulin doses from the pump. Additionally, information about participants' weight and total daily insulin dose were entered at setup. No plasma glucose data were provided to the algorithm.

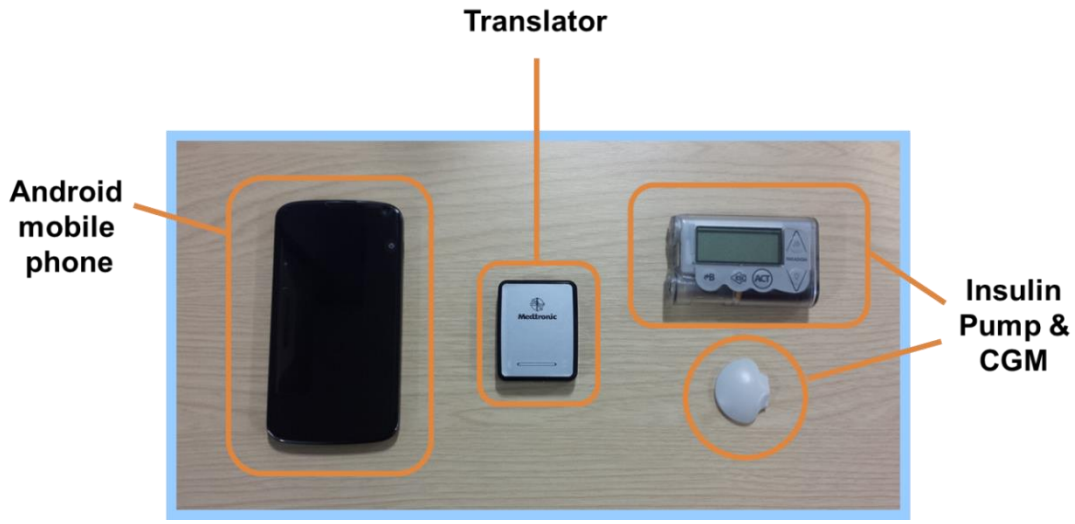

Figure 3.3. Amber closed-loop platform.

3.3.5 Sampling and assays

For the measurement of glucose and insulin concentration, venous blood samples were obtained every 30 minutes until 23:30, then hourly from 23:30 to 07:30. Plasma was immediately separated by centrifugation. Plasma glucose levels were determined in real time by YSI2300 STAT Plus analyser (Yellow Springs Instrument, Farnborough, UK) but were not used to inform the algorithm. Plasma insulin concentration was measured by immunochemiluminometric assay (IV2-001; Invitron Ltd, Monmouth UK) with an inter-assay variation of 7.1%, 2.4% and 7.1% at 89pmol/L, 488pmol/L and 873pmol/L, and an analytical sensitivity of 0.12pmol/L).

3.3.6 Study outcomes

The primary outcome was the time during closed-loop when plasma glucose levels were within the target range from 3.9 to 8.0 mmol/l in the overnight period from 22:30 until 7:30 on the following day.

Secondary outcomes included mean plasma glucose levels, glucose variability, time spent below and above the target range during observation period (22:30 to 07:30). All glucose outcomes were also compared with CGM sensor values. Glucose variability was

assessed by the standard deviation and the coefficient of variation. Hypoglycaemia burden was assessed by calculating the glucose area under the curve less than 3.5 mmol/l. Insulin delivery amounts were reported as total overnight basal insulin delivery. Sensor accuracy for each study arm was assessed using paired sensor and plasma glucose points. The bias (sensor minus plasma value) and relative absolute difference (RAD) (absolute difference divided by the reference value, expressed as percentage) were computed for each pair. Numerical accuracy outcomes were calculated across the whole range of measured glucose levels, as well as for euglycaemic (3.9–10.0 mmol/l), hypoglycaemic (<3.9 mmol/l), and hyperglycaemic (>10.0 mmol/l) ranges stratified according to plasma glucose measurements. Clinical accuracy was assessed by Clarke error grid analysis.

3.3.7 Statistical analysis

The statistical analysis plan was agreed upon by investigators in advance. All analyses were undertaken on an intention-to-treat basis. The respective values obtained during the two overnight randomized interventions were compared using a least-square regression model. Glucose outcomes and insulin outcomes were adjusted for period effect. Rank normal transformation analyses were used for highly skewed endpoints. Outcomes were presented as mean ± SD for normally distributed values or as median (interquartile range) for non-normally distributed values. Accuracy outcomes were summarized using descriptive statistics. Efficacy and accuracy metrics were calculated by GStat software (University of Cambridge, version 2.2), and statistical tests were carried out using SPSS software (IBM Software, Hampshire, UK version 21). A 5% significance level was used to declare statistical significance for all comparisons. All p values are two-sided.

3.4 RESULTS

3.4.1 Participants

We approached 15 patients with type 1 diabetes, 13 participants of which were consented (Figure 3.4). One participant dropped out during run-in (loss to follow-up).

12 subjects were randomised, completed both study periods, and provided data for analyses (

Table 3.1).

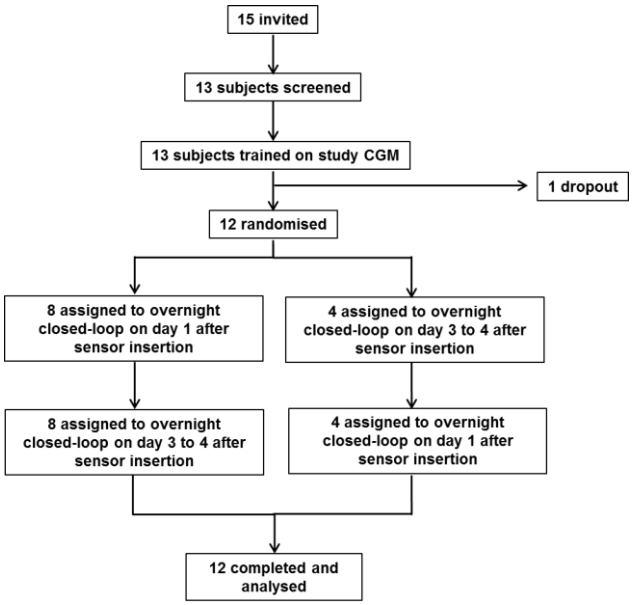

Figure 3.4. Flow of participants through the trial.

Table 3.1. Baseline characteristics of study participants.

	n=12 (mean ± SD)
Age (years)	16.7±1.9
Gender (male/female)	9/3
Weight (kg)	68.6±16.8
BMI (kg/m^2)	21.6±3.3
BMI z-score	0.26±1.26
Glycated haemoglobin at screening (%)	6.8±1.1
Glycated haemoglobin at screening (mmol/mol)	66±10
Duration of diabetes (years)	8.7±3.6
Duration on pump (years)	6.0±2.7

Total daily insulin (U/kg/day)	0.90±0.29

3.4.2 Overnight glucose control

Study outcomes during the overnight closed-loop periods (22:30 to 07:30) are summarized in Table 3.2. Plasma glucose and sensor glucose profiles during closed-loop on day 1 and day 3 to 4 after sensor insertion are shown in Figure 3.5.

3.4.2.1 Plasma glucose outcomes

Plasma glucose levels remained within the target range of 3.9 to 8.0 mmol/l (primary endpoint) for 58% and 56% of the time, respectively, when closed-loop was applied on day 1 or on day 3 to 4 (p=0.30, Table 3.2). No difference was found in the mean plasma glucose concentration (7.9±1.6 vs 7.8±1.8mmol/l, p=0.26). The proportion of time when plasma glucose was in hypoglycemic range (below 3.9mmol/l) and the area under the curve when plasma glucose was less than 3.5mmol/l were very low and comparable during the study periods. There was no difference in glucose variability between the study periods as measured by the standard deviation and coefficient of variation of plasma glucose.

3.4.2.2 Sensor glucose outcomes

The proportion of time that sensor glucose was in the target glucose range of 3.9 to 8.0mmol/l during closed-loop was comparable on day 1 and day 3 to 4 of sensor use (73±25% vs 71±21%, p=0.72; Table 3.2). Similarly, there was no difference in mean sensor glucose levels, the proportion of time above and below the target range, and variability in glucose readings during the two overnight study periods (Table 3.2).

3.4.2.3 Plasma vs sensor glucose

Despite similar closed-loop outcomes between interventions, direct comparison of sensor glucose readings and plasma glucose derived indices showed marked differences (Table 3.2). The proportion of time spent in target range of 3.9 to 8.0 mmol/l was significantly higher when calculations were based on sensor readings than for plasma glucose based calculations (p=0.014). Mean sensor glucose levels were

significantly lower than mean plasma glucose readings (p=0.010) as was time spent above target range (p=0.005).

3.4.2.4 Insulin delivery

Total overnight insulin delivery (22:30 to 07:30) did not differ between interventions (8.4 [6.0 to 14.4]U on day 1 of sensor insertion vs 11.3 [8.8 to 15.3]U on day 3 to 4, p=0.13), and resulted in similar plasma insulin levels (Figure 3.6). Variability in insulin delivery was similar during the two overnight visits (SD 0.7[0.6 to 1.0]U vs 0.8 [0.6 to 0.9]U, p=0.84).

Table 3.2. Comparison of overnight glucose outcomes. Plasma glucose and sensor glucose outcomes during overnight (22:30 to 07:30) closed-loop (CL) on day 1 of sensor insertion vs day 3 to 4 of sensor insertion. Data are mean ± SD or median (interquartile range).

	Plasma glucose			Sensor glucose			Plasma vs. sensor glucose
	CL day 1 (n=12)	CL day 3 to 4 (n=12)	P value	CL on day 1 (n=12)	CL on day 3 to 4 (n=12)	P value	P value
Time in target 3.9-8.0mmol/l (%)*	58±32	56±36	0.30	73±25	71±21	0.72	0.014
Time in target 3.9-10.0 mmol/l (%)	87 (63 to 100)	92 (72 to 99)	0.30	90 (79 to 100)	92 (84 to 98)	0.33	0.34
Mean glucose (mmol/l)	7.9±1.6	7.8±1.8	0.26	6.8±1.4	7.1±0.9	0.65	0.010
Hypoglycemia							
Less than 3.9mmol/l (%)	0.0 (0.0 to 3.2)	0.0 (0.0 to 1.8)	0.93	1.0 (0.0 to 4.4)	0.0 (0.0 to 3.5)	0.41	0.30
AUC_{day} <3.5mmol/l (mmol/l x min) †	0.0 (0.0 to 5.1)	0.0 (0.0 to 0.0)	0.11	0.0 (0.0 to 3.6)	0.0 (0.0 to 0.0)	0.37	0.96
Hyperglycemia							
Time spent at glucose levels (%)							
>8.0mmol/l	39±33	43±36	0.49	21±23	26±22	0.78	0.005
>10.0 mmol/l	0 (0 to 37)	9 (0 to 27)	0.58	1 (0 to 15)	4 (0 to 12)	0.68	0.23
Glucose variability							
SD of glucose (mmol/l)	1.2 (1.2 to 2.1)	1.4 (1.0 to 2.0)	0.26	1.5 (0.8 to 2.3)	1.4 (0.5 to 1.4)	0.29	0.92
CV of glucose (%)	18 (15 to 28)	18 (14 to 23)	0.38	22 (13 to 34)	20 (14 to 25)	0.15	0.63

* Primary endpoint: % of time with plasma glucose readings in target 3.9-8.0mmol/l

† AUC_{day}, Glucose area under curve below 3.5mmol/l per day

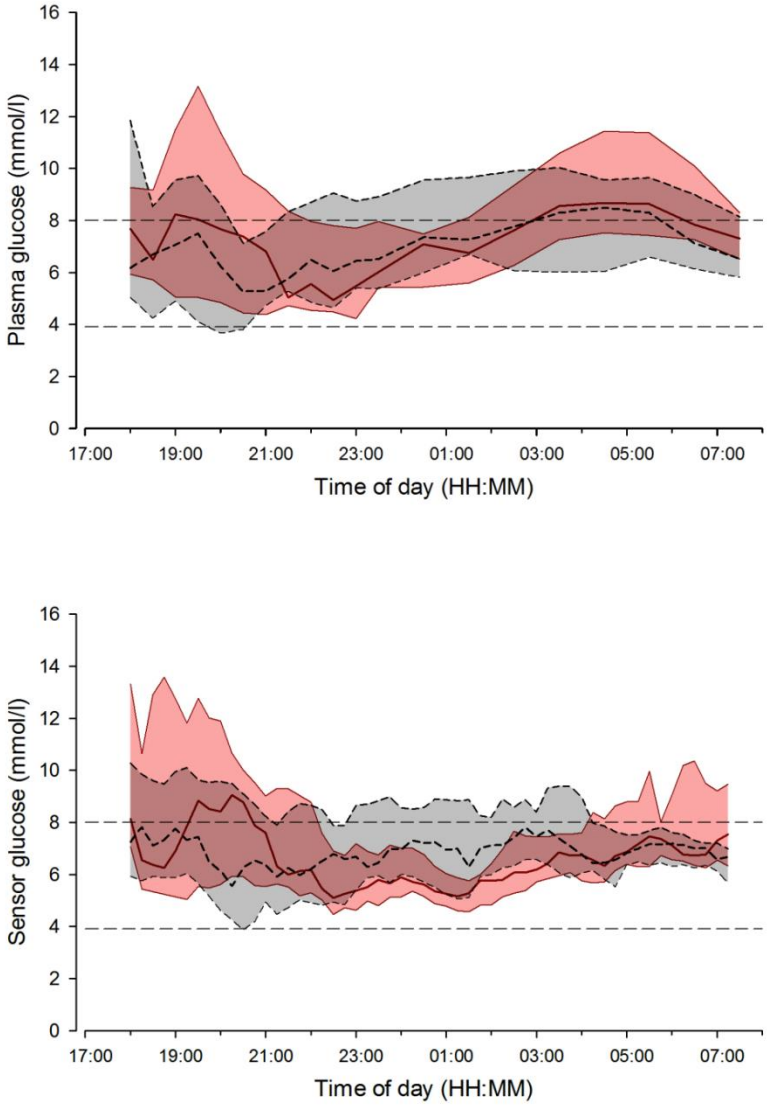

Figure 3.5. Overnight plasma and sensor glucose profiles. Median (interquartile range) of plasma glucose (top panel) and sensor glucose (bottom panel) during overnight closed-loop on day 1 of sensor insertion (solid red line and red shaded area) and closed-loop on day 3 to 4 of sensor insertion period (dashed black line and grey shaded area). The glucose range 3.9 to 8.0 mmol/l is indicated by horizontal dashed lines.

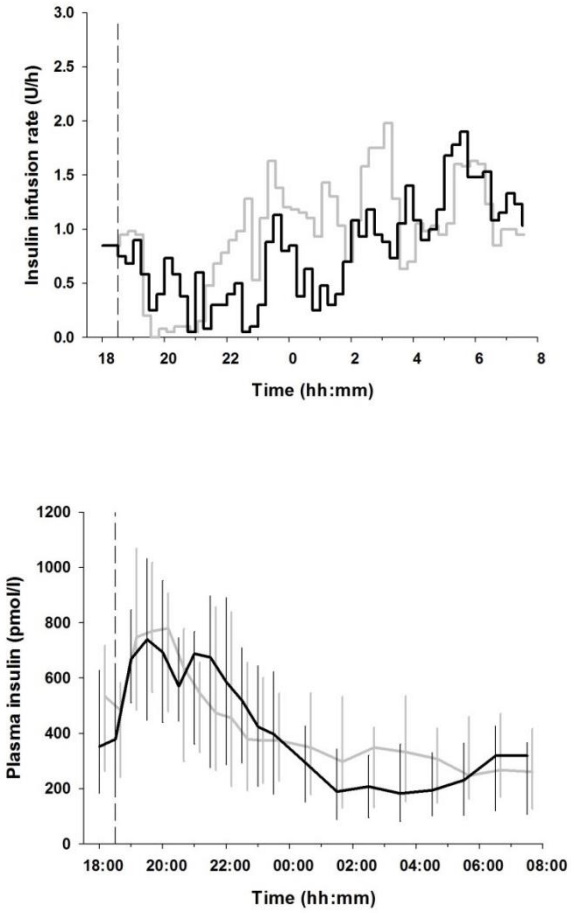

Figure 3.6. Overnight insulin infusion and plasma insulin profiles. Insulin infusion rates (top panel), and plasma insulin (bottom panel) are shown for closed-loop on day 1 of sensor insertion (black line) and closed-loop on day 3 to 4 of sensor insertion (grey line; median (IQR). The vertical dashed line indicates when closed-loop started and when the evening meal was consumed.

3.4.3 Sensor accuracy

Sensor accuracy evaluation is summarized in Table 3.3. On the closed-loop nights between 22:30 and 07:30, 126 sensor - plasma glucose pairs were analysed on day 1 after sensor insertion, and 123 on day 3 to 4. Across the whole glucose range, numerical sensor accuracy expressed as mean ARD was 19.8±15.0% on day 1 and 13.7±10.2% on day 3 to 4, respectively (separate sensor performance matrices for euglycaemic, hypo-and hyperglycaemic ranges are shown in Table 3.3). Mean bias for sensors on day 1 was -0.9±1.9mmol/l, and -0.7±1.4mmol/l on day 3 to 4, respectively. On day 1 of insertion the new generation Enlite sensor had 96.8% of measurements in Clarke Error Grid Zones A+B (Zone A, 61.9%; Zone B, 34.9%; Zone C, 0%; Zone D, 3.2%;

Zone E, 0%). On day 3 to 4, 98.3% of paired sensor data points were in Zones A+B (Zone A, 71.5%; Zone B, 26.8%; Zone C, 0%; Zone D, 1.6%; Zone E, 0%) (Table 3.3 and Figure 3.7).

Table 3.3. Numerical and clinical accuracy on day 1 compared to day 3 to 4 after sensor insertion (evaluated from 2230h to 0730h).

	Closed-loop on day 1 of sensor insertion (n=12)	Closed-loop on day 3 to 4 of sensor insertion (n=12)
Number of paired points	126	123
Mean plasma glucose (mmol/l)	7.9±1.6	7.8±1.8
Clarke error grid (%)		
Zone A	61.9	71.5
Zone B	34.9	26.8
Zone C	0	0
Zone D	3.2	1.6
Zone E	0	0
Median bias (mmol/l)	-0.6 (-1.6 to 0.4)	-0.2 (-1.7 to 0.3)
Mean bias (mmol/l)	-0.9±1.9	-0.7±1.4
Whole range (2.2–17.9mmol/l)		
Median AD (mmol/l)	1.1 (0.5 to 1.8)	0.8 (0.3 to 1.7)
Median ARD (%)	16.3 (7.5 to 28.6)	12.6 (4.7 to 20.9)
Mean AD (mmol/l)	1.5±1.5	1.1±1.0
Mean ARD (%)	19.8±15.0	13.7±10.2
Euglycaemia (3.9-8.0mmol/l)		
Number of paired points	71 (56%)	64 (52%)
Median ARD (%)	12.9 (7.5 to 28.5)	8.5 (4.2 to 16.9)
Hypoglycaemia (<3.9mmol/l)		
Number of paired points	8 (6%)	6 (5%)
Median ARD (%)	37.0 (31.0 to 40.2)	8.5 (5.0 to 17.8)
Hyperglycaemia (>8.0mmol/l)		
Number of paired points	47 (37%)	64 (43%)
Median ARD (%)	20.0 (7.4 to 37.4)	18.6 (7.0 to 25.2)

Bias - plasma glucose minus sensor glucose
AD – absolute difference
ARD – absolute relative difference
Values are mean ± SD or median (interquartile range)

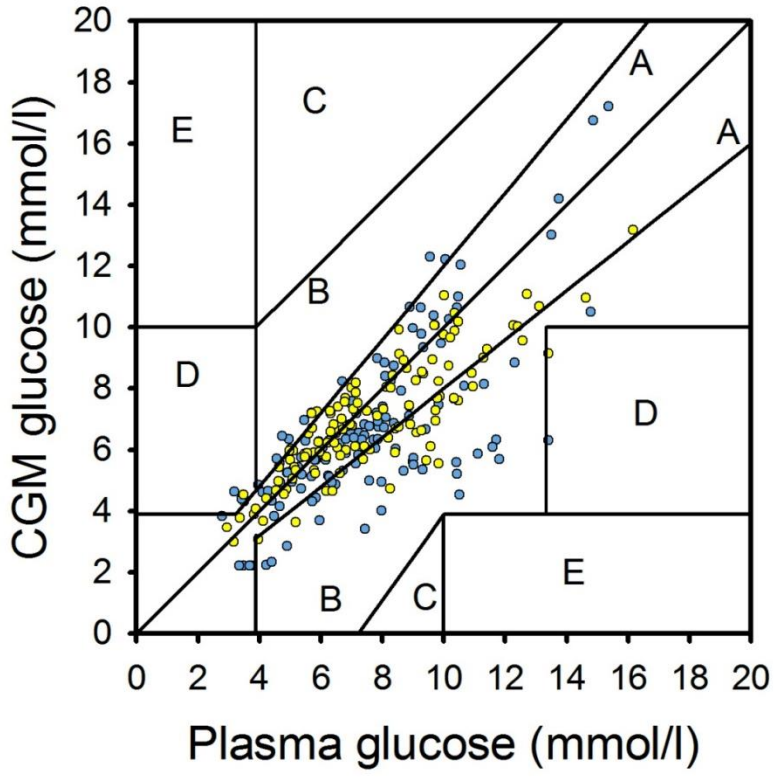

Figure 3.7. Clarke error grid of sensor and plasma glucose levels shown for closed-loop on day 1 of sensor insertion (blue dots) and closed-loop on day 3 to 4 of sensor insertion (yellow dots). Data collected from 2230h to 0730h are presented.

3.5 DISCUSSION

We document that overnight closed-loop glucose control using a model predictive control algorithm informed by sensor glucose on day 1 after insertion was similar to that achieved when closed-loop was initiated on day 3 to 4 of sensor life. Glucose levels were maintained between 3.9 and 8.0 mmol/l for a similar proportion of time, mean plasma glucose readings were comparable, and there were no differences in hypoglycaemia burden.

We observed sensor accuracy comparable to previously reported data [100,216,217,221,222], including reduced accuracy on day 1 of sensor insertion[100,216,217]. Notwithstanding the reduced accuracy on day 1, sensor life did not affect performance of our closed-loop system. We hypothesise that this is related to the robustness of our model predictive algorithm, which mitigates against sensor inaccuracy and has been safely and

effectively used in a range of populations and settings including pregnant women, adults, adolescents and children in unsupervised home application[190,195,223].

Outcomes based on sensor readings significantly inflated closed-loop performance compared to plasma glucose outcomes. This is in contrast to findings from an overnight inpatient study with a similar design conducted in young children using another sensor make, when plasma and sensor based outcomes were comparable[224]. In the present study, sensor-reported glucose levels were significantly lower than plasma glucose values. A similar trend was described by Calhoun et al.[217]. In view of these results, previously reported glucose outcomes based on Enlite sensor, including to benefits of sensor-based therapy regimen (e.g. sensor-augmented pump therapy, low glucose suspension, closed-loop trials), should be interpreted with caution.

The current study was limited by the relatively small sample size and short overnight intervention periods. A limited number of data points for sensor accuracy assessment were collected, particularly with respect to the hypoglycaemic range. The strengths of our study are the crossover randomized design, and the controlled environment to exclude potential confounders with respect to this particular research question.

In conclusion, overnight closed-loop glucose control in adolescents informed by Enlite glucose sensor on day 1 or day 3 to 4 after sensor insertion was comparable. The model predictive controller appears to mitigate against sensor inaccuracies.

4 Home use of overnight closed-loop in children and adolescents (APCam08)

4.1 BACKGROUND

Following extensive studies under controlled laboratory settings[223,225-228], investigations of closed-loop in transitional outpatient settings, incorporating remote monitoring and supervision by research staff in hotels[229] or at diabetes camps[178,179], have demonstrated improved glucose control and hypoglycaemia reduction[178,179,196,198]. However, first at-home unsupervised studies in adolescents have been limited to three to six weeks application of overnight close-loop [186,230,231]. There has been no previous evaluation of unsupervised closed-loop in free-living settings in children aged 12 years and younger.

4.2 STUDY OBJECTIVES

In the following, I present results of a multicentre twelve-week trial using overnight closed-loop in children and adolescents aged six to 18 years in free-living home settings. The hypothesis was that extended use of closed-loop insulin delivery without remote monitoring is feasible, improves glycaemic control and minimises the risk of hypoglycaemia in these age groups.

4.3 RESEARCH DESIGN AND METHODS

4.3.1 Study participants

Children and adolescents were recruited from paediatric diabetes centres at Addenbrooke's Hospital, Cambridge, UK, University College London Hospital, London, UK, and Leeds Teaching Hospital, Leeds, UK. Participants were at least six years of age and had been on insulin pump therapy for at least 3 months with good knowledge of insulin self-adjustment and carbohydrate counting, had glycated haemoglobin level below 86mmol/mol (10%), and were willing to use a closed-loop system overnight at home. Female participants of childbearing age had a negative urine human chorionic gonadotrophin pregnancy test at screening. The exclusion criteria included total daily insulin dose greater than 2 IU kg/day or less than 10 IU/day, recurrent incidents of

severe hypoglycaemia as defined by the International Society for Pediatric and Adolescent Diabetes in preceding six months (adolescents: severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions including episodes of hypoglycaemia severe enough to cause unconsciousness, seizures or attendance at hospital; children: severe hypoglycaemia is defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy – glucagon or intravenous glucose), untreated celiac disease, history of clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator, and on medication known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator.

The study protocol was approved by an independent research ethics committee, and received approval from regulatory authority in the UK (Medicines & Health products Regulatory Agency).

Participants aged ≥16 years and parents or guardians of participants aged <16 years signed informed consent; written assent was obtained from minors. The safety aspects of both studies were overseen by an independent Data Monitoring and Ethics Committee.

4.3.2 Study design

The study adopted an open label multicentre crossover randomized controlled design (see Figure 4.1). Following training on use of study insulin pump (Dana R Diabecare, Sooil, Seoul, South Korea) and CGM device (FreeStyle Navigator II, Abbott Diabetes Care, Alameda, California, USA), participants underwent a 2- to 8-week run-in period. Compliance on use of study pump and continuous glucose monitor for at least 10 days in the last 2 weeks of the run-in period were assessed prior to randomisation.

All participants were randomly assigned to twelve-weeks of automated closed-loop insulin delivery during the intervention period. The treatment periods were separated by a three to four-week washout during which they could continue to wear the

continuous glucose monitor and the study insulin pump and during which their standard pump settings were applied.

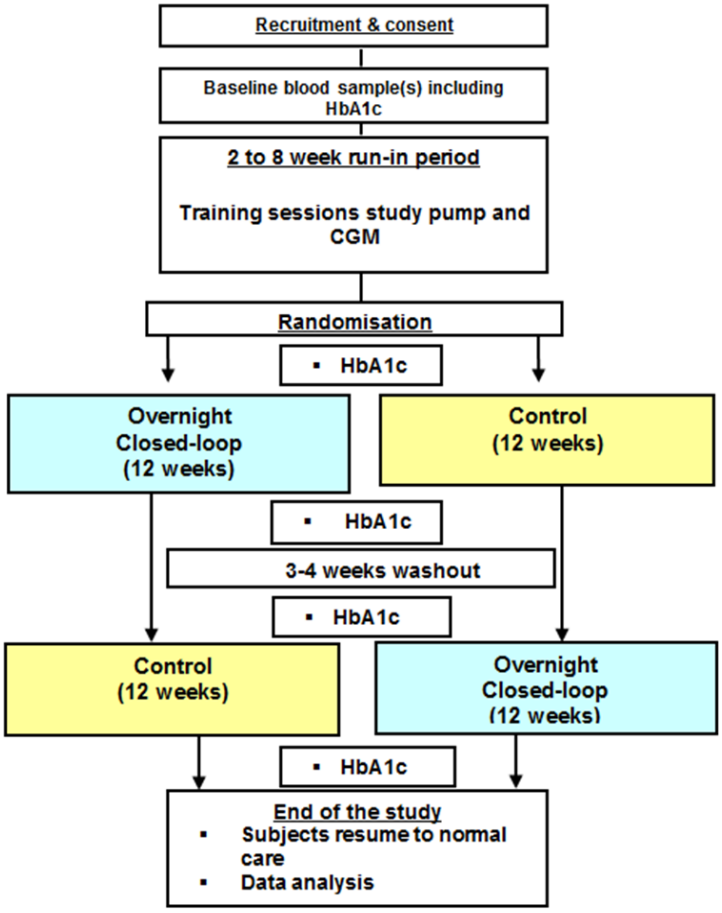

Figure 4.1. Study design

4.3.3 Study procedures

After consent, all participants and their caregivers were trained on the use of study pump and the study CGM device by experienced pump educators. Identical study insulin pump and CGM device were used during the two treatment periods. Each participants' usual basal insulin settings, insulin carbohydrate ratios and correction factors were programmed into the study pump. Participants' and caregivers' competency in using the study devices were assessed and documented by the respective pump educators. Additional device training was provided as required. Participants who were competent in using the study devices then underwent a minimum of a two-week run-in period. Data obtained from CGM device during run-in

was utilized for therapy optimisation. Adjustments of insulin therapy were carried out by members of the research team together with subjects' treating clinicians and specialist diabetes nurses. There was no written optimisation curriculum including formal tests to assess the adequacy of basal and bolus setup of participants' usual insulin pump therapy. At the end of the run-in period, compliance of study pump and the study continuous glucose monitoring device use were assessed. Those who had at least 12 days' worth of continuous glucose monitoring data were eligible to be randomized.

Randomization to the order of the two study interventions (closed-loop and control) was performed using a permuted block randomisation stratified by centre using a computer-generated random code. Masking was not applied.

On the first day of the closed-loop period, a training session on the use of the closed-loop system was provided by the research team at the participants' homes or at the clinical research facility. The session included training on connection and disconnection of closed-loop system, switching between closed-loop and usual pump therapy, responding to alarms and calibrating the system during the closed-loop mode. At the end of the training visit, competency in the use of the closed-loop system was assessed by the study team and blood samples for glycated haemoglobin were drawn and sent to the laboratory for analysis. Participants were instructed to initiate the system at home following their evening meal or at bedtime, and to discontinue it before breakfast the next morning. Participants used the closed-loop system at home without supervision for a total duration of 12 weeks. All participants were provided with a 24-hour telephone helpline to contact the study team in the event of any technical issues.

During the 12-week home study phase, standard local hypoglycaemia and hyperglycaemia treatment guidelines were followed. Participants were not restricted in their dietary intake or daily activities including physical activity. The application of the closed-loop system by participants during the trial was not limited to use within the UK and international travel was allowed.

Participants had identical planned contact with the study team during the two treatment periods. This included weekly phone or email contacts, and monthly study visits for data download, either conducted at the local hospital clinic or arranged at home/office/other meeting place according to the subjects' convenience. Each study intervention period lasted 12 weeks, with a 3-to 4-week washout period. Participants were allowed to continue to wear the study pump applying their standard pump settings, and the study continuous glucose monitoring device could be used as part of their standard diabetes management during the washout period. Blood sample was drawn for HbA1c analysis at the beginning and the end of each study intervention. HbA1c measurements for the children and adolescents study were performed centrally at Cambridge, UK.

4.3.4 Closed-loop system

The FlorenceD2W closed-loop system (University of Cambridge, Cambridge, UK) used in the study comprised a model predictive control algorithm on a tablet computer (Latitude 10, Dell, TX, USA), which was linked by cable to the continuous glucose monitoring receiver (FreeStyle Navigator II, Abbott Diabetes Care, Alameda, CA, USA). The tablet communicated with the study pump (Dana R Diabecare, Sooil, Seoul, South Korea) via Bluetooth wireless communication (see Figure 4.2).

Every 12 minutes, the control algorithm calculated an insulin infusion rate which was automatically sent to the study insulin pump. The control algorithm was initialised using pre-programmed basal insulin delivery downloaded from the study pump. Additionally, information about participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to the respective participant. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8 and 7.3mmol/l and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. Control algorithm version 0.3.30 was used (University of Cambridge, Cambridge UK).

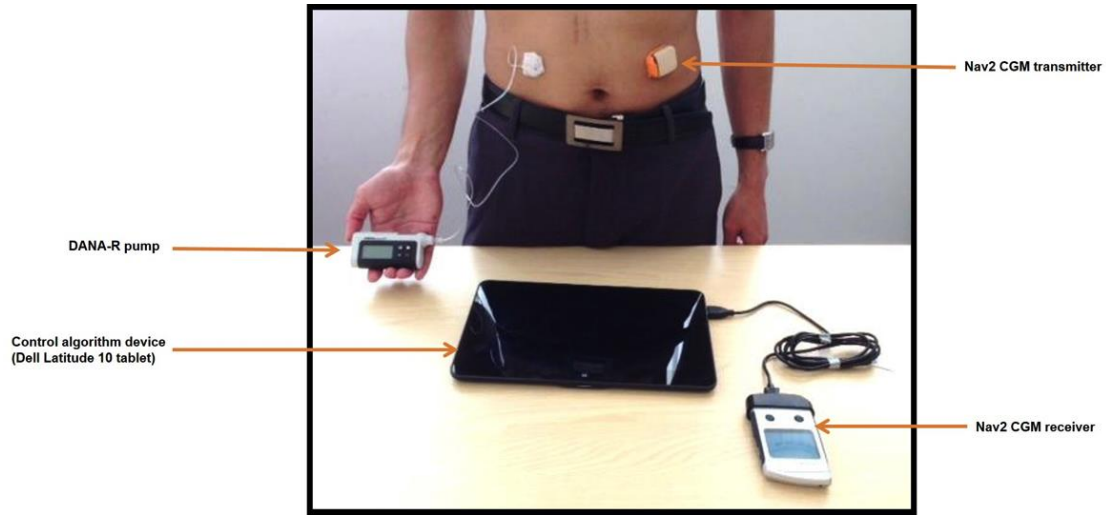

Figure 4.2. FlorenceD2W closed-loop system.

The continuous glucose monitoring receiver provided hypoglycaemia and hyperglycaemia alarms, the insulin pump provided standard alarms related to insulin delivery issues, and the smartphone alerted the user about aspects related to closed-loop operation such as when closed-loop was started, stopped or terminated. The tablet also visualized sensor glucose, insulin delivery, carbohydrate content, and other relevant data.

Participants were trained to perform a calibration check before starting closed-loop in the evening. If sensor glucose was above fingerstick glucose by more than 3 mmol/l, participants were advised to recalibrate the continuous glucose monitoring device. If sensor glucose became unavailable, pre-programmed insulin delivery was automatically restarted within 30 minutes or within 1 hour in case of other failures.

4.3.5 Study outcomes

The primary outcome was the proportion of time when nocturnal sensor glucose was in the target glucose range between 3.9 mmol/l and 8.0 mmol/l during the 12 week-long interventions.

Secondary outcomes included glycated haemoglobin, mean sensor glucose levels, glucose variability, time spent below and above the relevant glucose ranges during day-

and-night, daytime and overnight periods. Daytime was defined as between 08:00 and midnight; nighttime was classified as between midnight and 08:00. Glucose variability was assessed by the standard deviation and the coefficient of variation of sensor glucose. Hypoglycaemia burden was assessed by calculating the glucose sensor area under the curve less than 3.5 mmol/l. Insulin delivery amounts were reported as total daily, bolus and basal insulin doses, as well as total daytime and overnight insulin doses. Sensor glucose use and closed-loop use were evaluated.

4.3.6 Assays

C-peptide measurements were performed centrally in Swansea using chemiluminescence immunoassay (IV2-004; Invitron Ltd, Monmouth UK). Inter-assay variation was 7.8%, 4.3% and 6.7% at 268pmol/L, 990pmol/L and 1862pmol/L respectively. Analytical sensitivity for the C-peptide assay was 5pmol/L. Glycated haemoglobin was measured centrally in Cambridge using IFCC compliant ion exchange high performance liquid chromatography (G8 HPLC Analyzer, Tosoh Bioscience Inc., CA, USA; interassay CVs 1.3% at 31.2mmol/mol, 0.8% at 80.5mmol/mol).

4.3.7 Statistical analysis

The statistical analysis plan was agreed upon by investigators in advance. The analyses were performed on an intention-to-treat basis. Efficacy and safety data from all randomized participants with or without protocol violation including dropouts and withdrawals were included in the analyses. The respective values obtained during the 12-week randomized interventions contrasting the closed-loop system with the sensor augmented pump therapy were compared using a regression model that accounts for period effect. Residual values from the regression model were examined for an approximate normal distribution. Log transformed analyses were used for highly skewed values. Values were presented as mean±SD or as median (interquartile range) for each treatment (closed-loop or control). We calculated outcomes with GStat software (University of Cambridge, version 2.2). We did analyses with SPSS (IBM Software, Hampshire, UK version 21). A 5% significance level was used to declare statistical significance for all comparisons. All p values are two-sided.

4.4 RESULTS

4.4.1 Participants

29 participants were screened. 25 eligible participants were randomized. One participant voluntarily withdrew during the washout phase due to issues unrelated to closed-loop (see Figure 4.3). Baseline characteristics of study participants are shown in Table 4.1.

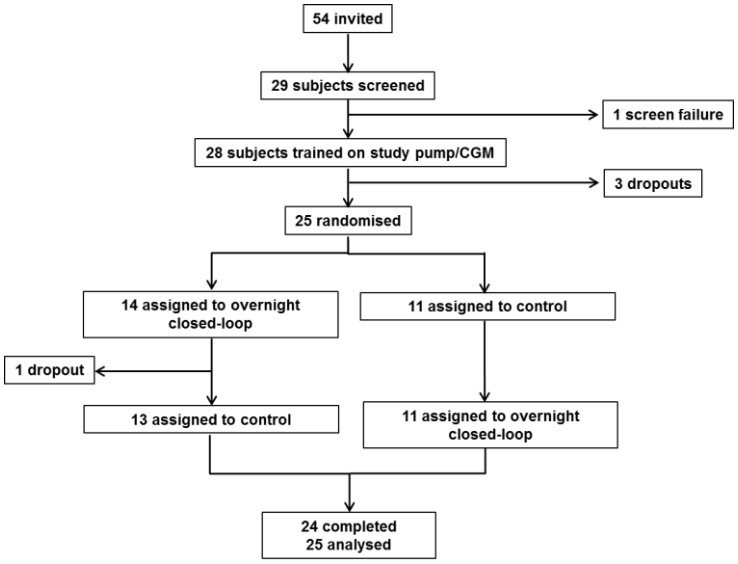

Figure 4.3. Study flow diagram.

Table 4.1. Baseline characteristics of study participants.

	n=25* (mean ± SD)
Age (years)	12.0±3.4
Gender (male/female)	14/11
Weight (kg)	43.9±16.6
BMI (kg/m^2)	18.9±3.5
BMI z-score	0.3±1.0
Glycated haemoglobin at screening (%)	8.1±0.9
Glycated haemoglobin at screening (mmol/mol)	65±10
Duration of diabetes (years)	4.7±2.6
Duration on pump (years)	3.3±1.8
Total daily insulin (U/kg/day)	0.89±0.24

*All C-peptide negative at non-hypoglycaemia (C-peptide less than 33pmol/l at fingerstick glucose equal or greater than 4mmol/l) except for 4 subjects with random c-peptide of 40, 40, 170, 530 (2 missed samples)

4.4.2 Outcomes

The primary and secondary glucose endpoints are shown in Table 4.2. The proportion of nocturnal time when glucose was in target range increased significantly during closed-loop intervention compared with control by mean of 24.5% (95% CI 20.6% to 28.4%, p<0.001; primary endpoint). Closed-loop significantly reduced overnight mean glucose (p<0.001, Figure 4.4) and time spent above target (p<0.001) compared to control. Proportion of time when sensor glucose was in hypoglycaemia (below 3.9 mmol/l and 2.8 mmol/l) and the area under the curve when sensor glucose was less than 3.5 mmol/l were low and comparable during the study periods. Closed-loop significantly reduced glucose variability measured by standard deviation of overnight sensor glucose and coefficient of variation between nights.

Table 4.2. Overnight glucose control (00:00 to 08:00) during closed-loop and control period.

	Closed-loop (n=25)	Control (n=24)	Paired difference*/ Paired ratio** (95% CI)	P value
Time spent at glucose level (%)				
3.9 to 8.0 mmol/l[†]	59.7 ± 11.5	34.4 ± 11.0	24.5 (20.6 to	<0.001
>8.0 mmol/l	37.1 ± 12.1	60.7 ± 13.2	-22.8 (-27.9 to -	<0.001
< 3.9 mmol/l	2.2 (1.8, 4.5)	3.5 (1.2, 5.9)	0.9 (0.6 to 1.5)	0.69
<2.8 mmol/l	0.3 (0.1, 0.5)	0.6 (0.1, 1.1)	0.7 (0.3 to 1.5)	0.19
AUC < 3.5 mmol/l (mol/l x min)[‡]	7.6 (3.0, 16.5)	16.4 (3.9, 31.4)	0.8 (0.3 to 1.9)	0.57
Mean glucose (mmol/l)	8.1 ± 1.2	9.8 ± 1.6	-1.6 (-2.1 to -1.2)	<0.001
SD of glucose (mmol/l)	3.3 ± 0.9	3.9 ± 0.7	-0.6 (-0.9 to -0.3)	<0.001
CV of glucose within days (%)	40.4 ± 6.8	40.6 ± 7.0	0.2 (-3.7 to 4.0)	0.95
CV of glucose between days (%)	27.6 ± 8.0	33.3 ± 6.5	-5.4 (-9.4 to -1.4)	0.013
HbA1c (mmol/mol)				
HbA1c pre-intervention	62±8	62±7	-	-
HbA1c post-intervention	60±12	63±7	-3 (-7 to 1)	0.17

Data shown are mean ± SD or median (IQR)
* Normally distributed data are presented as mean difference of closed-loop minus control, with 95% CI for mean. Positive value indicates measurement was higher during closed-loop period compared with control
** Non-normally distributed data are presented as ratio of closed-loop over control, with 95% CI for ratio. Value greater than unity indicates measurement was higher during closed-loop period compared with control
[†] Primary endpoint
[‡] AUC_{day}, Glucose area under curve below 3.5mmol/l per day

Following optimisation of sensor-augmented pump therapy during the run-in phase (HbA1c at recruitment: 65±10mmol/mol; HbA1c pre-intervention: 62±8 closed-loop,

62±7mmol/mol), there was no statistically significant difference between groups in HbA1 at the end of the intervention periods (p=0.17), but a trend to further reduction of HbA1c achieved by overnight closed-loop insulin delivery compared to control could be observed (Table 4.2).

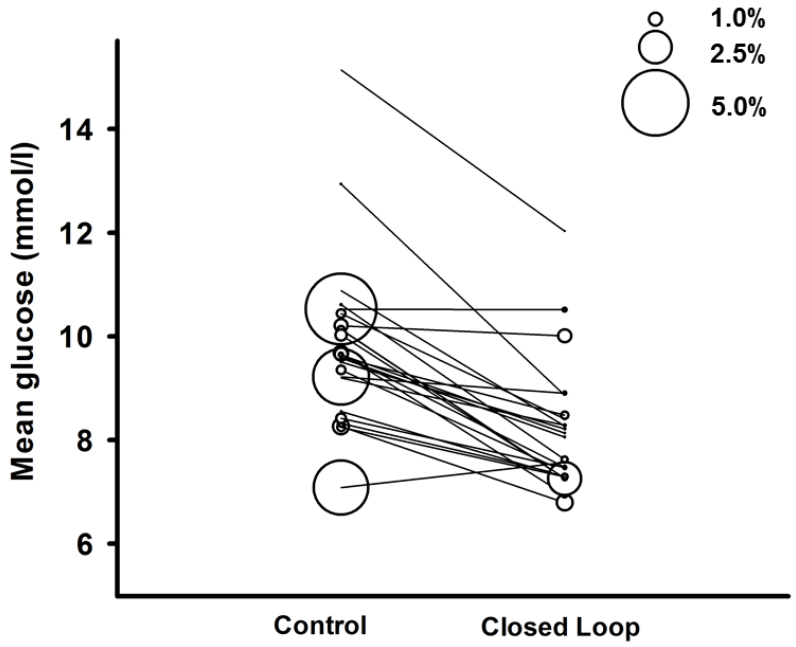

Figure 4.4. Individual values of overnight mean sensor glucose during overnight closed-loop study. The size of the bubble indicates the proportion of overnight time spent with low glucose below 2.8 mmol/l.

Twenty-four-hour sensor glucose and insulin delivery profiles (median and interquartile range) are shown in Figure 4.5. Glucose endpoints calculated over the 24-hour period are shown in Table 4.3. Application of overnight closed-loop significantly reduced 24-hour mean glucose (p=0.012) and increased proportion time spent within target range from 3.9 to 10 mmol/l (p<0.001). Closed-loop reduce the relative risk of time spent below 2.8 mmol/l over the 24h-period (p=0.028). The burden of hypoglycaemia during 24-hour period as measured by the area under the curve when sensor glucose was less than 3.5 mmol/l was significantly lower during closed-loop period (p=0.029).

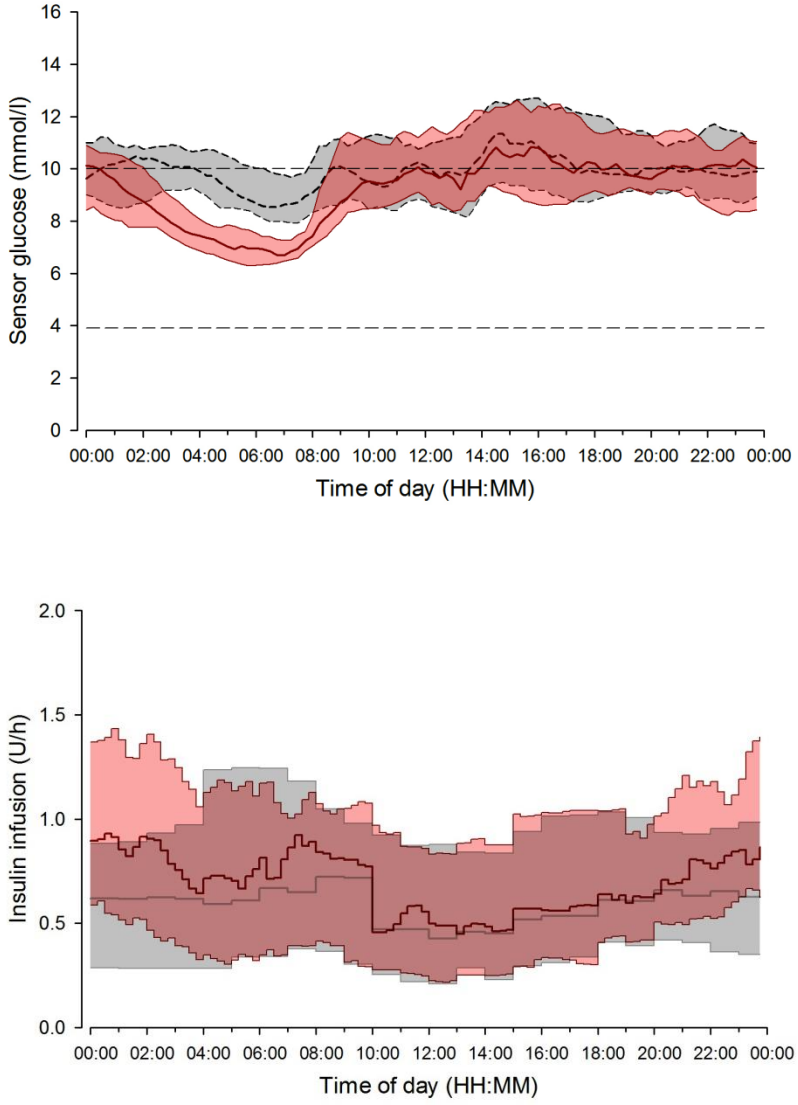

Figure 4.5. Sensor glucose and insulin profiles. Median (interquartile range) of sensor glucose (top panel) and insulin delivery (bottom panel) during closed-loop (solid red line and red shaded area) and control period (dashed black line and grey shaded area).

Table 4.3. Comparison of 24-hour glucose outcomes (midnight to midnight) during overnight closed-loop and control period.

	Closed-loop (n=25)	SAP (n=24)	Paired difference*/ Paired ratio**	P value
Time spent at glucose level (%)				
3.9 to 10.0 mmol/l	61.2 ± 11.9	51.6 ± 11.8	8.8 (6.1 to 11.6)	<0.001
>10.0 mmol/l	36.0 ± 12.5	44.5 ± 12.7	-7.7 (-10.8 to -4.5)	<0.001
< 3.9 mmol/l	3.1 (1.7, 3.5)	3.8 (1.4, 5.3)	0.8 (0.6 to 1.1)	0.23
< 2.8 mmol/l	0.2 (0.1, 0.4)	0.6 (0.1. 0.7)	0.4 (0.2 to 0.9)	0.028
AUC < 3.5 mmol/l (mmol/l x min)[†]	8.1 (4.1, 12.3)	12.3 (5.1, 21.5)	0.6 (0.4 to 0.9)	0.029
Mean glucose (mmol/l)	9.5 ± 1.6	10.1 ± 1.5	-0.5 (-0.9 to -0.1)	0.012
SD of glucose (mmol/l)	4.3 ± 1.0	4.3 ± 0.8	0.0 (-0.2 to 0.2)	0.96
CV of glucose within days (%)	44.6 ± 4.8	43.0 ± 5.1	1.9 (0.2 to 3.6)	0.039
CV of glucose between days (%)	20.3 ± 4.7	21.6 ± 3.9	-1.1 (-3.1 to 0.9)	0.29

Data shown are mean ± SD or median (IQR)
* Normally distributed data are presented as mean difference of closed-loop minus control, with 95% CI for mean. Positive value indicates measurement was higher during closed-loop period compared with control
** Non-normally distributed data are presented as ratio of closed-loop over control, with 95% CI for ratio. Value greater than unity indicates measurement was higher during closed-loop period compared with control
[†] AUC_{day}, Glucose area under curve below 3.5mmol/l per day

Daytime (08:00 to midnight) endpoints comparison is shown in Table 4.4. Mean glucose, proportions of time spent within, above, and below target range (3.9 to 10mmol/l) were comparable during the study periods. The area under the curve when sensor glucose was less than 3.5mmol/l (p=0.031) and the time spent below 2.8mmol/l (p=0.028) was significantly lower during closed-loop period. This was mainly attributed to 79% lower relative risk of time spent below 2.8mmol/l (95% CI 34% to 93%, p=0.010) compared to control during the post-breakfast period (08:00 to 12:00).

Table 4.4. Comparison of daytime glucose outcomes (08:00 to midnight) during overnight closed-loop and control period.

	Closed-loop (n=25)	SAP (n=24)	Paired difference*/ Paired ratio**	P value
Time spent at glucose level (%)l				
3.9 to 10.0 mmol/l	54.0 ± 12.8	51.3 ± 11.7	1.9 (-0.7 to 4.5)	0.18
>10.0 mmol/l	43.4 ± 13.7	45.3 ± 12.8	-1.0 (-4.0 to 2.0)_	0.56
< 3.9 mmol/l	2.5 (1.6, 3.6)	2.9 (1.3, 5.0)	0.8 (0.6 to 1.1)	0.12
<2.8 mmol/l	0.2 (0.4, 0.6)	0.4 (0.2 to 0.7)	0.4 (0.2 to 1.1)	0.028
AUC < 3.5 mmol/l (mmol/l x min)[†]	6.5 (3.2, 11.4)	9.8 (3.9, 22.8)	0.6 (0.4 to 1.0)	0.031
Mean glucose (mmol/l)	10.2 ± 1.8	10.3 ± 1.6	0.1 (-0.3 to 0.5)	0.69
SD of glucose (mmol/l)	4.5 ±1.0	4.5 ± 0.8	0.1 (-0.1 to 0.3)	0.36
Within days CV of glucose (%)	43.7 ± 4.7	43.6 ± 5.0	0.3 (-0.9 to 1.6)	0.60
Between days CV of glucose (%)	23.4 ± 5.0	23.6 ± 4.6	-0.3 (-2.2 to 2.1)	0.97

Data shown are mean ± SD or median (IQR)
* Normally distributed data are presented as mean difference of closed-loop minus control, with 95% CI for mean. Positive value indicates measurement was higher during closed-loop period compared with control
** Non-normally distributed data are presented as ratio of closed-loop over control, with 95% CI for ratio. Value greater than unity indicates measurement was higher during closed-loop period compared with control
[†] AUC_{day}, Glucose area under curve below 3.5mmol/l per day

Improved glycaemic control, particularly overnight, was achieved during closed-loop without increasing total overnight insulin dose (p=0.10, Table 4.5). Similarly, daytime insulin delivery and total daily insulin dose were comparable during the two interventions (Table 4.5). Overnight closed-loop was operating over a median of 9.3hours (7.7 to 10.6) per day. Participants wore the study continuous glucose monitor for a median of 22.1hours (21.3 to 22.8) per day during closed-loop, and for a median of 20.3hours (18.1 to 22.0) per day during control period.

Table 4.5. Insulin delivery overnight (midnight to 08:00), during the day (08:00 to midnight) and over 24 hours (midnight to midnight).

	Closed-loop (n=25)	SAP (n=24)	Paired difference*/ Paired ratio** (95% CI)	P value
Overnight (00:00 to 08:00) insulin (U)	7.6 (5.0 to 12.5)	7.7 (5.0 to 12.3)	1.05 (0.99 to 1.11)	0.10
Daytime (08:00 to 00:00) insulin (U)	36.3 (16.5 to 42.8)	29.7 (17.9 to 45.5)	1.00 (0.95 to 1.05)	0.92
Total daily insulin (U/day)	41.4±20.3	40.9±20.6	0.3 (-1.5 to 2.0)	0.79
Total bolus insulin (U/day)	18.8 (13.4 to 33.2)	20.4 (14.0 to 37.6)	0.91 (0.86 to 0.97)	0.008
Total basal insulin (U/day)	18.5±10.0	16.1±9.6)	2.2 (1.6 to 2.8)	<0.001

Data shown median (IQR)
* Normally distributed data are presented as mean difference of closed-loop minus control, with 95% CI for mean. Positive value indicates measurement was higher during closed-loop period compared with control
** Non-normally distributed data are presented as ratio of closed-loop over control, with 95% CI for ratio. Value greater than unity indicates measurement was higher during closed-loop period compared with control

4.4.3 Adverse events

Three serious adverse events unrelated to study devices occurred in this trial. One participant during closed-loop was hospitalized due to a viral gastroenteritis receiving rehydration therapy. Two episodes of severe hypoglycemia (hypoglycaemic seizures) not attributable to control algorithm insulin advice occurred in one and the same participant during the closed-loop period. No hospitalisation took place. On both occasions closed-loop was not operational when the event occurred, and the participant was receiving own standard insulin pump therapy insulin rate. The first event happened in the evening before the closed-loop system was set-up and started. When regaining consciousness again, hypoglycemia was treated orally by paramedics, glucose levels normalised and full clinical recovery ensued. The second event happened mid-morning. Post-hoc analysis identified that closed-loop had been interrupted about three hours prior to the event. The participant's mother was woken up by the low sensor glucose alarm, and started to treat the hypoglycemia episode orally, when tonic-clonic activity started. The mother then proceeded to administer intramuscular glucagon. The seizure activity ceased and glucose level normalised. There were no long-

term sequelae, and no further medical attention was needed. Details of all adverse events are provided in Table 4.6.

Table 4.6. List of adverse events.

	Run-in period	Closed-loop period	Open-loop period	Washout period
Respiratory tract infections	-	-	-	1
Fractured finger	-	1	-	-
Sensor insertion site inflammation	-	1	-	-
Ketonaemia related to intercurrent illness	-	2	-	-
Hyperglycemia related to infusion set occlusion	-	2	-	-
Severe hypoglycemia	-	2	-	-
Hospitalization due to gastroenteritis	1	-	-	-

4.5 DISCUSSION

Our findings show the feasibility, safety, and efficacy of twelve-week overnight application of unsupervised closed-loop insulin delivery in children and adolescents. Overnight closed-loop use significantly increased time when nocturnal sensor glucose was within target range and reduced mean glucose. Extended benefits from overnight closed-loop use in children and adolescents were seen over the daytime and full 24-hour-period including reduced time spent with sensor readings in significant hypoglycaemia (below 2.8mmol/l) and reduced burden of hypoglycaemia, which was mainly accredited to the post-breakfast period.

Hypoglycaemia presents a challenge and limitation to intensive insulin therapy in type 1 diabetes[232]. The advent of threshold-suspend pump therapy[140] and more recently predictive low glucose suspend[147] may reduce the burden of hypoglycaemia. However, these approaches are not designed to step up insulin delivery and do not address the issue of hyperglycaemia. The advantage of a closed-loop system is the finely-tuned instantaneously responsive modulation of insulin delivery both below and above the pre-set pump regimen, allowing for improvements in time spent in target glucose range and lowering of mean glucose without increasing time spent in hypoglycaemia.

In spite of improvements in glycaemic control during the run-in period, a trend towards further reduction in glycated haemoglobin was achieved following overnight closed-loop use. Closed-loop achieved more consistent glucose values despite high night-to-night variability in insulin requirements. This explains the reduction in glucose variability observed between nights.

The current results build upon our experience and previous findings from shorter trials of unsupervised closed-loop studies during free daily living[230,231,233]. Other closed-loop studies in the outpatient or home setting have been performed over a shorter duration and under remote monitoring or close supervision[183,186,234]. Adults and adolescents using a dual-hormone (insulin and glucagon) closed-loop system in an outpatient setting for five days had reduction in mean sensor glucose level compared to standard pump therapy, with significant reduction in percentage time spent below 3.9mmol/l in adults but not adolescent participants[196]. Compared to insulin-alone closed-loop, children and adolescents using a dual-hormone closed-loop system for three nights at a diabetes camp had significantly reduced nocturnal hypoglycaemia events and time spent below 3.9 mmol/l with comparable mean sensor glucose levels[198].

The strength of our studies is the multicentre design allowing safety and efficacy to be evaluated over wider participant demographic, thus supporting generalisability. The studies were performed without remote monitoring or close supervision, thereby providing an opportunity to assess the real-world use and applicability of a novel technology. We did not restrict participants' dietary intake, and after the initial two weeks physical activity or geographical movements were also permitted. Participants were allowed to travel and use the system when driving or when abroad. The comparator was 'state-of-the-art' sensor augmented insulin pump therapy. A crossover design was adopted, which had the benefit of enabling each participant to act as his/her own control; confounding period or carry-over effects were not detected.

Sensor glucose wear in both groups was high and comparable (>20 hours per day) between study periods. The study was limited by the number of devices each participant had to use. Technological progress may allow further integration of devices and reduce this burden.

In conclusion, we demonstrated that extended use of overnight closed-loop at home over twelve weeks during free daily living without supervision is feasible in children and adolescents with type 1 diabetes. Improvements in glucose control and reductions in hypoglycaemia burden were observed. Our results pave the way for adoption of closed-loop technologies in clinical practice.

5 Home use of day-and-night closed-loop in adolescents (Dan04 studies)

5.1 BACKGROUND

The majority of adolescents and young adults with type 1 diabetes are poorly controlled[54,235,236] accelerating the onset of early micro- and macrovascular complications [45,46]. Diabetes management in adolescence is complicated by psychological and physiological changes accompanying puberty[237]. Apart from hypoglycemia[232], reduced therapy adherence is a major obstacle to achieving tight glucose control[238]. Diabetic ketoacidosis is more common[30,239], omission of or delayed insulin boluses with meals or snacks is widespread[238,240], and discontinuation of insulin pump therapy is highest among adolescents[241]. Sensor-augmented insulin pump therapy[113] and threshold-suspend features may alleviate the burden of hypoglycaemia and improve outcomes[141,147], but acceptance and use of continuous glucose monitoring systems is notably reduced amongst teenagers[108,113]. Furthermore, threshold-suspend and predictive low glucose management insulin pump therapy do not address the issue of hyperglycaemia, the major challenge of diabetes management in adolescence.

The artificial pancreas (closed-loop systems) modulates insulin delivery below and above pre-set insulin pump delivery in response to real-time sensor glucose levels and can potentially reduce both hypo- and hyperglycaemia. Following evaluations in children and adolescents in laboratory settings [156,173,174] and diabetes camps [196-198], first at-home studies of up to three-month applications of overnight closed-loop have demonstrated improved glucose control and reduced the burden of hypoglycaemia [188,242,243]. However, prior to below mentioned trials, home studies of unsupervised day-and-night closed-loop application have been restricted to adults only[243,244]. There has been no previous evaluation of unsupervised day-and-night closed-loop in free-living settings in adolescents aged 10 to 18 years.

5.2 STUDY OBJECTIVES

In this chapter, I summarise the results of two home trials conducted in adolescents with type 1 diabetes: The Dan04 studies. Day-and-night closed-loop was applied over 7-days (Dan04 Study 1), and 21-days, respectively (Dan04 Study 2). We hypothesized that day-and-night use of hybrid closed-loop insulin delivery without remote monitoring would be feasible, safe and could improve glycaemic control compared to sensor-augmented pump therapy in this population.

5.3 RESEARCH DESIGNS AND METHODS

5.3.1 Study participants

Study participants for both trials were identified from paediatric diabetes clinics at Addenbrooke's Hospital (Cambridge, United Kingdom) and University College London Hospital (London, United Kingdom). Study 1 was conducted between September and November 2014, Study 2 was carried out between May and July 2015. Key inclusion criteria were age 10-18 years, diagnosis of type 1 diabetes, treatment with insulin pump therapy for at least three months, willingness to perform at least four fingerstick glucose measurements per day, and HbA1c ≤11% (97mmol/mol). Exclusion criteria included established nephropathy, neuropathy, or proliferative retinopathy, total daily insulin dose ≥2.0 U/kg or <10 U/day, significant hypoglycaemia unawareness, more than one incident of severe hypoglycaemia within 6 months prior to enrolment, more than one episode of diabetic ketoacidosis within 12 months prior to enrolment, pregnancy and breast-feeding. Participants aged ≥16 years and parents or guardians of participants aged <16 years signed informed consent; written assent was obtained from minors before study related activities.

Prior to initialization of the studies, approval was sought and received from the local independent research ethics committee and the UK regulatory authority (Medicines & Health products Regulatory Agency). An independent Data Safety and Monitoring Board oversaw the studies and was informed of all unanticipated adverse events that occurred during the studies.

5.3.2 Study designs

Both studies adopted an open-label prospective single centre randomized crossover design contrasting automated closed-loop insulin delivery and sensor-augmented pump therapy (Figure 5.1). Study intervention periods lasted one week (Study 1) and three weeks (Study 2) each with a 1 to 4-week washout period. The studies were performed under free-living home conditions without remote monitoring or supervision by research staff, and participants went about their usual daily routines and activities. The participants were free to consume any meals of their choice and no restrictions were imposed on travelling or moderate exercise. All participants had access to a 24-hour telephone helpline to contact the study team in the event of study-related issues.

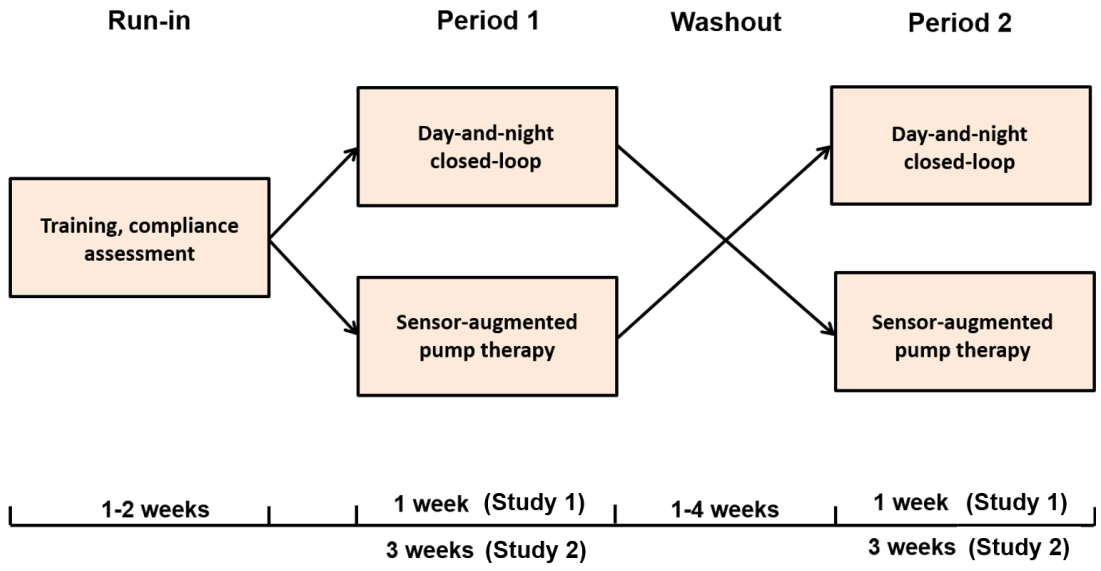

Figure 5.1. Study designs (Study 1 and Study 2).

5.3.3 Study procedures

Blood samples for baseline HbA1c and non-hypoglycaemia C-peptide levels were taken at enrolment in both trials. At the start of the run-in phases, participants were trained on the use of the study insulin pump (DANA Diabecare R; Sooil, Seoul, South Korea)

and study real-time continuous glucose monitoring device (FreeStyle Navigator II; Abbott Diabetes Care, Alameda, CA), which are off-the-shelf devices and do not offer low glucose suspend functionality. The study insulin pump was programmed with the respective participant's usual basal settings, usual insulin-to-carbohydrate ratios and correction factors and delivered rapid-acting insulin analogue (insulin aspart, Novo Nordisk, Bagsvaerd, Denmark; or insulin lispro, Eli Lilly, Indianapolis, US). Participants were advised to use the bolus calculator for all meals during the entire study. Ability and competency to use study devices was formally assessed and additional training was provided as required. Over a one to two-week run-in phase, participants in both trials were required to use the study pump and collect at least five days' worth of sensor glucose to pass the compliance assessment. Data obtained during run-in phases were utilized for therapy optimisation as per usual clinical practice.

After the run-in periods, participants underwent two seven-day periods (Study 1) or two 21-day periods (Study 2) respectively, in random order, during which glucose was controlled either by sensor-augmented insulin pump therapy or by hybrid closed-loop insulin delivery. The two treatment interventions were separated by one to four-week wash-out periods during which the participants could continue using the study insulin pump applying their standard pump settings. Continuous glucose monitoring was discontinued during wash-out.

Randomisation assignments were unblinded, but allocation between treatment sequences was concealed from the study staff until after randomisation, which was conducted the day prior to the first interventions. Random permuted blocks were used for treatment sequence allocation.

On the first day of the closed-loop periods, a two- to three-hour training session was provided by the investigators at the clinical research facility, including initiation and discontinuation of the closed-loop system, switching between closed-loop and usual pump therapy, meal bolus procedure, and the use of study devices during exercise. Prandial boluses were advised to be delivered before the meals using the pump's standard bolus calculator. Competency in the use of closed-loop system was assessed prior to discharge. After the training session, participants continued the study

intervention for the next seven days (Study 1) or 21 days (Study 2), respectively, under free-living conditions in their home and school environment. Automated closed-loop insulin delivery was continued during exercise of mild to moderate intensity, and exercise was announced to the algorithm. Participants were advised to discontinue closed-loop and follow their usual insulin pump therapy for certain activities such as periods of strenuous exercise, diving or contact sports.

The number of planned contacts with the study team was identical during the two study periods. Participants used the study pump and the study real-time continuous glucose monitoring device during both study periods and were advised to calibrate the continuous glucose monitoring device according to the manufacturer's instructions. The built-in glucometer was used for all fingerstick measurements; participants were free to decide on alarm thresholds for the continuous glucose monitoring device. Standard clinic guidelines for hypoglycaemia and hyperglycaemia treatment were followed. All participants were provided with a 24-hour telephone helpline to contact the study team in the event of study-related issues.

5.3.4 Closed-loop system

The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, UK)[245] comprised a model predictive control algorithm (Study 1: Version 0.3.30; Study 2: Version 0.3.41, University of Cambridge) residing on a smartphone (Study 1: Nexus 4, LG, South Korea; Study 2: Galaxy S4, Samsung, South Korea), which communicated wirelessly with continuous glucose monitoring receiver through a purpose made translator unit (Triteq, Hungerford, UK) (see Figure 5.2). Every 12 min, the control algorithm calculated a new insulin infusion rate which was automatically set on the study insulin pump. The calculations utilized a compartment model of glucose kinetics[246] describing the effect of rapid-acting insulin analogues and the carbohydrate content of meals on glucose levels. In these trials, a hybrid closed-loop approach was applied, in which participants additionally administered prandial insulin for all meals using the standard bolus calculator. Bolus calculations as provided by the study pump's built-in bolus calculator took into account carbohydrate content of meals, insulin on board, and entered capillary blood glucose readings. The control algorithm was

initialized using pre-programmed basal insulin doses downloaded from the study pump. Additionally, information about participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to the particular participant. The apparent total daily dose was modified based on sensor glucose levels achieved during closed-loop on previous days. In the algorithm version used in Study 2 (Version 0.3.41), this learning capability was made more responsive compared to versions 0.3.30 (Study 1). Enhanced adaptability was further supported by additional adaptation to varied insulin needs during the daytime and overnight periods. In both trials, the treat-to-target control algorithms aimed to achieve glucose levels between 5.8mmol/l and 7.3mmol/l and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. Though devices were advised to be kept in vicinity of each other, a wireless transmission range of several meters allowed for flexibility in terms of device wear, and appropriate cases, clips and pouches were provided.

Participants performed a calibration check before breakfast and the evening meal. If the sensor glucose was above the fingerstick glucose by >3.0mmol/l, the continuous glucose monitoring device was manually recalibrated. There was no recalibration for sensor under reading. These instructions resulted from an in silico evaluation of hypoglycaemia and hyperglycaemia risk[247] using the validated Cambridge simulator[248].

If sensor glucose became unavailable or in case of other failures, pre-programmed insulin delivery automatically restarted within 30-60 min. This limited the risk of insulin under- and over delivery[247]. Safety rules limited maximum insulin infusion and suspended insulin delivery if glucose was ≤4.3 mmol/l or when sensor glucose was rapidly decreasing.

The continuous glucose monitoring receiver provided hypoglycaemia and hyperglycaemia alarms, the insulin pump provided standard alarms, and the smartphone alerted the user about aspects related to closed-loop operation such as when closed-loop started or stopped.

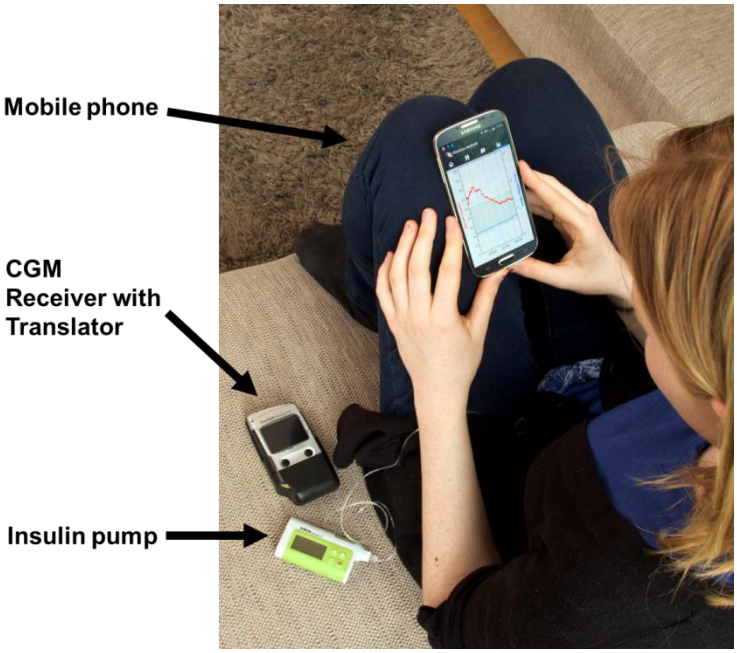

Figure 5.2. FlorenceD2A closed-loop system.

5.3.5 Study outcomes

The primary outcome in both studies was the proportion of time when glucose was in the target range (3.9-10.0mmol/l) during the seven-day study periods (Study 1) or 21-day periods (Study 2), respectively. Secondary outcomes included mean sensor glucose levels, glucose variability, and time spent below and above glucose target. Outcomes were calculated during day-and-night, daytime and overnight periods; daytime was classified as between 08:00 and midnight, and night-time as between midnight and 08:00. Glucose variability was assessed by the standard deviation and the coefficient of variation of sensor glucose. Hypoglycaemia burden was assessed by calculating the glucose sensor area under the curve less than 3.5mmol/l.

5.3.6 Participant-reported outcomes (Study 2 only)

In Study 2, a trial experience questionnaire was completed by participants at the conclusion of the closed-loop phase. The questionnaire was composed of seven questions, four of which were closed questions. The three open questions requested comments and suggestions from participants regarding (1) what they liked about the

closed-loop system, (2) what they did not like about the system, and (3) what additional features they would like to have in a closed-loop system.

5.3.7 Assays

In both trials, HbA1c was measured using ion exchange high performance liquid chromatography (G8 HPLC Analyzer, Tosoh Bioscience Inc., CA, US; interassay CVs 1.3% at 31.2mmol/mol, 0.8% at 80.5mmol/mol). C-peptide measurements were performed using chemiluminescence immunoassay (IV2-004; Invitron Ltd, Monmouth UK; inter-assay variation 7.8%, 4.3% and 6.7% at 268pmol/l, 990pmol/l and 1,862pmol/l, respectively). Analytical sensitivity for the C-peptide assay was 5pmol/l.

5.3.8 Statistical analyses

The statistical analysis plans were agreed upon by investigators in advance. All analyses were undertaken on an intention-to-treat basis. Efficacy and safety data from all randomized participants with or without protocol violation were included in the analyses. The respective values obtained during the seven-day (Study 1) and 21-day (Study 2) intervention periods contrasting the closed-loop system against the sensor-augmented pump therapy were compared using a least-square regression model. Sensor glucose outcomes were adjusted for baseline glucose level and period effect; insulin outcomes for period effect. Rank normal transformation analyses were used for highly skewed endpoints. Outcomes were presented as mean ± SD for normally distributed values or as median (interquartile range) for non-normally distributed values. In Study 1, secondary outcomes for daytime and nighttime periods were excluded from calculating p-values to limit multiple comparisons. Outcomes were calculated using GStat software (University of Cambridge, version 2.2). Analysis was done using SPSS (IBM Software, Hampshire, UK version 21). A 5% significance level was used to declare statistical significance. All p-values are two-sided.

5.4 RESULTS

5.4.1 Study 1

5.4.1.1 Participants

Fourteen subjects were screened. The flow of participants through the study is shown in Figure 5.3. One participant did not meet the inclusion/exclusion criteria, and another voluntarily withdrew consent and did not complete the run-in phase. Twelve eligible participants were randomized, completed the study, and provided data for analyses (8 males; age 15.4±2.6 years; diabetes duration 8.2±3.4 years; HbA1c 8.3±0.9% [68±10mmol/mol]; insulin pump therapy duration 5.6±2.9years; total daily insulin dose 0.84±0.22 U/kg/day]) (see Table 5.1).

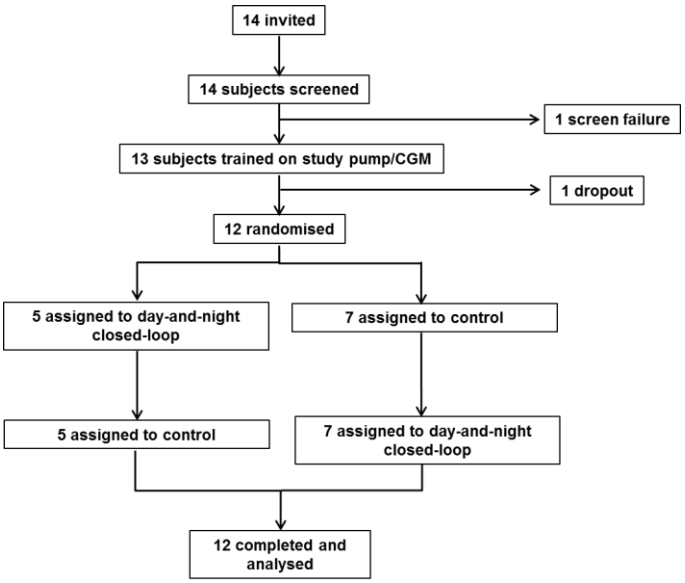

Figure 5.3. Flow of participants through the trial (Study 1).

Table 5.1. Baseline characteristics of study participants (Study 1).

	n=12* (mean ± SD)
Age (years)	15.4±2.6
Gender (male/female)	8/4
BMI (kg/m^2)	21.4±2.7
BMI z-score	0.57±0.80
Glycated haemoglobin at screening (%)	8.3 ± 0.9
Glycated haemoglobin at screening (mmol/mol)	68±10
Duration of diabetes (years)	8.2±3.4
Duration on pump (years)	5.6±2.9
Total daily insulin (U/kg/day)	0.84±0.22

* All C-peptide negative at non-hypoglycaemia (C-peptide less than 33pmol/l at fingerstick glucose equal or greater than 4mmol/l) except for one participant with a level of 262 pmol/l

5.4.1.2 Day-and-night glucose control and insulin delivery

The primary endpoint - the proportion of time sensor glucose was in the target glucose range of 3.9 to 10.0mmol/l - significantly increased during closed-loop ($p<0.001$, Table 5.2). 24-hour sensor glucose and insulin delivery profiles are shown in Figure 5.4. Closed-loop significantly reduced the mean glucose ($p=0.001$) and time spent above target glucose level ($p<0.001$) without increasing time spent in hypoglycaemia (Table 5.2 and Figure 5.4). Proportion of time when sensor glucose was in hypoglycaemic range (below 3.9mmol/l and 2.8mmol/l) and the area under the curve when sensor glucose was less than 3.5mmol/l were low and comparable during the study periods.

There was a difference in glucose variability between study periods as measured by the standard deviation ($p=0.044$), but no difference when calculating the coefficient of variation of sensor glucose. Increased time when glucose was in target range and reduced mean glucose was achieved by closed-loop through increased variability of basal insulin delivery ($p<0.001$) but without increasing total daily insulin ($p=0.50$). Higher total basal insulin delivery during closed-loop ($p=0.001$) was offset by a trend towards lower bolus delivery ($p=0.09$) presumably due to lower glucose levels resulting in reduced correction boluses (Table 5.2).

Table 5.2. Comparison of glucose control and insulin delivery over 7 days during closed-loop and control period (Study 1)

	Closed-loop (n=12)	SAP (n=12)	Paired difference*	P value
Time spent at glucose level (%)				
3.9 to 10.0 mmol/l†	72 (59 to 77)	53 (46 to 59)	19 (5 to 25)	<0.001
>10.0 mmol/l	26 (21 to 35)	43 (38 to 52)	-17 (-26 to -7)	<0.001
< 3.9 mmol/l	2.9 (1.8 to 4.8)	1.8 (0.9 to 5.1)	0.9 (-1.6 to 3.1)	0.21
<2.8 mmol/l	0.2 (0.0 to 0.6)	0.1 (0.0 to 0.6)	0.1 (-0.1 to 0.6)	0.63
AUC < 3.5 mmol/l (mol/l x min)‡	6.4 (2.8 to 23.7)	4.3 (1.8 to 13.6)	2.5 (-2.8 to 19.2)	0.40
Mean glucose (mmol/l)	8.7±1.1	10.1±1.3	-1.4±1.1	0.001
SD of glucose (mmol/l)	3.5 (3.3 to 4.2)	4.0 (3.6 to 4.6)	-0.5 (-1.1 to 0.3)	0.044
CV of glucose within days (%)	41 (40 to 45)	39 (38 to 44)	5 (-3 to 7)	0.32
CV of glucose between days (%)	18 (11 to 22)	19 (17 to 25)	0 (-11 to 8)	0.55
Total daily dose (U/day)	57.3 (45.6 to 65.2)	56.6 (44.7 to 61.3)	0.3 (-4.0 to 4.6)	0.50
Total bolus (U/day)	31.8 (21.2 to 41.0)	38.3 (26.4 to 41.4)	-5.1 (-6.5 to -0.7)	0.09
Total basal (U/day)	24.3 (22.8 to 28.8)	20.3 (19.1 to 22.1)	6.6 (1.7 to 9.1)	0.001
CV of basal insulin (%)	94 (91 to 104)	16 (13 to 26)	78 (67 to 88)	<0.001

Data are presented as mean ± SD or median (interquartile range). p-values adjusted for period effect.
*Closed-loop minus control. A positive value indicates the value was higher on the closed-loop compared with control
† Primary endpoint
‡AUC_{day}, Glucose area under curve below 3.5mmol/l per day

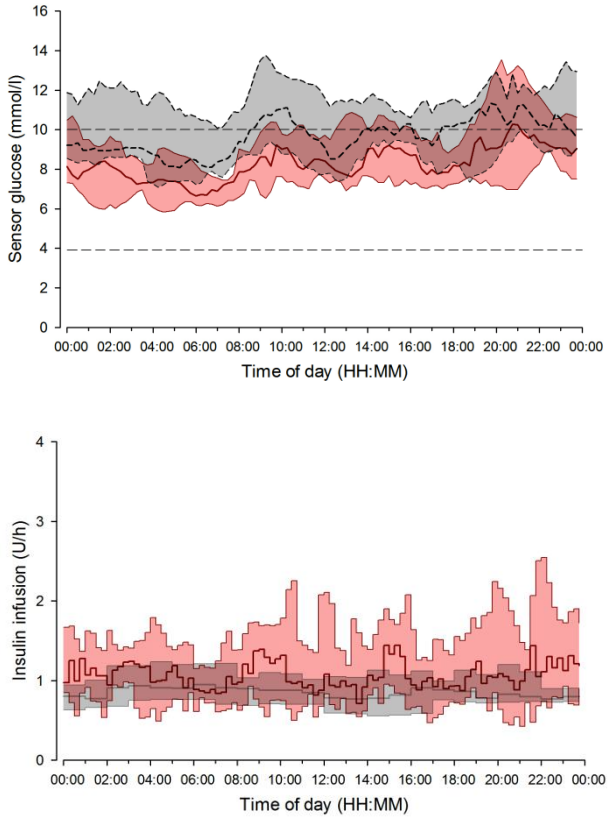

Figure 5.4. 24-hour sensor glucose and insulin profiles. Median (interquartile range) of sensor glucose (top panel) and insulin delivery (bottom panel) during closed-loop (solid red line and red shaded area) and control period (dashed black line and grey shaded area) from midnight to midnight. The glucose range 3.9 to 10.0 mmol/l is denoted by horizontal dashed lines (top panel).

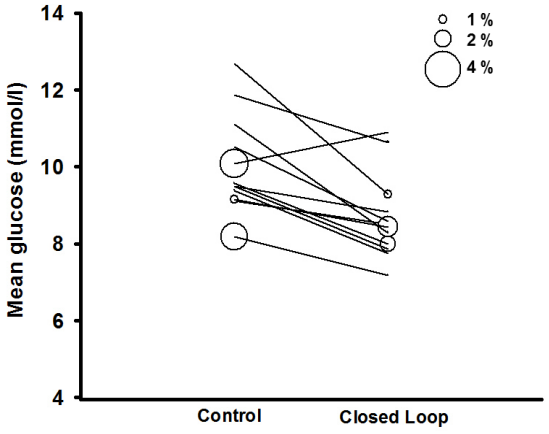

Figure 5.5. Individual values of mean sensor glucose during day-and-night closed-loop study. The size of bubble indicates the proportion of time spent with low glucose below 2.8mmol/l.

5.4.1.3 Daytime and overnight glucose control and insulin delivery

Secondary outcomes calculated for daytime and overnight periods are shown in Table 5.3. Daytime and overnight outcomes were similar to outcomes over day-and-night. Proportion of time when sensor glucose was in daytime target range (3.9 to 10.0mmol/l) and overnight target range (3.9 to 8.0mmol/l) tended to be higher during closed-loop compared to control [daytime: 66% (55% to 68%) vs. 49% (46% to 51%); overnight: 63% (49% to 78%) vs. 40% (30% to 48%)]. Daytime mean glucose (9.4±1.2mmol/l vs. 10.3±1.4mmol/l) and overnight mean glucose (7.8±1.8mmol/l vs. 9.7±1.8mmol/l) tended to be lower during closed-loop without a difference in total daytime and overnight insulin amount.

5.4.1.4 Adverse events

No serious adverse events or severe hypoglycaemic episodes were observed during either study period. Two participants measured mild to moderate elevated blood ketones (>2.00mmol/l) associated with hyperglycaemia, one participant during closed-loop and one participant in the control period. These events were attributed to infusion set failures and were all self-managed.

5.4.1.5 Utility analysis

Closed-loop was operational over a median of 82 % (75% to 96%) of time. Availability of sensor glucose was 98% (93% to 100%) during closed-loop and 97% (92% to 100%) during control period. On average, closed-loop was interrupted 1.1 times (0.6 to 1.5) per subject per day. Apart from two occasions requiring closed-loop system reset by research staff, the participants were able to resolve issues on their own, such as restarting closed-loop after loss of pump connectivity or sensor data unavailability.

Table 5.3. Daytime and nighttime glucose control and insulin delivery during closed-loop and control period (Study 1).

	Closed-loop (n=12)	Control (n=12)
Daytime (from 08:01 to 23:59)		
Time spent at glucose level (%)		
3.9 to 10.0mmol/l	66 (55 to 68)	49 (46 to 51)
>10.0mmol/l	31 (29 to 44)	48 (40 to 53)
<3.9mmol/l	2.5 (1.2 to 4.4)	2.4 (0.7 to 4.5)
AUC_{day} <3.5mmol/l (mmol/l x min)*	6.4 (1.0 to 12.1)	4.4 (0.0 to 9.9)
Mean glucose (mmol/l)	9.4±1.2	10.3±1.4
Within day SD of glucose (mmol/l)	3.1 (3.0 to 3.6)	3.4 (3.1 to 3.8)
CV of glucose within day (%)	35 (31 to 39)	33 (31 to 36)
CV of glucose between days (%)	18 (14 to 27)	21 (18 to 25)
Daytime insulin delivery (U)	44.5 (35.0 to 47.8)	44.3 (33.2 to 52.0)
Nighttime (from midnight to 08:00)		
Time spent at glucose level (%)		
3.9 to 8.0mmol/l	63 (49 to 78)	40 (30 to 48)
>8.0mmol/l	31 (18 to 43)	56 (50 to 68)
<3.9mmol/l	2.3 (0.9 to 5.4)	1.1 (0.0 to 5.4)
AUC_{day} <3.5mmol/l (mmol/l x min)†	6.1 (0.0 to 26.1)	2.3 (0.0 to 5.4)
Mean glucose (mmol/l)	7.8±1.8	9.7±1.8
Within night SD of glucose (mmol/l)	1.7 (1.4 to 2.2)	1.8 (1.6 to 1.9)
CV of glucose within night (%)	23 (22 to 26)	19 (17 to 22)
CV of glucose between nights (%)	26 (15 to 35)	31 (28 to 39)
Overnight insulin delivery (U)	11.5 (10.2 to 18.6)	11.3 (8.9 to 17.2)

Data are presented as mean ± SD or median (interquartile range). p-values adjusted for period effect.
*AUC_{day}, Glucose area under curve below 3.5mmol/l per day

5.4.2 Study 2

5.4.2.1 Participants

We approached 17 subjects, 12 of which gave consent/assent and completed the study (7 males; age 14.6±3.1 years; diabetes duration 7.8±3.5 years; HbA1c 8.5±0.7% [69±8mmol/mol]; insulin pump therapy duration 5.5±2.6years; total daily insulin dose 0.82±0.18 U/kg/day], all C-peptide negative except for two participants with levels of 61 and 262 pmol/l) (see Figure 5.6 and Table 5.4).

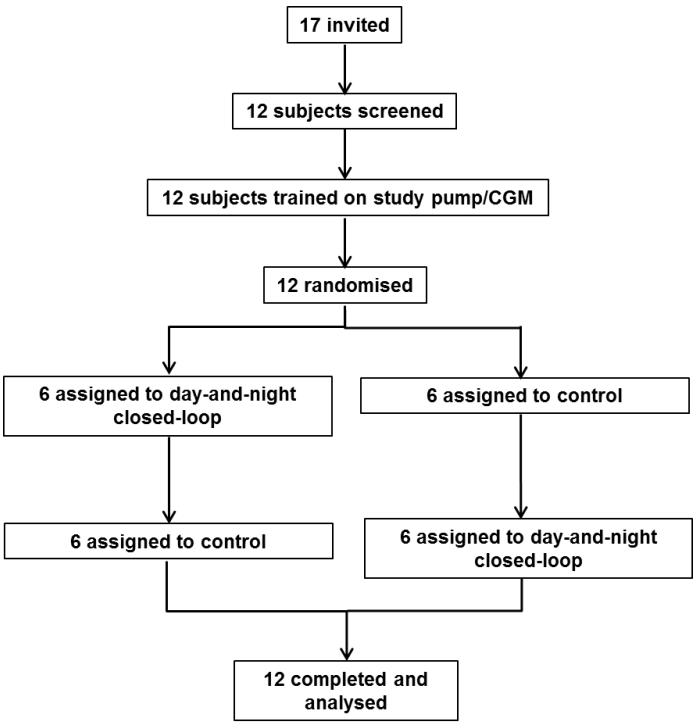

Figure 5.6. Flow of participants through the trial (Study 2).

Table 5.4. Baseline characteristics of study participants (Study 2).

	n=12* (mean ± SD)
Age (years)	14.6±3.1
Gender (male/female)	7/5
Weight (kg)	
BMI (kg/m^2)	21.3±4.4
BMI z-score	0.56±1.19
Glycated haemoglobin at screening (%)	8.5±0.7
Glycated haemoglobin at screening (mmol/mol)	69±8
Duration of diabetes (years)	7.8±3.5
Duration on pump (years)	5.5±2.6
Total daily insulin (U/kg/day)	0.82±0.18

* All C-peptide negative at non-hypoglycaemia (C-peptide less than 33pmol/l at fingerstick glucose equal or greater than 4mmol/l) except for two participants with levels of 61 and 262 pmol/l

5.4.2.2 Day-and-night glucose control and insulin delivery

Primary and secondary endpoints are summarized in Table 5.5. Twenty-four-hour sensor glucose and insulin delivery profiles are shown in Figure 5.7. The proportion of time that sensor glucose was in the target glucose range of 3.9 to 10.0mmol/l (primary endpoint), was increased during closed-loop compared to control period ($p<0.001$). The mean glucose level was significantly lower with closed-loop use ($p=0.001$, Figure 5.8) as was the time spent above the target glucose range ($p<0.001$). The proportion of time spent with sensor readings in hypoglycaemia (below 3.9mmol/l and 2.8mmol/l,) and the area under the curve when sensor glucose was less than 3.5mmol/l were low and comparable during the study interventions.

Glucose variability, measured as the standard deviation and the coefficient of variation of sensor glucose level within 24 hours and between days, did not differ between study periods. Higher percentage of time when glucose was in target range and lower mean glucose levels were achieved by closed-loop through increased variability of basal insulin delivery ($p<0.001$; Table 5.5 and Figure 5.7) and slightly higher total daily insulin dose ($p=0.006$). Basal insulin delivery during closed-loop was significantly higher than during control intervention ($p=0.001$). Overall bolus insulin requirements during closed-loop were significantly lower ($p=0.009$), as was the number of overall bolus administrations per day ($p=0.015$). Fewer correction boluses [0.2 (0.1 to 0.4) vs. 0.9

(0.1 to 1.4) per day, closed-loop vs. control, p=0.015] but not meal boluses [4.8 (4.6 to 6.1) vs. 5.8 (4.1 to 7.0), p=0.48) were observed during closed-loop.

Table 5.5. Comparison of glucose control and insulin delivery over 21 days during closed-loop and control period.

	Closed-loop (n=12)	Control (n=12)	Paired difference*	P value
Day-and-night glucose control Time spent at glucose level (%)				
3.9 to 10.0mmol/l†	66.6±7.9	47.7±14.4	18.8±9.8	<0.001
>10.0mmol/l	29.7±9.2	49.1±16.5	-19.3±11.3	<0.001
>16.7mmol/l	5.1 (0.8 to 5.6)	8.0 (1.9 to 17.4)	-3.6 (-11.9 to -0.65)	<0.001
<3.9mmol/l	4.3 (1.4 to 5.2)	2.4 (0.3 to 5.7)	0.4 (-2.2 to 1.3)	0.33
<2.8mmol/l	0.3 (0.0 to 0.5)	0.1 (0.0 to 0.7)	-0.1 (-0.4 to 0.2)	0.49
AUC_{day} <3.5mmol/l (mmol/l x min) ‡	11.1 (1.2 to 17.4)	2.7 (0.2 to 20.4)	0.0 (-10.5 to 6.8)	0.21
Mean glucose (mmol/l)	8.7±0.9	10.5±1.8	-1.8±1.3	0.001
Within day SD of glucose (mmol/l)	3.7±0.7	4.2±0.8	-0.5±0.7	0.013
CV of glucose within day (%)	40.5 (38.1 to 47.7)	38.3 (36.7 to 43.7)	1.2 (-2.6 to 6.7)	0.18
CV of glucose between days (%)	19.0 (13.8 to 23.7)	17.4 (14.9 to 24.0)	-0.5 (-3.9 to 6.0)	0.94
Day-and-night insulin delivery				
Total daily insulin (U/day)	53.5 (39.5 to 72.1)	51.5 (37.6 to 64.3)	4.5 (1.6 to 6.5)	0.006
Total bolus insulin (U/day)	28.3 (16.7 to 32.6)	29.4 (23.6 to 37.6)	-4.4 (-8.1 to -1.4)	0.009
Total basal insulin (U/day)	25.8 (23.0 to 41.2)	19.9 (14.8 to 26.3)	7.6 (3.8 to 14.4)	0.001
SD of basal insulin delivery (U/hour)	1.2 (1.0 to 1.9)	0.3 (0.1 to 0.3)	1.1 (0.8 to 1.6)	<0.001
CV of basal insulin delivery	106.7 (97.2 to	23.9 (12.8 to 35.2)	79.2 (77.1 to 91.3)	<0.001
Bolus administrations (Number/day)	4.9 (4.8 to 6.3)	6.3 (5.1 to 7.6)	-1.1 (-1.5 to -0.2)	0.015

Data are presented as mean ± SD or median (interquartile range). p-values adjusted for period effect.
*Closed-loop minus control. A positive value indicates the value was higher on the closed-loop compared with control
† Primary endpoint
‡AUC_{day}, Glucose area under curve below 3.5mmol/l per day

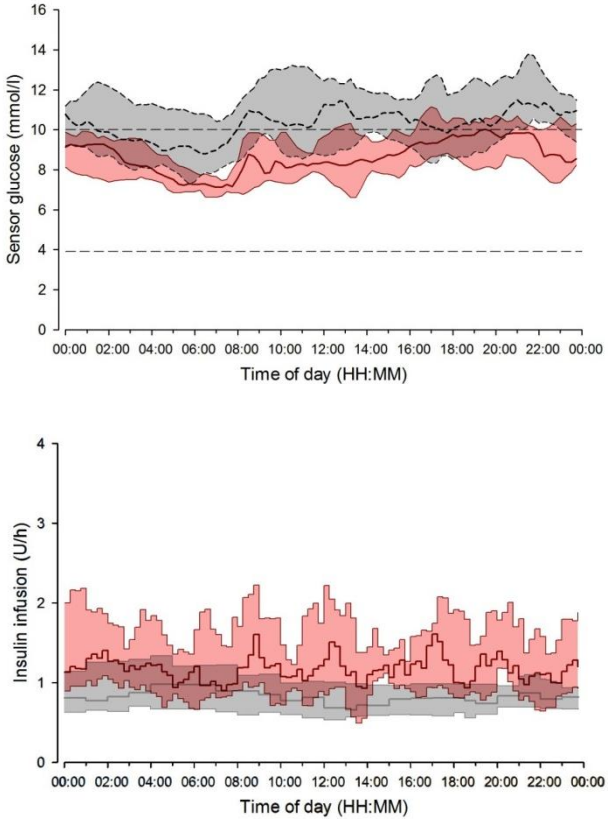

Figure 5.7. 24-hour sensor glucose and insulin profile. Median (interquartile range) of sensor glucose (top panel) and insulin delivery (bottom panel) during closed-loop (solid red line and red shaded area) and control period (dashed black line and grey shaded area) from midnight to midnight. The glucose range 3.9 to 10.0 mmol/l is denoted by horizontal dashed lines (top panel).

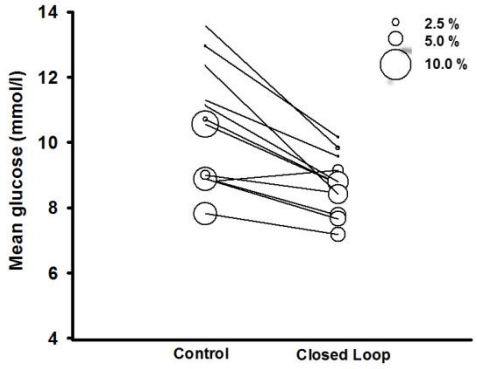

Figure 5.8. Individual values of mean sensor glucose during day-and-night closed-loop study. The size of bubble indicates the proportion of time spent with low glucose below 2.8mmol/l

5.4.2.3 Daytime and overnight glucose control and insulin delivery

Secondary outcomes calculated for daytime (08:00 to midnight) and overnight periods (midnight to 08:00) are shown in Table 5.6. The daytime (p=0.002) and overnight (p=0.002) mean glucose were significantly lower during closed-loop use (p=0.002). The proportion of time that the glucose level was within the wide target range (3.9 to 10.0mmol/l) and overnight target range (3.9 to 8.0mmol/l) were higher during closed-loop compared to control (p<0.001) without a difference in total daytime and overnight insulin amount. The percentage of time spent with sensor readings below target range did not differ between the two interventions during daytime and overnight.

5.4.2.4 Adverse events

No serious adverse events or severe hypoglycaemic episodes were observed during either study period. Three adverse events were documented, none of which was related to study devices or study procedures. One participants during control intervention measured elevated urine ketone levels associated with hyperglycaemia. This event was attributed to a viral infection and was self-managed. One participant during closed-loop and another participant during control period required oral antibiotic treatment due to respiratory tract infections without metabolic deterioration.

5.4.2.5 Utility analysis

Availability of sensor glucose data was 95% (91% to 98%) during closed-loop and higher than 90% (73% to 96%) recorded during control period (p=0.036). Closed-loop was operational over 82% (76% to 88%) of time.

Table 5.6. Daytime and nighttime glucose control and insulin delivery during closed-loop and control period.

	Closed-loop (n=12)	Control (n=12)	Paired difference*	P value
Daytime (from 08:01 to 23:59)				
Time spent at glucose level (%)				
3.9 to 10.0mmol/l	62.9±8.9	45.7±13.7	17.1±12.2	0.001
>10.0mmol/l	33.0±10.7	51.8±15.7	-18.7±13.7	0.001
<3.9mmol/l	4.2 (1.0 to 6.5)	1.2 (0.3 to 3.9)	0.3 (-0.8 to 4.1)	0.15
AUC_{day} <3.5mmol/l (mmol/l x min)†	11.2 (0.9 to 17.0)	2.0 (0.2 to 12.3)	-0.4 (-5.0 to 12.8)	0.26
Mean glucose (mmol/l)	9.0±1.0	10.8±1.9	-1.8±1.5	0.002
Within day SD of glucose (mmol/l)	3.9±0.8	4.3±0.9	-0.4±0.9	0.10
CV of glucose within day (%)	42.8 (37.9 to 49.8)	39.0 (36.0 to 42.6)	3.0 (-3.7 to 8.7)	0.20
CV of glucose between days (%)	19.2 (17.4 to 25.6)	21.6 (16.5 to 23.1)	-2.4 (-5.8 to 3.5)	0.86
Daytime insulin delivery (U)	42.7 (31.2 to 53.6)	42.8 (30.9 to 48.4)	3.5 (0.0 to 6.3)	0.24
Nighttime (from midnight to 08:00)				
Time spent at glucose level (%)				
3.9 to 8.0mmol/l	54.4±13.8	33.4±16.3	20.9±12.7	<0.001
>8.0mmol/l	42.8±14.0	62.0±19.4	-19.3±14.5	0.001
<3.9mmol/l	2.5 (1.1 to 4.2)	3.9 (0.3 to 7.2)	-1.3 (-4.9 to 1.4)	0.70
AUC_{day} <3.5mmol/l (mmol/l x min)*	5.3 (1.6 to 19.7)	4.7 (0.0 to 21.8)	1.2 (-20.0 to 5.9)	0.56
Mean glucose (mmol/l)	8.2±1.1	9.8±2.0	-1.6±1.4	0.002
Within night SD of glucose (mmol/l)	3.1±0.9	3.8±0.7	-0.7±0.7	0.008
CV of glucose within night (%)	37.3±6.8	39.3±7.3	-2.0±9.9	0.53
CV of glucose between nights (%)	26.7±8.5	30.9±6.4	-4.2±10.1)	0.20
Overnight insulin delivery (U)	11.5 (9.5 to 17.3)	11.0 (8.5 to 15.0)	0.6 (-0.5 to 3.5)	0.18

Data are presented as mean ± SD, median (interquartile range)

* Closed-loop minus control. A positive value indicates the value was higher on the closed-loop compared with control

† AUC_{day}, glucose area under curve below 3.5mmol/l per day

5.4.2.6 Questionnaire

All 12 participants completed the questionnaire. Results of the four closed questions are shown in Figure 5.9. 100% (12/12) of the participants were confident with the closed-loop system regulating their blood glucose and insulin delivery. 83.3% (10/ 12) of subjects stated that using the closed-loop system, they required less time managing their diabetes, and two participants (16.7%) were unsure about this statement. The majority of participants (91.7% [11/12]) expressed fewer concerns about their glucose control while using closed-loop. Improved sleep was indicated by 75% (9/12) of participants, whereas 8.3% (1/12) slept worse, and 16.7% (2/12) were unsure about the impact of the closed-loop system on their sleep.

Key positive themes of the closed-loop system as described by participants in the free-text section of the questionnaire were improved glucose control, a relief of diabetes management, and specific features of the closed-loop handset allowing remote meal bolusing and data review. Key negative themes were the number and size of devices, the necessity to carry around the equipment all the time, CGM and pump alarms, connectivity and CGM calibration issues. According to participants, future closed-loop systems should be smaller, ideally integrating all different devices into one single device. Sensor life should be longer, and additional features to facilitate carbohydrate estimation should be implemented.

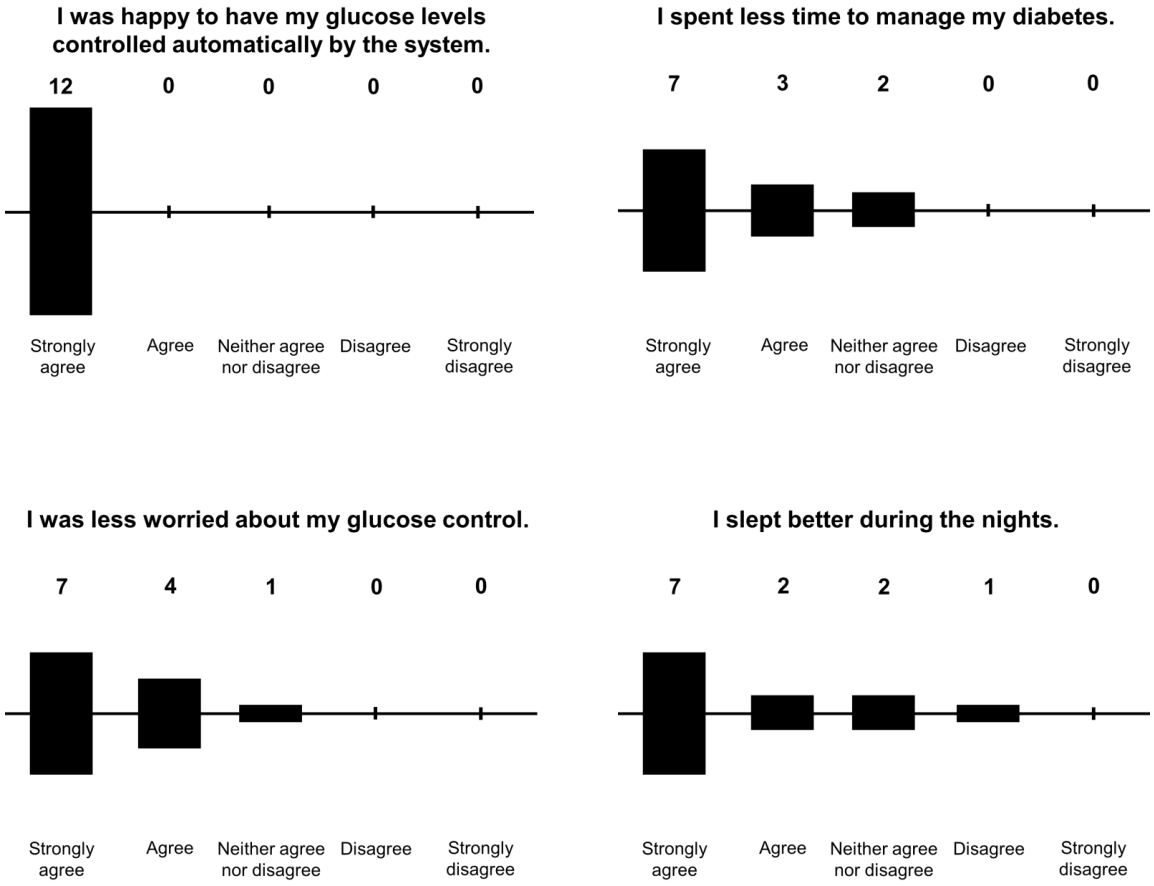

Figure 5.9. Questionnaire results. The numbers at the top of each graph indicate the total number of answers out of 12 responses.

5.5 DISCUSSION

These are the first trials investigating day-and-night application of closed-loop insulin delivery under free-living conditions in adolescents with type 1 diabetes. Results of the presented studies demonstrate the feasibility of unsupervised free-living home use of 24/7 hybrid closed-loop in this challenging population. Closed-loop increased the time when glucose was in the target range while reducing the mean glucose. These improvements were achieved without increasing the risk of hypoglycaemia. Total daily insulin dose delivered during closed-loop intervention was similar (Study 1) or slightly increased (Study 2) compared to control intervention.

The occurrence of hypoglycaemia exposure in the present studies was low. Compared with previously published day-and-night adult outpatient studies using single-

hormone[243,244] or dual-hormone approaches with glucagon co-administration[196], participants in the present studies spent less time at glucose levels below 3.9mmol/l during control period. During the closed-loop study arm our results matched the findings observed in adults (Table 5.7). In our adolescent cohorts, the 24/7 hybrid closed-loop system managed to keep time in hypoglycaemia at a low level while significant reductions in hypoglycaemia risk using closed-loop in outpatient settings were observed in populations with greater rates of hypoglycaemia or in more challenging environments such as diabetes camps during prolonged outpatient closed-loop studies in adults using single-hormone[243,249] or dual hormone (glucagon co-administration) closed-loop approaches across different age groups [196-198]. We instructed study participants to perform calibration checks twice a day and to recalibrate the sensor when large over-reading but not under-reading occurred, to reduce the risk of sensor-error induced hypoglycaemia which is of particular concern during closed-loop insulin delivery. The advent of novel technologies such as threshold-suspend insulin pump therapy[141] and more recently predictive low glucose suspend[147] may reduce hypoglycaemia risk. However, these approaches are not designed to increase insulin delivery and do not address the issue of hyperglycaemia, which poses major challenges in diabetes management of adolescents. The important advantage of a closed-loop system is highly responsive graduated modulation of insulin delivery both below and above the pre-set pump regimen, allowing for improvements in time spent with target glucose values and reduction of mean glucose without increased hypoglycaemia.

Findings from Study 2 trial extends findings from our previous home trials in children and adolescents (including Study 1)[188,190,243], which were limited by either overnight application [188,243] or a shorter intervention period (Study1)[190]. While benefits of closed-loop in these trials as well as in our previous adult trials[243,244] tended to be greater overnight compared to daytime, results of Study 2 study show consistent improvements in glucose levels overnight and during daytime. Possible explanations include closed-loop mitigating against missed meal boluses in suboptimally controlled adolescents. Additionally, we applied control algorithm with enhanced adaptivity.

Poorly controlled teenagers may be among those most benefiting from closed-loop systems.

In Study 2, prolonged periods of sensor under-reading resulting in hypoglycaemia over-reporting were identified in one participant during closed-loop intervention underscoring challenges associated with quantifying hypoglycaemia using glucose sensor data. No similar findings were observed during control intervention. While results in Table 5.5 and Table 5.6 and in the results section are based on the original data, Figure 5.8 shows data excluding periods of sensor under-reading (see Appendix D, Figures 8.1 to 8.5 for details of excluded data).

Table 5.7. Comparison of percentage of time spent below 3.9 mmol/l during day-and-night closed-loop studies in outpatient settings.

Study population	Settings	Sample size	Intervention period	Time spent at glucose level below 3.9mmol/l (%)		Reference
				Closed-loop	**Control**	
Adults*	mixed†	20	5 days	4.1±3.5	7.3±4.7	[196]
Adults‡	home	17	1 week	3.1±2.6	4.3±3.6	[244]
Adults‡	home	33	12 weeks	3.1±1.9	4.3±3.9	[243]
Adolescents‡	home	12	1 week	3.7±2.7	3.3±3.7	Dan04 Study 1
Adolescents‡	home	12	3 weeks	3.7±2.2	3.2±3.3	Dan04 Study 2

Data are presented as mean ± SD

* Dual-hormone closed-loop vs. usual care (45% of participants used real-time continuous glucose monitoring during usual care)

† Control: home; closed-loop: restricted geographical area during day & hotel overnight

‡ Single-hormone closed-loop vs. sensor-augmented pump therapy

In Study 2, total daily insulin requirements during closed-loop were modestly higher than during control intervention, which was due to higher basal insulin delivery. Inherent to closed-loop systems, algorithm directed insulin delivery was more variable than basal insulin delivery during the control period. More pronounced increases in total insulin delivery during closed-loop intervention [24%[250] to 33%[196] of total daily insulin dose] were previously described in studies of dual hormone systems, where potential insulin overdosing can be mitigated by co-administration of glucagon. Higher insulin requirements during closed-loop in the present study may reflect under-

insulinisation in sub-optimally controlled adolescents. Interestingly, we observed reduced bolus amounts and fewer boluses per day during closed-loop intervention. We attribute this finding to fewer correction doses, but the observation might also reflect reduced bolus adherence for meals and snacks during closed-loop. The unsupervised design of the study precludes reliable interpretation of the finding.

Closed-loop use and sensor wear were high in our cohorts. The closed-loop technology was well perceived in line with previously published data [199]. Though the number of devices and system alarms were reported to be drawbacks, participants expressed trust in the technology, and reduced burden of diabetes including less time spent managing diabetes and fewer worries about glycaemic control. Further miniaturization and integration of devices, prolonged sensor life, and simplified meal management are preferable features of future closed-loop systems which may enhance usability. Given high closed-loop utilisation in adolescents, the positive perception of this technology and its benefits in terms of glycaemic control demonstrated by the present study, closed-loop represents a promising tool to address glycaemic deterioration commonly seen in adolescence[48,237].

A fully closed-loop system without meal announcement would be particularly applicable in the adolescent population. However, the absorption rate of currently available rapid acting insulin analogues is not fast enough to effectively control postprandial glucose excursions without anticipatory insulin bolus. Our premise is that present closed-loop systems will benefit from meal announcement but have to be able to cope with missed meal boluses safely and efficaciously, should these occur.

The strengths of our studies include the integration of closed-loop into normal life including use at school, during weekends and on holidays. The studies were performed without remote monitoring or close supervision. No restrictions were imposed on dietary intake, moderate physical activity or travel. The comparator was ‘state-of-the-art’ sensor-augmented insulin pump therapy. A crossover design had the benefit of each participant acting as his/her own control. Weaknesses include the small sample sizes, the still relatively short study duration, and restricted use of the closed-loop system during strenuous exercise. The current closed-loop prototype system requires

participants to wear and carry multiple devices. Further integration of devices may reduce this burden and enhance usability of closed-loop systems, particularly during physical activity.

In conclusion, we have demonstrated that day-and-night hybrid closed-loop can be used safely in suboptimally controlled adolescents at home without supervision over a period of up to 21 days. Its benefits include increased time when glucose is in the target range and reduced mean glucose. Larger and longer studies are warranted.

6 Home use of day-and-night closed-loop in very young children (KidsAP)

6.1 BACKGROUND

Despite advances in insulin pump and sensor technology, the majority of small children with type 1 diabetes are still unable to achieve optimal glycaemic control. Application of closed-loop insulin delivery systems in a range of populations and settings, including children and adolescents in home settings, has been shown to improve glycaemic control and reduce the burden of hypoglycaemia[191,243,251]. Only a few closed-loop studies have been performed in very young children with type 1 diabetes[184,185,224]. All of them were of very short duration, and were conducted under close supervision by research staff, e.g. at research facilities or diabetes camps. Performance of closed-loop systems in small children in unsupervised home settings is yet to be determined.

Current insulin pumps allow the adjustment of small basal rates, but accurate dosing becomes difficult with the small increments needed in very young children[252]: Frequently less than 0.1U/h of insulin are delivered compared to 1.0U/h in adults. Dosing accuracy of commonly used insulin pumps was shown to be lower at 0.1 U/h than at a 1 U/h rate with an at least three times higher flow error over 1 hour at 0.1 U/h and a deviation from the scheduled rate of up to 13%.[253] Diluting insulin in children with very low insulin requirements as commonly applied in many paediatric diabetes centres might help mitigate this issue. Compelling evidence, however, for the use of diluted insulin is missing; hardly any studies using diluted insulin have been performed. Anecdotal data suggest that use of diluted insulin in small children on insulin pump therapy might be beneficial, with positive effects such as decreased glycaemic variability, reduced occurrence of unexplained hyperglycaemia and reduced frequency of insulin infusion set issues (i.e. air bubbles)[254]. In a closed-loop setting, results from an overnight research facility based RCT suggest that use of diluted insulin in very young children might lead to reduced hypoglycaemia and reduced glucose variability, as well as less variable insulin absorption.[224,255]

6.2 STUDY OBJECTIVES

The clinical trial described in this chapter is part of the KidsAP project funded by the European Commission's Horizon 2020 Framework Programme. The multinational, multi-centre project assesses the ability of closed-loop insulin delivery to improve glucose control in the most vulnerable population with type 1 diabetes: children aged 1 to 7 years. In a pilot study, we aimed to evaluate the feasibility of closed-loop in home settings and the potential benefit of diluted insulin use during closed-loop in this population. In the following, I present the results of the first 5 participants completing the trial at the Cambridge study site.

6.3 RESEARCH DESIGNS AND METHODS

6.3.1 Study participants

Study participants included in this analysis were identified from paediatric diabetes outpatient clinics at Addenbrooke's Hospital (Cambridge, United Kingdom) and University College London Hospital (London, United Kingdom). Recruitment of these participants took place between August and October 2017. Key inclusion criteria were age between 1 and 7 years (inclusive), diagnosis of type 1 diabetes for at least six months, treatment with insulin pump therapy for at least three months, and HbA1c ≤11% (97mmol/mol). Exclusion criteria included total daily insulin dose ≥2.0 U/kg/day, and more than two incidents of severe hypoglycaemia within 6 months prior to enrolment. Parents or guardians of participants signed informed consent before study related activities were initiated. Whenever possible, assent of study participants was obtained in addition to the consent of the parents or legal representatives.

6.3.2 Study design

The study adopted an open-label, randomised, two-period crossover design contrasting closed-loop glucose control using diluted insulin (U20) and closed-loop using standard insulin strength (U100) in young children with type 1 diabetes in the home setting. Two intervention periods lasted three weeks each with one to four

weeks of washout in between. The order of the two interventions was random (see Figure 6.1)

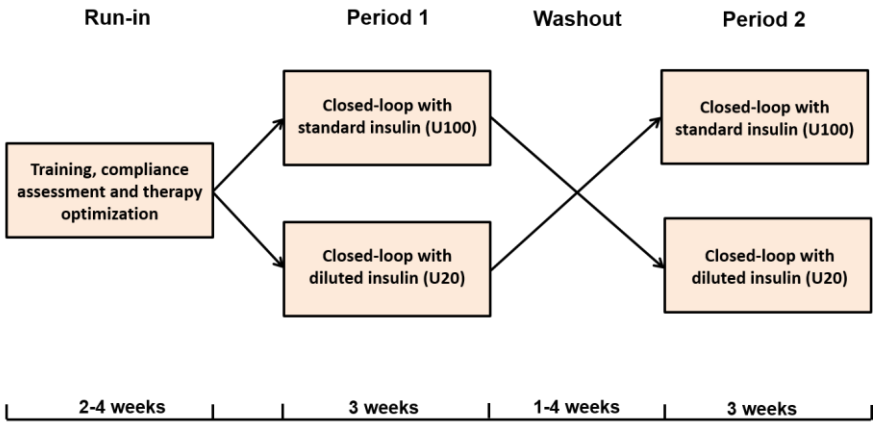

Figure 6.1. Study design

6.3.3 Study procedures

At enrolment, capillary blood samples were taken for analysis of HbA1c. At the start of the run-in phase, participants received training regarding the use of the study pump and the study real-time continuous glucose monitoring system (Medtronic 640G system; Medtronic, Northridge, CA) including low glucose suspend functionality. Participants used the study pump's standard bolus calculator for all meals throughout the study.

At the end of the 1 to 2-week run-in period, compliance in the use of study pump and continuous glucose monitoring were assessed. Participants with at least 8 days' worth of continuous glucose monitoring data were randomly assigned to receive either 3 weeks of hybrid closed-loop insulin delivery with standard insulin aspart (U100) followed by hybrid closed-loop insulin delivery with diluted insulin aspart (U20), or vice versa. Permuted block randomization was applied and assignment was unblinded.

The two intervention periods were separated by a 1 to 4-week washout period during which the participants could continue using the study insulin pump and real time continuous glucose monitoring system.

On the first day of the first closed-loop period, participants attended the clinical research facility. This 1- to 2-hour visit included training on initiation and discontinuation of the closed-loop system, switching between closed-loop and usual pump therapy, meal bolus procedure, and the use of study devices during periods of increased physical activity. Competency in using closed-loop system was assessed. Following discharge, participants continued the study intervention for the next 21 days under free-living settings in their home and school environment. Participants were not remotely monitored or supervised. The participants were free to consume meals of their choice and no restrictions were imposed on travelling. We encouraged participants to continue closed-loop use during periods of increased physical activity including PE and organised sports, and to announce these periods to the algorithm. At the start of the closed-loop arm using diluted insulin, closed-loop training additionally covered use of diluted insulin. Prior to starting closed-loop with diluted insulin, pump settings were adapted accordingly and reviewed by two members of the research team. Carers at nursery or school also received closed-loop training by the study team as required.

Participants were advised to calibrate the continuous glucose monitoring device according to the manufacturer's instructions; they were free to decide on alarm settings for the continuous glucose monitoring device. All participants were provided with a 24-hour telephone helpline to contact the study team in the event of study-related issues.

6.3.4 Insulin dilution

Rapid-acting insulin analog aspart (Novo Nordisk, Bagsvaerd, Denmark) only was administered by the study pump. Standard U-100 insulin aspart (100U/ml) was used during run-in, washout, and in the study arm using standard strength insulin. U-20 insulin aspart (20U/ml) was used during the study arm using closed-loop with diluted insulin. Dilution of insulin aspart was performed by qualified members of the study team using 'Insulin diluting Medium for NovoRapid (insulin aspart) and Levemir (insulin detemir)' (Novo Nordisk, Bagvaerd, Denmark). A fixed 1:5 dilution ratio (U20 insulin) was used across all study participants rather than individual ratios based on individual

insulin needs: The reasons for this were threefold A) to allow better comparability between the interventions when using two standardised insulin formulations B) previously published data using the Cambridge MPC algorithm also compared use of U20 insulin and use of U100 insulin aspart C) 1:5 dilution was deemed to be a good compromise to guarantee insulin delivery at reasonable volumes across the expected distribution of insulin requirements in this age range (a few units per day in toddlers aged 1 year up to 20 units per day in gradeschoolers aged 7 years)

6.3.5 Closed-loop system

The FlorenceM closed-loop system (University of Cambridge, Cambridge, UK) comprised a next generation sensor augmented Medtronic insulin pump 640G (Medtronic Minimed, CA, USA) incorporating the Medtronic Enlite 3 family real time CGM and low glucose feature (predictive low glucose management and low glucose suspend) and a model predictive control algorithm (version 0.3.41, University of Cambridge) on a smartphone (Galaxy S4, Samsung, South Korea), which communicated wirelessly with the insulin pump through a proprietary translator device included in the smartphone's enclosure (see Figure 6.2). The smartphone was locked down to exclusively run the control algorithm. All other applications and functionality (e.g. making and receiving calls, text messaging, internet browsing and playing games) were not available. Every 10 min, the control algorithm calculated an insulin infusion rate which was set on the study insulin pump. In this trial, a hybrid closed-loop approach was applied, which required participants/guardians to count carbohydrates and use a standard bolus calculator for premeal boluses as per usual practice. The control algorithm was initialized using pre-programmed basal insulin delivery downloaded from the study pump. Additionally, information about participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to the respective participant. The apparent total daily dose was modified based on sensor glucose levels achieved during closed-loop on previous days. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8mmol/l and 7.3mmol/l and adjusted the actual target glucose level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions.

Figure 6.2. FlorenceM closed-loop system prototype. (A) The system consists of a continuous glucose monitoring (CGM) transmitter with Enlite 3 sensor, an insulin pump (modified 640G pump) integrated with the CGM receiver and a mobile phone running the control algorithm. (B) and (C) Photos of a participant (obtained with consent) using the closed-loop system.

6.3.5.1 Safety precautions during closed-loop

Participants were trained to perform a calibration check before breakfast and evening meal. If the sensor glucose was above the fingerstick glucose by >3.0mmol/l, the continuous glucose monitoring device was recalibrated. These instructions resulted from an in silico evaluation of hypoglycaemia and hyperglyacemia risk[247] using the validated Cambridge simulator[248].

If sensor glucose became unavailable or in case of other failures, pre-programmed insulin delivery automatically restarted within 30-60 min. This limited the risk of insulin under- and over delivery (36). Safety rules limited maximum insulin infusion and suspended insulin delivery if glucose was ≤4.3mmol/l or when sensor glucose was rapidly decreasing. The low glucose suspend feature had to be turned on during closed-loop operation as additional safety layer in case of communication failure between the

smartphone and the insulin pump. The low glucose threshold was set between 2.8 and 3.9 mmol/l as per decision of local principle investigators and family preferences.

6.3.6 Study outcomes

The primary efficacy outcome was the proportion of time when glucose was in the target range (3.9-10.0mmol/l) during the 21-day study periods as recorded by continuous glucose monitoring. Secondary outcomes included mean sensor glucose concentrations, glucose variability, time spent at glucose levels <3.9mmol/l (hypoglycaemia) and >10.0mmol/l (hyperglycaemia), and insulin delivery. Secondary outcomes were calculated over 24h, daytime and overnight periods; daytime was classified between 08:00 and midnight, and nighttime between midnight and 08:00. Glucose variability was assessed by the standard deviation and the coefficient of variation of sensor glucose. Hypoglycaemia burden was assessed by calculating the glucose sensor area under the curve less than 3.5mmol/l.

6.3.7 Assays

HbA1c at recruitment for characterization of the study population was measured locally using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) aligned method and following National Glycohaemoglobin Standardization Program (NGSP) standards.

6.3.8 Statistical analyses

The statistical analysis plan was agreed upon by investigators in advance. All analyses were carried out on an intention-to-treat basis. Efficacy and safety data from all randomized participants were included in the analyses. The respective values obtained during the 21-day randomized interventions were compared using a least-square regression model. Sensor glucose and insulin outcomes were adjusted for period effect. Rank normal transformation analyses were used for highly skewed endpoints. Outcomes were presented as mean ± SD for normally distributed values or as median (interquartile range) for non-normally distributed values. Outcomes were calculated using GStat software (University of Cambridge, version 2.3). Analysis was done using

SPSS (IBM Software, Hampshire, UK version 25). A 5% significance level was used to declare statistical significance. All p-values are two-sided.

6.3.9 Sample size

To estimate the total sample size, data were taken from our overnight closed-loop study in young children[224]. Based on estimate of 10% improvement in time in target with an SD of 13%, 20 subjects are required to achieve the desired 90% power and an alpha level of 0.05 (two-tailed). Up to 30 subjects were planned to be recruited, 24 to be randomised; applying a 20% dropout rate following randomisation provided 20 completed subjects.

For the purpose of my thesis, I focused on the participants recruited and followed up in Cambridge only, who were the first subjects to complete this multicentre trial. Hence, my sample size is under-powered, and results have to be interpreted cautiously.

6.4 RESULTS

6.4.1 Participants

14 subjects were screened. The flow of participants through the trial is shown in Figure 6.3. Five eligible participants were randomized, completed the study, and provided data for analyses (2 males; age 3.7±2.1 years; diabetes duration 2.0±1.8 years; HbA1c 7.7±0.9% [60±9mmol/mol]; total daily insulin dose 10.9±3.7 U/day]) (see Table 6.1).

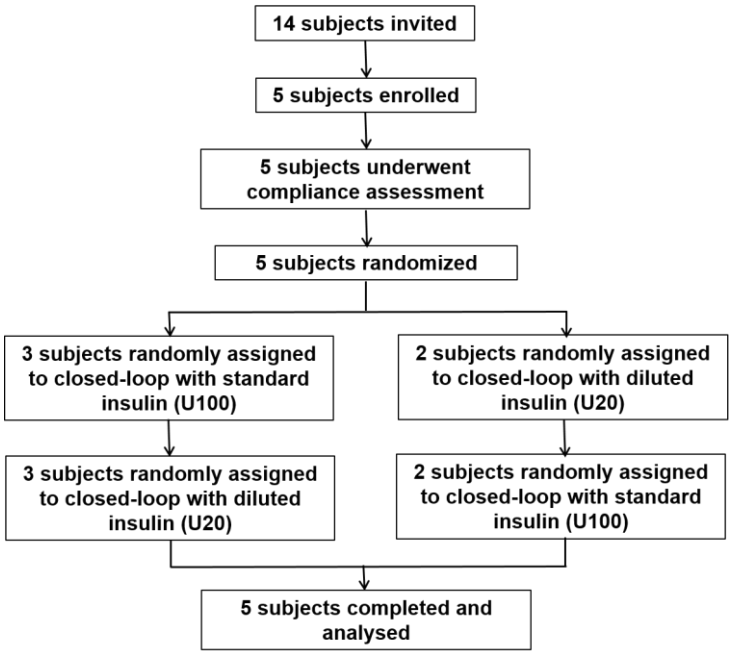

Figure 6.3 Flow of participants through the trial

Table 6.1 Baseline characteristics of study participants

	n=5 (mean ± SD)
Age (years)	3.7±2.1
Gender (male/female)	2/3
Height (cm)	98.7±18.2
Weight (kg)	16.5±4.9
BMI (kg/m^2)	16.9±2.0
BMI z-score	0.5±1.1
Glycated haemoglobin at screening (%)	7.7±0.9
Glycated haemoglobin at screening (mmol/mol)	60±9
Duration of diabetes (years)	2.0±1.8
Duration on pump (years)	1.9±1,7
Total daily insulin (U/day)	10.9±3.7

6.4.2 Outcomes

6.4.2.1 Day-and-night glucose control, insulin delivery and utility analysis

Primary and secondary outcomes are shown in Table 6.2. The primary endpoint - the proportion of time sensor glucose was in the target glucose range of 3.9 to 10.0mmol/l

- was similar and not statistically different between interventions (63.7 ± 5.3% vs. 67.5 ± 6.6%; closed-loop with diluted insulin [U20] vs. closed-loop with standard insulin [U100]; p=0.60). The twenty-four-hour sensor glucose profile is shown in Figure 6.4.

There was no difference in achieved mean glucose levels (8.7 ± 0.6mmol/l vs. 8.5 ± 0.6mmol/l; U20 vs. U100; p=0.85) and glucose variability (within day standard deviation [SD] of glucose, coefficient of variation [CV] within day, and CV of glucose between days; see Table 6.2) between both interventions.

The proportion of time when sensor glucose was below 3.9mmol/l (5.0% [3.0% to 5.1%] vs. 4.7% [3.8% to 4.9%]; U20 vs. U100; p=0.88] and the area under the curve when sensor glucose was less than 3.5mmol/l (see Table 6.2) were low and comparable during the study periods. The proportion of time spent with sensor readings in clinically significant hypoglycaemia, i.e. <3.0mmol/l, was not different between interventions either (1.1% [0.4% to 1.5%] vs. 1.2% [0.9% to 1.7%]; U20 vs. U100; p=0.70).

Total daily insulin delivery did not differ between interventions (12.5U [9.6U to 12.5U] vs. 12.2 [9.0 to 12.5]; U20 vs. U100; p=0.28). There was no difference in total basal (p=0.55) nor total bolus insulin requirements either (p=0.70; see Table 6.2).

Closed-loop was operating over a median of 82% (75 to 85) of time during the closed-loop arm using diluted insulin, and 83% (78 to 88) during closed-loop with standard strength insulin (p = 0.43). Participants wore the study continuous glucose monitor for a median of 94% of time during both closed-loop intervention arms (see Table 6.2).

Table 6.2 Comparison of glucose control and insulin delivery over 21 days during closed-loop with diluted insulin (U20) and closed-loop with standard strength insulin (U100).

	Diluted (U20) (n=5)	Non-diluted (U100) (n=5)	P value
Primary endpoint			
% Time in range (3.9-10.0 mmol/L)	63.7 ± 5.3	67.5 ± 6.6	0.60
Overall glucose control			
Mean glucose (mmol/L)	8.7 ± 0.6	8.5 ± 0.6	0.85
Within day SD of glucose (mmol/l)	3.6 ± 0.4	3.4 ± 0.4	0.52
CV of glucose within day (%)	41.3± 1.4	39.5± 2.6	0.10
CV of glucose between days (%)	13.3 ± 0.8	12.6± 2.2	0.37
Hypoglycaemia			
% Time <3.9 mmol/L	5.0 (3.0 to 5.1)	4.7 (3.8 to 4.9)	0.88
% Time <3.5 mmol/L	2.8 (1.1 to 2.8)	2.7 (1.8 to 3.1)	0.75
% Time <3.0 mmol/L	1.1 (0.4 to 1.5)	1.2 (0.9 to 1.7)	0.70
AUCday <3.5mmol/l (mmol/l)†	20.0 (6.2 to 23.1)	19.8 (13.4 to 27.8)	0.50
Hyperglycaemia			
% Time >10.0 mmol/L	33.0 (29.1 to 35.9)	26.7 (23.2 to 29.8)	0.62
% Time >16.7 mmol/L	3.1 (1.5 to 3.5)	1.7 (1.1 to 4.2)	0.78
Insulin delivery			
Total insulin (U/day)	12.5 (9.6 to 12.5)	12.2 (9.0 to 12.5)	0.28
Basal insulin (U/day)	5.9 (5.7 to 6.7)	5.5 (5.3 to 6.1)	0.55
Bolus insulin (U/day)	5.8 (4.4 to 6.8)	6.4 (4.3 to 6.7)	0.70
Utility			
CGM use (% of time)	94 (92 to 94)	94 (91 to 95)	0.80
CL use (% of time)	82 (75 to 85)	83 (78 to 88)	0.43

Data are presented as mean ± SD or median (interquartile range). p-values adjusted for period effect.
† AUC_{day}, Glucose area under curve below 3.5mmol/l per day

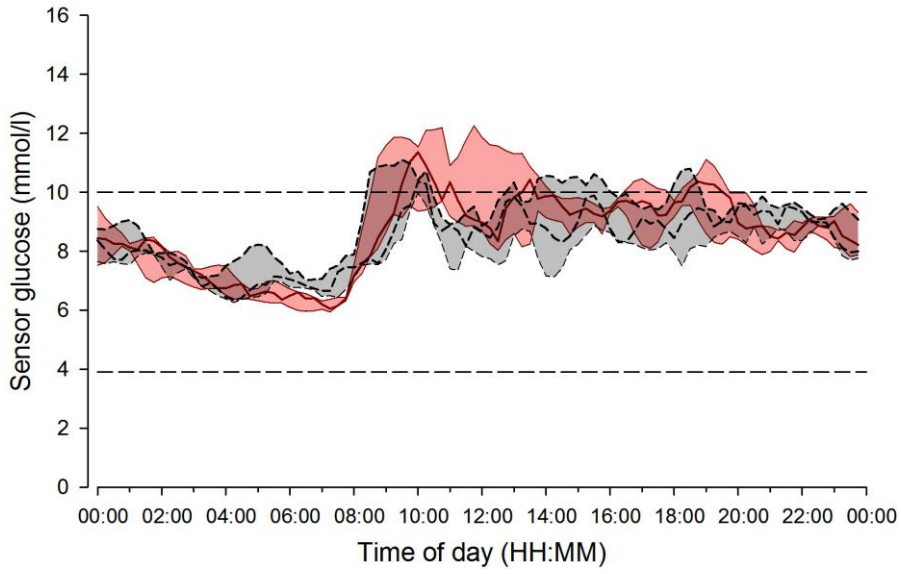

Figure 6.4 24-hour sensor glucose profiles. Median (interquartile range) of sensor glucose during closed-loop with diluted insulin (solid red line and red shaded area) and closed-loop with standard strength insulin (dashed black line and grey shaded area) from midnight to midnight. The glucose range 3.9 to 10.0 mmol/l is denoted by horizontal dashed lines.

Daytime and overnight glucose control and insulin delivery

Secondary outcomes calculated for daytime (from 08:01 to 23:59) and overnight (from midnight to 08:00) periods are shown in Table 6.3. The proportion of time when daytime sensor glucose was in target range (3.9 to 10.0mmol/l) tended to be slightly lower during closed-loop with diluted insulin compared to closed-loop with standard insulin (53.4 ± 6.6% vs. 59.7 ± 7.8%; U20 vs. U100), while the proportion of time spent with sensor readings below 3.9mmol/l (5.5% [2.7% to 6.4%] vs. 4.3% [3.8% to 5.5%]; U20 vs. U100) and daytime mean glucose (9.5 ± 0.8mmol/l vs. 9.1 ± 0.8mmol/l; U20 vs. U100) tended to be slightly higher when using diluted insulin. There was no difference in daytime insulin requirements between interventions (see Table 6.3). The proportion of time when sensor glucose was in target range overnight (3.9 to 10.0mmol/l) was high and very similar during closed-loop with diluted insulin and closed-loop with standard insulin (84.1 ± 4.8% vs 83.0 ± 10.0%; U20 vs. U100). When looking at a tighter overnight target range (3.9 to 8.0 mmol/l), the percentage of time in range as achieved with diluted insulin seemed to be higher (71.0 ± 9.8 vs. 62.9 ± 13.5; U20 vs. U100). Nighttime mean glucose tended to be slightly lower during closed-loop with diluted insulin (7.1 ± 0.6mmo/l vs. 7.4 ± 0.7mmol/l; U20 vs. U100). The percentage of time with sensor glucose levels below 3.9 mmol/l and the percentage of time spent in clinically

significant hypoglycaemia (below 3.0 mmol/l) were low and comparable between interventions (see Table 6.3). There was no difference with respect to overnight insulin requirements (Table 6.3).

Table 6.3 Daytime and nighttime glucose control and insulin delivery during both closed-loop intervention arms

	Diluted (U20) (n=5)	Non-diluted (U100) (n=5)
Daytime (from 08:01 to 23:59)		
Overall glucose control		
% Time in range (3.9-10.0 mmol/l)	53.4 ± 6.6	59.7 ± 7.8
Mean glucose (mmol/l)	9.5 ± 0.8	9.1 ± 0.8
Standard deviation (mmol/l)	3.9 (3.6 to 3.9)	3.4 (3.3 to 4.0)
Hypoglycaemia		
% Time <3.9 mmol/l	5.5 (2.7 to 6.4)	4.3 (3.8 to 5.5)
% Time <3.0 mmol/l	1.4 (0.5 to 2.0)	1.1 (1.1 to 1.9)
Insulin Delivery		
Total insulin (U/day)	9.7 (7.9 to 10.9)	9.8 (7.5 to 10.7)
Nighttime (from midnight to 08:00)		
Overall glucose control		
% Time in range (3.9-10.0 mmol/l)	84.1 ± 4.8	83.0 ± 10.0
% Time in range (3.9-8.0 mmol/l)	71.0 ± 9.8	62.9 ± 13.5
Mean glucose (mmol/l)	7.1 ± 0.6	7.4 ± 0.7
Standard deviation (mmol/l)	2.4 ± 0.4	2.3 ± 0.5
Hypoglycaemia		
% Time <3.9 mmol/l	3.5 (2.9 to 4.0)	3.7 (3.7 to 4.3)
% Time <3.0 mmol/l	0.6 (0.5 to 0.7)	0.8 (0.3 to 1.3)
Insulin delivery		
Total insulin (U/day)	3.3 (3.1 to 4.0)	3.0 (2.9 to 4.2)

Data are presented as mean ± SD or median (interquartile range).

6.4.2.3 Adverse events

No severe hypoglycaemia, no diabetic ketoacidosis, nor any other adverse event occurred during the whole study period (run-in, intervention arms, wash-out) in these 5 subjects.

6.5 DISCUSSION

To our knowledge, this is the first and longest randomised controlled trial investigating day-and-night application of closed-loop insulin delivery in very young children with type 1 diabetes during free-living conditions. Preliminary results of my analysis including data from the first five participants completing this multicentre trial suggest that single hormone 24/7 hybrid closed-loop insulin delivery can be safely and effectively applied in young children aged one to seven years with type 1 diabetes in unsupervised home settings.

The present study builds on previous observations in older children, adolescents and adults about benefits of day-and-night closed-loop therapy using Cambridge model predictive control in free living conditions[190,191,243,256]. In the present analysis, we document good glucose control in younger children who may greatly benefit from closed-loop technology. Similar results with respect to the percentage of time spent in the target range and in hypoglycaemia were obtained in this population as compared with older children and adolescents using the same algorithm[190,191,243].

Automated insulin delivery using a modular model predictive control approach in children aged five to nine years was investigated by Del Favero et al. documenting reduced overnight exposure to hypoglycaemia as compared with sensor-augmented insulin pump therapy in a camp setting with close supervision by research staff[184]. Although closed-loop was not associated with improvements in the time spent in target and even led to increased mean glucose levels, the study was the first to evaluate closed-loop therapy in pre-schoolers and children in outpatient settings. The achieved time in target (56.8±13.5%) using their closed-loop system was lower than the findings from our study in free-living conditions without supervision.

Other than closed-loop use in children as young as 1 years and older, the novelty of our study is the use of diluted insulin to enhance the accuracy of delivery of small insulin doses. However, preliminary results suggest that there is no benefit of using diluted insulin in a closed-loop setting. Across the whole range of insulin requirements used in this age group, insulin delivery via latest generation Medtronic 640G insulin pump seems to work equally well at very low rates compared to insulin delivery at standard rates. Of course, data from this preliminary analysis need to be interpreted cautiously. Results from all 24 randomised participants and additional sub-group analyses will more reliably clarify the role of diluted insulin; use of diluted insulin in those with very little insulin requirements might still be beneficial.

In our study, closed-loop system performed particularly well overnight compared with daytime. A similar trend - though not as pronounced as in very young children - was also observed in our previous trials in older populations[190,191,243]. With over 80% spent in target range of 3.9 to 10.0mmol/l (84.1± 4.8% and 83.0± 10.0%, respectively; U20 and U100) mean overnight glucose levels just above 7 (7.1± 0.6 mmol/l and 7.4 ± 0.7 mmol/l; U20 and U100), our closed-loop system seems to outperform other systems of automated insulin delivery evaluated in outpatient settings in younger age groups: Del Favero reported overnight percentage in target (3.9 to 10.0mmol/l) of 56.0± 22.5% and a mean glucose of 9.6± 2.0 mmol/l in 5 to 9-year olds[184]. 6 to 14-year-old patients enrolled in the RCT by Forlenza et al. achieved a proportion of time with sensor reading in the target range of 76±9% and mean glucose levels of 8.2 ± 0.7mmol/l[257].

The current analysis was limited by the small number of patients included. The estimated sample size from our power calculation for the entire trial was 24 randomised subjects who will be recruited at seven clinical sites. Moreover, a prototype modular closed-loop system was used with the size of the devices as well as connectivity issues being the main drawbacks for outpatient use. Nevertheless, sensor glucose wear (median 94% for both arms) and closed-loop use (median 82% and 83% of time, respectively; U20 and U100) in both groups was high and comparable between study periods. Technological progress may allow further integration of devices and reduce this burden. Detailed feedback from users was collected separately and will be

analysed along with a battery of questionnaires evaluating the psychosocial impact of closed-loop technology.

The strengths of our study included the crossover randomized design that had the benefit of each participant acting as his/her own control. The studies were performed without remote monitoring or close supervision, thereby providing an opportunity to assess the real-world use and applicability of a novel technology. We did not restrict participants' dietary intake, physical activity or geographical movements.

In conclusion, results from this preliminary analysis suggest that hybrid closed-loop insulin delivery using the model predictive control approach is safe and efficacious to maintain day-and night glycaemic control in young children with type 1 diabetes in free daily living. In very young children, insulin dilution to potentially enhance accuracy of insulin delivery does not appear to be of additional benefit using automated insulin delivery and latest generation insulin pump technology. Our findings support research into closed-loop therapy in preschool children, who may greatly benefit from this novel therapeutic approach.

7 Conclusions

7.1 SUMMARY OF RESULTS AND IMPLICATIONS

My thesis comprises a series of five randomised clinical trials evaluating safety, feasibility, and efficacy of closed-loop insulin delivery systems in children and adolescents with type 1 diabetes. Automated closed-loop insulin delivery was mainly applied in free-living conditions during overnight and day-and-night periods in different paediatric populations and age groups including children as young as 1 year of age up to 18-year-old young adults.

In Chapter 3, I presented results from a mechanistic inpatient study. I demonstrated that in spite of differences in sensor accuracy, sensor life did not affect closed-loop performance or safety of its use. We hypothesised that this was related to the robustness of our control algorithm, apparently mitigating against sensor inaccuracy. Given the inconsistency of glucose sensor function over the full lifetime of sensors used at this stage, these findings were encouraging with respect to the home application of the closed-loop systems.

Results from studies in Chapters 4 to 6 showed the benefit of closed-loop insulin delivery during overnight as well as day-and-night applications across all paediatric age groups in free daily living. The unsupervised nature of these home studies allowed a more realistic estimation on actual closed-loop performance in real-life and utility of closed-loop systems. Participants' use of day-and-night closed-loop was high, i.e. over 80% of time, in all three day-and-night studies.

In the overnight study (Chapter 4), I showed the feasibility of extended use of overnight closed-loop systems in home settings over a period of three months in children aged six years and older. Overnight closed-loop significantly improved glycaemic control in terms of increased time spent within normal glucose range, reduced mean glucose and reduced time spent hyperglycaemic. Extended benefits from overnight closed-loop use were seen over the full 24-hour period including reduced burden of hypoglycaemia. This was achieved by greater variability of insulin delivery by closed-loop, with comparable total insulin delivery overnight to sensor-augmented pump therapy.

Using a portable, wireless closed-loop system (Chapter 5), day-and-night application was tested in adolescents with type 1 diabetes within two clinical studies with up to 3-week intervention periods. Results of these studies demonstrated that the use of closed-loop in this challenging population is safe, feasible and efficacious. It increased time when glucose was in the target range (3.9 to 10.0mmol/l) while reducing the mean glucose. These improvements were achieved without increasing the risk of hypoglycaemia. The technology, despite its 'prototype status', was well perceived by adolescents, and might be a promising tool to address glycaemic deterioration usually seen in this population.

In very young children aged one to seven years, preliminary findings from a multi-centre, multinational trial suggest that day-and-night application of closed-loop insulin delivery in free daily living is feasible, safe and efficacious (Chapter 6). Though insulin requirements were low in our participants, dilution of insulin in a closed-loop setting might not be of additional benefit. Given the multiple challenges of diabetes management in this age group, these results are particularly encouraging.

Overall, the research described in my thesis provides key insights into the clinical evaluation of closed-loop technology. My work highlights the great potential of this technology to improve glucose control in children and adolescents with type 1 diabetes and helps build a strong body of evidence for the use of closed-loop in clinical practice.

7.2 STRENGTHS

The closed-loop studies as described in Chapters 4 to 6 were performed without supervision in real world free-living conditions. Evaluations without supervision or close remote monitoring represent the ultimate challenge in providing unequivocal assessment of closed-loop performance under free living conditions. Study participants used closed-loop on their own accord, therefore allowing accurate assessment of usability by the intended user of the technology.

All studies adopted a randomised crossover-design. Statistical plans for all studies were agreed upon by investigators in advance thereby reducing bias, and all data analyses were performed on an intention-to-treat basis.

The studies included in my thesis were among the first outpatient closed-loop studies conducted in children and adolescent with type 1 diabetes. The 3-month overnight study in Chapter 4 is the longest randomised closed-loop home study in children and adolescents to date. The studies summarised in Chapter 5 represent the first trials investigating day-and-night application of closed-loop insulin delivery under free-living conditions in adolescents with type 1 diabetes. In Chapter 6, preliminary results of the first evaluation of closed-loop technology in free daily living in very young children with type 1 diabetes aged one to seven years are presented. With our group's pioneering role in the closed-loop field, we helped pave the way for future real life closed-loop use in children and adolescents with type 1 diabetes.

The Cambridge model-predictive hybrid closed-loop approach was successfully evaluated in children and adolescents with type 1 diabetes across all age groups from 1-year-old toddlers to 18-year-old young adults. Complementary to our group's work on closed-loop use in adults with type 1 diabetes including pregnant women, this supports the application of our closed-loop technology in a wide range of people with type 1 diabetes.

For studies described in Chapters 4 and 5, the comparator was "state-of-the-art" sensor-augmented pump therapy without any degree of glucose responsive regulation of insulin delivery. Closed-loop outperformed the best, most widely available technology in terms of efficacy. Therefore, the studies may facilitate future analyses including health economic evaluations by organisations providing reimbursement guidelines.

7.3 LIMITATIONS

The studies described in this thesis have a number of limitations. The total number of patients studied - five to 25 per trial - is still small. Additionally, closed-loop technology in home settings was mainly assessed in less well controlled diabetes (mean HbA1c ranging from 7.7% to 8.5% in the studied populations). Well controlled patients (HbA1c <7.5%), patients with poorly controlled diabetes, and other groups such as patients with impaired awareness of hypoglycaemia or history of recurrent severe hypoglycaemia, have not been studied so far, though these subgroups might benefit most from automated insulin delivery systems.

All studies included in this thesis focused on 'time in range' as the primary outcome. As baseline hypoglycaemia rates were low in our populations, particularly among teenagers, most studies failed to demonstrate a significant or relevant reduction in mild hypoglycaemia. The trials included were too short for severe hypoglycaemia to occur. Moreover, recurrent severe hypoglycaemia or hypoglycaemia unawareness have been listed as specific exclusion criteria in the trials. Hence, the impact of our closed-loop approach on severe hypoglycaemia remains unclear.

Compared to a fully integrated closed-loop system, our modular prototype systems consisted of more than one device. The number and actual size of study devices that needed to be carried by participants during closed-loop home use were perceived as a burden and major limitation. Although progress was made from the overnight to the day-and-night studies with respect to wireless communication and device size, further integration is certainly needed if consistent use of the technology in long-term studies and outside the research setting is to be sustained.

In all our studies, benefits of closed-loop use during the day remain less pronounced relative to the overnight period. Limiting factors include sub-optimal meal management by participants using our hybrid closed-loop approach (sub-optimal carbohydrate counting, insulin-to-carbohydrate ratios and timing of bolus delivery), pharmacokinetic delays of CGM sensor reliability and subcutaneous rapid acting analogues, and utility restriction due to number and size of devices, particularly during physical activity. In our free-living settings, data on physical activity were not

systematically tracked and not reliably collected, and limited information related to exercise was used to inform the algorithm.

7.4 ONGOING STUDIES

Following these evaluations of closed-loop use in short to medium term studies, larger controlled trials of longer duration were needed for a true assessment of the merits of closed-loop treatment. Since the completion of the studies described in my thesis, together with my supervisor and the Cambridge AP team I have substantially contributed to the setup and conduction of a number of large-scale, multicentre trials which are still ongoing. As no interim or final analysis was performed during my time of studies in Cambridge, I was not able to include results from these trials in my thesis. However, a brief description of the studies is given below. My duties and responsibilities for each of these trials are summarised in Appendix A. Study synopses of the trials can be found in Appendix E, F, G.

7.4.1 APCam11

The APCam11 trial is a 3-month home study evaluating the efficacy, utility and safety of day-and-night hybrid closed-loop in children, adolescents and adults with type 1 diabetes aged six years and older. The comparator is sensor-augmented pump therapy. The study adopts an open-label, multi-centre, randomised, single-period, parallel design. Paediatric and adult sites in the UK and the US were involved. 84 subjects were included. Primary endpoint will be the percentage of time spent with sensor readings in the target glucose range (3.9 to 10.0 mmol/l).

7.4.2 DAN05

In DAN05 trial, we evaluate 6-month use of day-and-night hybrid closed-loop in children and adolescents aged six to 18 years. It is an open-label, multi-centre, randomized, single-period, parallel design study. The comparator is insulin pump therapy alone. Paediatric sites in the UK and in the US will be involved. 130 subjects will be included. Primary endpoint will be HbA1c at the 6-month visit.

7.4.3 CLOuD

In CLOuD we assess 24-month closed-loop use from onset of type 1 diabetes in youth aged 10 to 18 years. The purpose of this study is to test the impact of continued intensive metabolic control using closed-loop insulin delivery after diagnosis on residual beta cell function compared to standard insulin therapy. It adopts an open-label, multicentre, randomised, single-period, parallel design study. Beta-cell function is assessed by mixed-meal-tolerance test. The primary endpoint is the area under the meal stimulated C-peptide curve during a mixed-meal-tolerance test at 12 months post diagnosis. We will aim to recruit 96 subjects from six UK sites within two weeks of diagnosis.

7.5 CONCLUDING REMARKS AND PERSPECTIVE

The research studies described in my thesis highlight the current status and the roadmap for the development of closed-loop insulin delivery systems in children and adolescents with type 1 diabetes. My work provides the evidence that real-world application of closed-loop technology is feasible, safe and effective.

With the approval of the first hybrid closed-loop system (MiniMed 670G pump, Medtronic) by the FDA in September 2016 based on a safety study[99,166] and its market introduction in the USA in early 2017, single hormone closed-loop systems have entered mainstream clinical practice. Further tuning and refinements of the first generation of artificial pancreas systems are expected.

Optimising glucose control during rapid glycaemic fluctuations observed during meal-times and exercise is still challenging for closed-loop systems. The absorption rate of rapid acting insulin analogues is not fast enough which delays onset and prolongs insulin action[258]. These delays are complicated by the inherent 5-15 minutes' lag between glucose levels in the vascular and interstitial space[259,260] . Both factors may damp closed loop performance during daytime. Adjunctive therapies including pramlintide and glucagon-like peptide-1, both delaying gastric emptying and suppressing meal-induced glucagon secretion[163-165], or use of inhaled insulin [261], which acutely increases systemic insulin levels, might mitigate against meal-induced rise in

glucose levels. Ancillary technologies such as site-warming[262] and co-administration of hyaluronidase[263] accelerate absorption and action of rapid-acting insulin analogues. The advent of faster insulin aspart with an earlier onset of appearance, and four-and-a half times greater serum exposure in the first 15-minutes post-injection, or similar ultra-rapid insulin analogues may help address some of these issues.

Integrating inputs from activity trackers such as accelerometers and heart rate monitors into closed-loop systems may further improve closed-loop performance during physical activity[264], but valid and reliable methods to assess exercise duration and modalities, and thus accurately inform control algorithms are still lacking.

Bi-hormonal artificial pancreas may provide additional benefit and reduce hypoglycaemia or mean glucose. Current limitations, however, are increased device complexity and cost compared to single hormone system, unavailability of dual chamber pumps and instability of current glucagon preparation during extended pump use. Developments are ongoing to establish dual-chamber pump devices and stable glucagon preparation for use in bi-hormonal closed-loop systems[265]. Regarding uncertainty of safety and tolerability associated with chronic subcutaneous glucagon, long-term data from human studies are needed.

Smaller and more user-friendly devices may be particularly important for children[170]. At present, modular systems are most commonly used including multiple handheld research devices to receive signals, compute and control insulin delivery in closed-loop prototypes. This complexity might increase risk of communication and connectivity problems. As closed-loop devices may be vulnerable to cybersecurity threats, e.g. interference with wireless protocols and unauthorised data retrieval[266], implementation of secure communications protocols will be needed. The development of fully integrated systems might overcome these issues, and may additionally reduce the burden of devices.

In most closed-loop studies, study participation is limited to pump users only, who are – despite increased popularity of insulin pumps – still not reflective of the overall population of children and adolescents with type 1. This selection bias inevitably

diminishes overall generalisability of study findings with respect to glycaemic control, hypoglycaemia and psychosocial outcomes. In fact, better glycaemic control and reduced patient effort may entice a larger proportion of patients currently managing their diabetes with multiple daily injections without CGM. Future studies need to enrol a sufficient number of pump and CGM naïve patients. Other subgroups including patients with hypoglycaemia unawareness and complications of diabetes should be enrolled so that safety, efficacy and utility analysis can be performed in these. Future research may include identifying sub-populations which may benefit most.

The timeline to application of further closed-loop systems in clinical practice encompasses regulatory approvals with reassuring attitudes of regulatory agencies such as the US Food and Drug Administration. Multinational closed-loop clinical trials and pivotal studies of prolonged 6 to 24-month duration are underway or in preparation including adults and paediatric populations.

Cost-effectiveness evaluation of closed-loop is to be determined to support access and inform reimbursement decision-making. In addition to conventional endpoints such as glycated haemoglobin, quality of life is to be included to assess burden of disease management and hypoglycaemia. A concerted effort is underway to develop measures that more adequately than existing tools capture the extent to which human and psychological factors play a role in the uptake and efficient use of AP systems[267,268].

Altogether, my thesis outlines the feasibility of real-world use of closed-loop applications in children and adolescents with type 1 diabetes. I highlight the progress made so far and the potential of this technology. Future studies by our group and others will further advance the field. Over the past decade, international and national funders provided grants of more 200M USD for closed-loop academic research, and device manufacturers have committed significant resources towards commercialisation. A notable milestone has been achieved with the translation of research into clinical use of algorithm-driven glucose responsive insulin delivery in the form of a hybrid artificial pancreas system. Further success and wider availability of this technology will largely be dependent upon further regulatory approvals and upon ensuring that infrastructures and support are in place for healthcare professionals

providing clinical care, including training resources, and that structured education is provided for patients.

At present, industry-driven and academic research teams working on closed-loop technology are occupied with phase 3 trials or earlier, suggesting that other commercially viable products will not emerge from these projects for some time. In the meantime, a small but vocal community of people rallying behind the mantra #WeAreNotWaiting are designing and operating their own do-it-yourself artificial pancreas systems (DIY APS) by reverse-engineering standard continuous glucose monitors and insulin pumps[269]. Traditional regulatory approval pathways for medical devices are bypassed. The DIY APS community is an example of open-source collaboration providing more advanced (although not fully tested), customisable, and modular functionality, which pushes and stimulates the whole field in terms of system and algorithm design.

Apart from fully integrated hybrid closed-loop systems developed by a single manufacturer combining insulin pump, CGM and control algorithm in a single device (e.g. the already available Medtronic 670G system), modular systems will sooner or later enter the market utilising open-protocol-based control through different commercially developed devices and software. Standard insulin pumps and CGM devices from different manufacturers will seamlessly and securely connect with mobile phones or other portable devices (e.g., by using Bluetooth technology) running either a DIY algorithm application or a mobile medical application fully approved for algorithm-driven insulin delivery.

The coming decade will be marked by more and more advanced closed-loop insulin delivery systems which will become the standard of care for people with type 1 diabetes including children and adolescents. More biological technologies such as the bioartificial pancreas and ‘smart’ insulin strategies (including encapsulated islets, glucose- responsive polymer encapsulation of insulin and molecular modification of insulin) will follow but will take considerably longer to demonstrate safety and efficacy in humans[270,271]. Alongside with interventions to preserve b-cell function, artificial

pancreas approaches will serve as a solid bridge to a cure for type 1 diabetes until stem-cell therapy or other curative interventions become available.

8 Appendices

8.1 APPENDIX A: STUDY SPECIFIC RESPONSIBILITIES

CHAPTER 2 – APCAM09 STUDY

1. Development of study design and protocol
2. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
3. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
4. Recruitment of participants
5. Training participants on the use of study insulin pump and CGM devices
6. Conducting overnight closed-loop studies including venous sampling for plasma glucose at the clinical research facility.
7. Development of statistical analysis plan
8. Data and statistical analysis
9. Writing manuscript and manuscript submission
10. Presentation of results at the 9th International Conference on Advanced Technologies & Treatments for Diabetes in Milan, Italy, in 2016.

CHAPTER 3 – APCAM08 STUDY

1. Development of study design and protocol
2. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
3. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
4. Recruitment of participants
5. Training participants on the use of study insulin pump and CGM devices
6. Conducting closed-loop clinical studies in Cambridge
7. Training and supervising collaborators in Leeds and at UCLH London on study conduct and use of closed-loop system

8. Providing report and update to the *Data and Safety Monitoring Board*
9. Development of statistical analysis plan
10. Data and statistical analysis
11. Writing manuscript

CHAPTER 4 – DAN04 STUDIES

1. Development of study designs and protocols
2. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
3. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
4. Recruitment of participants
5. Training participants on the use of study insulin pump and CGM devices
6. Conducting closed-loop clinical studies in Cambridge
7. Providing reports and update to the *Data and Safety Monitoring Board*
8. Development of statistical analysis plans
9. Data and statistical analyses
10. Writing manuscripts and manuscript submissions
11. Presentation of results at the ADA (75th scientific sessions) in Boston, USA, in 2015 (Study 1), at the 9th International Conference on Advanced Technologies & Treatments for Diabetes in Milan, Italy, in 2016 (Study 2), and at the 42nd Annual Conference of the International Society for Pediatric and Adolescent Diabetes in Valencia, Spain, in 2016 (pooled analysis Study 1 & Study 2)

CHAPTER 5 - KIDSAP01 STUDY

1. Preparation of documents for the research proposal submitted to the European Commission's Horizon2020 programme
2. Development of study design and protocol

3. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
4. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
5. Recruitment of participants
6. Training participants on the use of study insulin pump and CGM devices
7. Conducting closed-loop clinical studies in Cambridge
8. Training and supervising collaborators in the UK, Luxembourg, Germany and Austria on study conduct and use of closed-loop system
9. Providing report and update to the *Data and Safety Monitoring Board*
10. Development of statistical analysis plan
11. Data and statistical analysis
12. Writing manuscript

CHAPTER 6

APCAM11 STUDY

1. Development of study design and protocol
2. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
3. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
4. Recruitment of participants
5. Training participants on the use of study insulin pump and CGM devices
6. Conducting closed-loop clinical studies in Cambridge
7. Training and supervising collaborators in Leeds and at Edinburgh on study conduct and use of closed-loop system
8. Providing report and update to the *Data and Safety Monitoring Board*
9. Writing manuscript

DAN05 STUDY:

1. Development of study design and protocol
2. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
3. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
4. Recruitment of participants
5. Training participants on the use of study insulin pump and CGM devices
6. Conducting closed-loop clinical studies in Cambridge
7. Providing report and update to the *Data and Safety Monitoring Board*

CLOUD STUDY

1. Development of study design and protocol
2. Preparation of documents for regulatory approvals (including consent/assent forms, patient information sheets, etc)
3. Attending the Research Ethics Committee (REC) meeting and follow up with the REC regarding any open queries
4. Recruitment of participants
5. Training participants on the use of study insulin pump and CGM devices
6. Conducting closed-loop clinical studies in Cambridge
7. Training and supervising collaborators in Liverpool, Nottingham, Oxford and Southampton on study conduct and use of closed-loop system
8. Providing report and update to the *Data and Safety Monitoring Board*

8.2 APPENDIX B: ASSISTANCE, COLLABORATION AND FUNDING

CHAPTER3– APCAM09

The following investigators from University of Cambridge contributed to the work. Janet M. Allen, Research Nurse (RN), Dr Malgorzata E. Wilinska, Dr Yue Ruan, Dr Hood Thabit, Dr Carlo L. Acerini, Prof David B. Dunger, and Dr Roman Hovorka. Prof Peter C Hindmarsh (University College, London, UK) and Dr Vijith Puthi (Peterborough District Hospital, Peterborough, UK) helped in identifying potential recruits. Staff at the Addenbrooke's Wellcome Trust Clinical Research Facility provided support during overnight visits. Josephine Hayes (University of Cambridge) provided administrative support. Karen Whitehead (University of Cambridge) provided laboratory support. Sara Hartnell (Addenbrooke's Hospital) supported study pump and CGM training. Jino Han (Medtronic) and Barry Keenan (Medtronic, presently Alfred Mann Foundation) supported the development of the Amber system. The Core Biochemical Assay Laboratory (Keith Burling), University of Cambridge, the Institute of Life Sciences (Gareth Dunseath), Swansea University, carried out biochemical analyses.

Funding: This work was funded by the JDRF (#22-2011-668). Additional support for the Artificial Pancreas work by National Institute for Health Research Cambridge Biomedical Research Centre and Wellcome Strategic Award (100574/Z/12/Z).

CHAPTER 4 – APCAM08

The following investigators from the APCam Consortium contributed to the work: University of Cambridge, Cambridge, UK – Dr Carlo L Acerini, Janet M Allen RN, Prof David B Dunger, Dr Daniela Elleri, Samantha J Goode, Josephine Hayes, Dr Roman Hovorka, Dr Helen R Murphy, Dr Zoe A Stewart, Dr Hood Thabit, Dr Malgorzata E Wilinska; Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK - Sara Hartnell BSc; Leeds Children's Hospital, Leeds, UK – Dr Fiona M Campbell MD, Jane Exall RN, Dr James Yong; Institute of Child Health, University College London Hospital, London, UK – Prof Peter C Hindmarsh, Jennifer Pichierri MSc; Jaeb Center, Tampa, FL, USA – Peiyao Cheng MPH, Dr Craig Kollman, John Lum MS, Nelly Njeru BA, Judy Sibayan MPH; Leicester University Hospitals NHS Trust, Leicester, UK – Jasdip Mangat MSc.

Funding: Supported by grant from the JDRF (22-2011-668), with additional support for the artificial pancreas work from a National Institute for Health Research Cambridge Biomedical Research Centre and Wellcome Strategic Award (100574/Z/12/Z).

CHAPTER5– DAN04 STUDIES

The following investigators contributed to the work and served as co-authors of the published manuscript: University of Cambridge, UK: Janet M. Allen RN, Dr Malgorzata E. Wilinska, Dr Hood Thabit, Dr Zoe Stewart, Dr Carlo L. Acerini, Prof David B. Dunger, Dr Roman Hovora; Jaeb Center, Tampa, FL – Peiyao Cheng MPH, Dr Craig Kollman. I also thank the staff at the Addenbrooke's Wellcome Trust Clinical Research Facility for their support. In addition, I thank Jasdip Mangat and John Lum (Jaeb Center) for their support of the development and validation of the closed-loop system; Josephine Hayes (University of Cambridge) for administrative support; Karen Whitehead (University of Cambridge) for laboratory support; the staff at Addenbrooke's Hospital for their support; Sara Hartnell and Sonja Slegtenhorst for study pump training; and The Core Biochemical Assay Laboratory (Keith Burling), University of Cambridge, and the Institute of Life Sciences (Gareth Dunseath), Swansea University, for carrying out the biochemical analyses, Prof Peter Hindmarsh (University College, London, U.K.) for help in identifying potential recruits, and Prof John Pickup (Guy's Hospital, London, U.K.), Prof Irl Hirsch (University of Washington School of Medicine), and Prof Howard Wolpert (Joslin Diabetes Center) for serving on the data safety and monitoring board.

Funding: This study received support from the National Institute of Diabetes and Digestive and Kidney Diseases (1R01-DK-085621-01). Additional support for the artificial pancreas work was received from JDRF, National Institute for Health Research Cambridge Biomedical Research Centre, and the Wellcome Strategic Award (100574/Z/12/Z).

CHAPTER 6 – KIDSAP01

The following investigators from the KidsAP Consortium contributed to the work: University of Cambridge, Cambridge, UK: Dr Carlo L Acerini, Janet M Allen RN, Nicole Barber, Josephine Hayes, Dr Roman Hovorka, Dr Malgorzata E Wilinska; Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK: Sara Hartnell, Sonja Slegtenhorst; Medical University of Graz, Graz, Austria: Dr Elke Fröhlich-Reiterer; Medical University of Innsbruck, Innsbruck, Austria: Dr Sabine Hofer; Jaeb Centre for Health Research, Tampa, FL, USA: Nathan Cohen, Dr Craig Kollman; University of Leeds, Leeds, UK: Dr Fiona Campbell; University of Leipzig, Leipzig, Germany: Dr Thomas Kapellen; University of Luxembourg, Luxembourg: Dr Carine de Beaufort; Medical University of Vienna, Vienna, Austria: Prof Birgit Rami-Merhar

Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 731560. The Jaeb Center for Health Research is funded by JDRF under the grant 3-SRA-2016-297-M-N.

8.3 APPENDIX C: ACHIEVEMENTS

Awards:

American Diabetes Association Young Investigator Travel Grant Award 2015

ISPAD Young Investigator Award 2018

Publications directly linked to work described in my thesis:

CHAPTER 2

- Tauschmann M, Hovorka R. Insulin pump therapy in youth with type 1 diabetes: toward closed-loop systems. Expert Opin Drug Deliv. 2014 Jun;11(6):943-55.
- Tauschmann M, Hovorka R. 2016. Glucose monitoring and insulin pump therapy in the management of children and adolescents with type 1 diabetes. In: Scaramuzza A et al. eds. Research into childhood-onset diabetes. Cham: Springer International Publishing Switzerland
- Tauschmann M, Hovorka R. Insulin delivery and nocturnal glucose control in children and adolescents with type 1 diabetes. Expert Opin Drug Deliv. 2017 Dec;14(12):1367-1377.
- Tauschmann M, Hovorka R. Technology in the management of type 1 diabetes – present status and future prospects. Nat Rev Endocrinol. 2018 Aug;14(8):464-475.

CHAPTER 3

- Tauschmann M, Allen JM, Wilinska ME, Ruan Y, Thabit H, Acerini CL, Dunger DB, Hovorka R. Sensor life and overnight closed-loop: A randomized clinical trial. J Diabetes Sci Technol. 2017 May;11(3):513-521.

CHAPTER 4

- Thabit H*, Tauschmann M*, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, Acerini CL, Dellweg S, Benesch C, Heinemann L, Mader JK, Holzer M, Kojzar H, Exall J, Yong J, Pichierri J, Barnard KD, Kollman C, Cheng P, Hindmarsh PC, Campbell FM, Arnolds S, Pieber TR, Evans ML, Dunger DB, Hovorka R; APCam Consortium; AP@home Consortium. Home use of an artificial beta cell in Type 1 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2129-40.
  ** Drs. Thabit and Tauschmann contributed equally to this article.*

CHAPTER 5

- Tauschmann M, Allen JM, Wilinska ME, Thabit H, Stewart Z, Cheng P, Kollman C, Acerini CL, Dunger DB, Hovorka R. Day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes: A free-living, randomized clinical trial. Diabetes Care. 2016 Jul; 39(7):1168-74.

- Tauschmann M, Allen JM, Wilinska ME, Thabit H, Acerini CL, Dunger DB, Hovorka R. Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with type 1 diabetes: a 3-week, free-living, randomized cross-over trial. Diabetes Care. 2016 Nov;39(11):2019-2025.

CHAPTER 6

- Tauschmann M, Allen JM, Slegtenhorst S, Barber N, Wilinska ME, Ruan Y, Cohen N, Kollman C, Acerini CL, De Beaufort C, Campbell F, Fröhlich-Reiterer EE, Hofer S, Kapellen T, Rami-Merhar B, Hovorka R. KidsAP - Home use of day-and-night hybrid closed-loop insulin delivery in very young children with type 1 diabetes: a 3-week, randomized pilot trial. *[Manuscript in preparation for submission to peer-reviewed journal]*

Other publications:

- Elleri D, Allen JM, Tauschmann M, El-Khairi R, Benitez-Aguirre P, Acerini CL, Dunger DB, Hovorka R. Feasibility of overnight closed-loop therapy in young children with type 1 diabetes aged 3-6 years: comparison between diluted and standard insulin strength. BMJ Open Diabetes Res Care. 2014 Dec 11;2(1):e000040.

- Ruan Y, Elleri D, Allen JM, Tauschmann M, Wilinska ME, Dunger DB, Hovorka R. Pharmacokinetics of diluted (U20) insulin aspart compared with standard (U100) in children aged 3-6 years with type 1 diabetes during closed-loop insulin delivery: a randomised clinical trial. Diabetologia. 2015 Apr;58(4):687-90.

- Tauschmann M, Thabit H, Leelarathna L, Elleri D, Allen JM, Lubina-Solomon A, Stadler M, Walkinshaw E, Iqbal A, Choudhary P, Wilinska ME, Heller SR, Amiel SA, Evans ML, Dunger DB, Hovorka R. Factors associated with glycemic control during free-living overnight closed-loop insulin delivery in children and adults with type 1 diabetes. J Diabetes Sci Technol. 2015 Oct 7;9(6):1346-7.

- Farrington C, Allen J, Tauschmann M, Randell T, Trevelyan N, Hovorka R. Factors affecting recruitment of participants for studies of diabetes technology in newly diagnosed youth with type 1 diabetes: A qualitative focus group study with parents and children. Diabetes Technol Ther. 2016 Sep;18(9):568-73.

- Bally L, Thabit H, Kojzar H, Mader JK, Qerimi-Hyseni J, Hartnell S, Tauschmann M, Allen JM, Wilinska ME, Pieber TR, Evans ML, Hovorka R. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol. 2017 Apr;5(4):261-270.

- Barnard KD, Wysocki T, Ully V, Mader JK, Pieber TR, Thabit H, Tauschmann M, Leelarathna L, Hartnell S, Acerini CL, Wilinska ME, Dellweg S, Benesch C, Arnolds S, Holzer M, Kojzar H, Campbell F, Yong J, Pichierri J, Hindmarsh P, Heinemann L, Evans ML, Hovorka R. Closing the loop in adults, children and adolescents with suboptimally controlled type 1 diabetes under free living conditions: A psychosocial substudy. J Diabetes Sci Technol. 2017 Nov;11(6):1080-1088.

- Ruan Y, Thabit H, Leelarathna L, Hartnell S, Wilinska ME, Tauschmann M, Dellweg S, Benesch C, Mader JK, Holzer M, Kojzar H, Evans ML, Pieber TR, Arnolds S, Hovorka R; AP@home consortium. Faster insulin action is associated with improved glycaemic outcomes during closed-loop insulin delivery and sensor-augmented pump therapy in adults with type 1 diabetes. Diabetes Obes Metab. 2017 Oct;19(10):1485-1489.

- Bally L, Thabit H, Tauschmann M, Allen JM, Hartnell S, Wilinska ME, Exall J, Huegel V, Sibayan J, Borgman S, Cheng P, Blackburn M, Lawton J, Elleri D, Leelarathna L, Acerini CL, Campbell F, Shah VN, Criego A, Evans ML, Dunger DB, Kollman C, Bergenstal RM, Hovorka R. Assessing the effectiveness of a 3-month day-and-night home closed-loop control combined with pump suspend feature compared with sensor-augmented pump therapy in youths and adults with suboptimally controlled type 1 diabetes: a randomised parallel study protocol. BMJ Open. 2017 Jul 13;7(7):e016738.

- Lawton J, Blackburn M, Allen J, Campbell F, Elleri D, Leelarathna L, Rankin D, Tauschmann M, Thabit H, Hovorka R. Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. BMC Endocr Disord. 2018 Feb 20;18(1):12.

- Ruan Y, Bally L, Thabit H, Leelarathna L, Hartnell S, Tauschmann M, Wilinska ME, Evans ML, Mader JK, Kojzar H, Dellweg S, Benesch C, Arnolds S, Pieber TR, Hovorka R. Hypoglycaemia Incidence and Recovery During Home Use of Hybrid Closed-Loop Insulin Delivery in Adults with Type 1 Diabetes. Diabetes Obes Metab. 2018 Mar 25. doi: 10.1111/dom.13304. [Epub ahead of print]

- Bekiari E, Kitsios K, Thabit H, Tauschmann M, Athanasiadou E, Karagiannis T, Haidich AB, Hovorka R, Tsapas A. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ. 2018 Apr 18;361:k1310

- Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, Maahs DM. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and

management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2018 Oct;19 Suppl 27:178-192.

- Sherr JL, Tauschmann M, Battelino T, de Bock M, Forlenza G, Roman R, Hood KK, Maahs DM. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes technologies. Pediatr Diabetes. 2018 Oct;19 Suppl 27:302-325.

- DeSalvo DJ, Miller KM, Hermann JM, Maahs DM, Hofer SE, Clements MA, Lilienthal E, Sherr JL, Tauschmann M, Holl RW; T1D Exchange and DPV registries. Continuous Glucose Monitoring (CGM) and Glycemic Control Among Youth with Type 1 Diabetes (T1D): International comparison from the T1D Exchange and DPV Initiative. Pediatr Diabetes. 2018 Nov;19(7):1271-1275.

- Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, Ruan Y, Sibayan J, Kollman C, Cheng P, Beck RW, Acerini CL, Evans ML, Dunger DB, Elleri D, Campbell F, Bergenstal RM, Criego A, Shah VN, Leelarathna L, Hovorka R; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet. 2018 Oct 13;392(10155):1321-1329.

Presentations at scientific meetings (international):

- Tauschmann M, Allen JH, Slegtenhorst S, Barber N, Wilinska ME, Ruan Y, Cohen N, Kollman C, Acerini CL, De Beaufort C, Campbell F, Fröhlich-Reiterer EE, Hofer S, Kapellen T, Rami-Merhar B, Hovorka R on behalf of KidsAP Consortium. KiDSAP - Home use of the Artificial Pancreas in very young children with type 1 diabetes: The pilot study. 11th International Conference on Advanced Technologies & Treatments for Diabetes; 14-17 Feb 2018; Vienna, Austria [poster]

- Tauschmann M, Allen JH, Slegtenhorst S, Wilinska ME, Barber N, Thorpe A, Scott EM, Northam L, Lawton J, Farrington C, Roze S, Cohen N, Kollman C, Dunger DB, Acerini CL, Ghatak A, Randell T, Besser R, Trevelyan N, and Hovorka R. Closed-loop from onset in childhood type-1 diabetes (CLOuD): A randomised controlled trial to assess the effect of closed-loop insulin delivery on residual beta-cell function. 11th International Conference on Advanced Technologies & Treatments for Diabetes; 14-17 Feb 2018; Vienna, Austria [poster]

- Tauschmann M. Update on Artificial Pancreas Research in Cambridge, 43th Annual Conference of the International Society for Pediatric and Adolescent Diabetes; 18-21 Oct 2017, Innsbruck, Austria [oral presentation]

- Tauschmann M, Allen JH, Wilinska ME, Thabit H, Acerini CL, Dunger DB, Hovorka R. Unsupervised home use of day-and-night closed-loop insulin delivery: A pooled analysis of randomized controlled studies in adolescents with type 1 diabetes. the 42nd Annual Conference of the International Society for Pediatric and Adolescent Diabetes; 26-29 Oct 2016, Valencia, Spain [poster presentation]

- Tauschmann M, Allen JH, Wilinska ME, Thabit H, Acerini CL, Dunger DB, Hovorka R. Home us of day-and-night closed-loop insulin delivery in adolescents with type 1 diabetes: A randomised clinical trial. 9th International Conference on Advanced Technologies & Treatments for Diabetes; 03-06 Feb 2016; Milan, Italy [oral presentation]

- Tauschmann M, Allen JH, Wilinska ME, Thabit H, Acerini CL, Dunger DB, Hovorka R. Sensor operation duration does not affect overnight closed loop efficacy: A randomised clinical trial. 9th International Conference on Advanced Technologies & Treatments for Diabetes; 18-21 Feb 2016; Milan, Italy [poster]

- Tauschmann M, Allen JM, Wilinska ME, Thabit H, Stewart Z, Cheng P, Kollman C, Acerini CL, Dunger DB, Hovorka R. Day and Night Closed Loop Insulin Delivery in Young People with Type 1 Diabetes: A Free-Living, Randomised Clinical Trial. ADA 75th scientific sessions; 05-09 Jun 2015; Boston, MA, US [oral presentation, Young Investigator Travel Grant Award]

- Tauschmann M, Thabit H, Elleri D, Lubina-Solomon A, Stadler M, Heller SR, Amiel SA, Evans ML , Dunger DB, Hovorka R. Performance during unsupervised closed loop in children and adults with type 1 diabetes: What makes the

difference?; 8th International Conference on Advanced Technologies & Treatments for Diabetes; 18-21 Feb 2015; Paris, France [poster]

- Tauschmann M, Thabit H, Leelarathna L, Elleri D, Allen JM, Lubina-Solomon A, Stadler M, Walkinshaw E, Iqbal A, Choudhary P, Heller SR, Amiel SA, Evans ML , Dunger DB, Hovorka R. Factors influencing overnight closed loop performance during free living in children and adults with type 1 diabetes. Diabetes Technology Meeting; 06-08 Nov 2014, Bethesda, Maryland, US [Poster]

- Tauschmann M, Thabit H, Leelarathna L, Elleri D, Allen JM, Lubina-Solomon A, Stadler M, Walkinshaw E, Iqbal A, Choudhary P, Heller SR, Amiel SA, Evans ML , Dunger DB, Hovorka R. Factors predictive of overnight closed loop performance during free living in children and adults with type 1 diabetes. 50th EASD Annual Meeting; 15-19 Sep 2014; Vienna, Austria [Poster]

8.4 APPENDIX D: DAN04 SUPPLEMENTARY APPENDIX

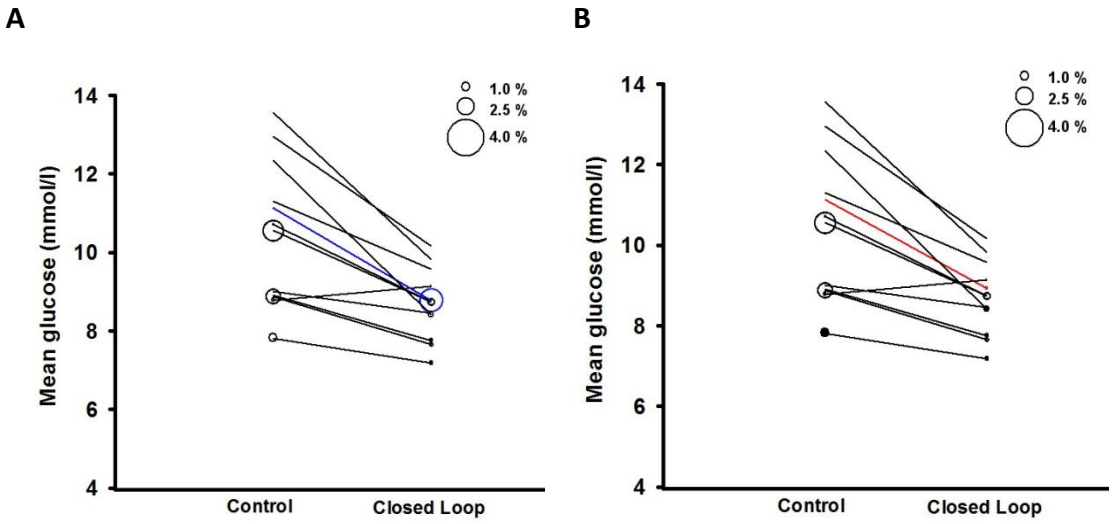

Figure 8.1. Individual values of mean sensor glucose values during closed-loop and control periods. The size of bubble indicates the proportion of time spent with low glucose below 2.8mmol/l. Panel A: Blue line indicates Subject 21 when mean glucose and percentage of time spent below 2.8 mmol/l are calculated using original data. Panel B: Red line indicates Subject 21 when mean glucose and percentage of time spent below 2.8 mmol/l are calculated based on cleaned data with excluded sensor under-reading (erroneously low glucose sensor values).

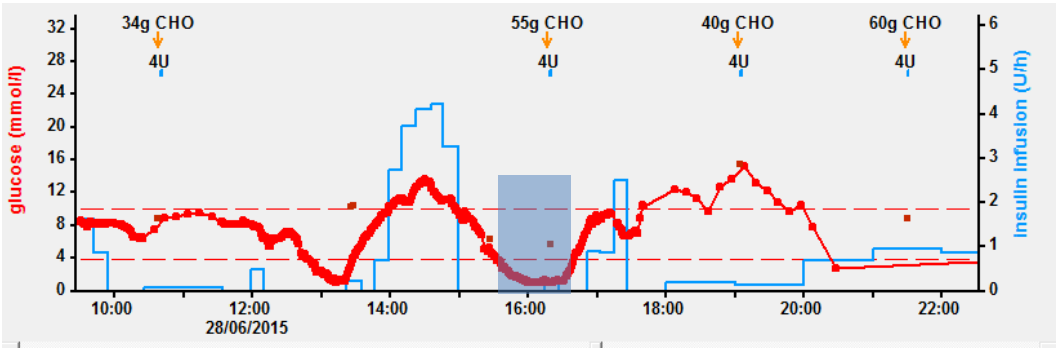

Figure 8.2. Subject 21, 28 June 2015: Sensor under-reading starting at 15:32 and ending at 16:40 (denoted by blue shaded area). Discrepancy noted between capillary blood glucose measurements (dark red squares) and sensor glucose levels (light red line) red during this period (at 16:19 capillary glucose 5.7 mmol/l vs sensor glucose 1.0 mmol/l). A period of 01:08 hours was excluded during exploratory analysis.

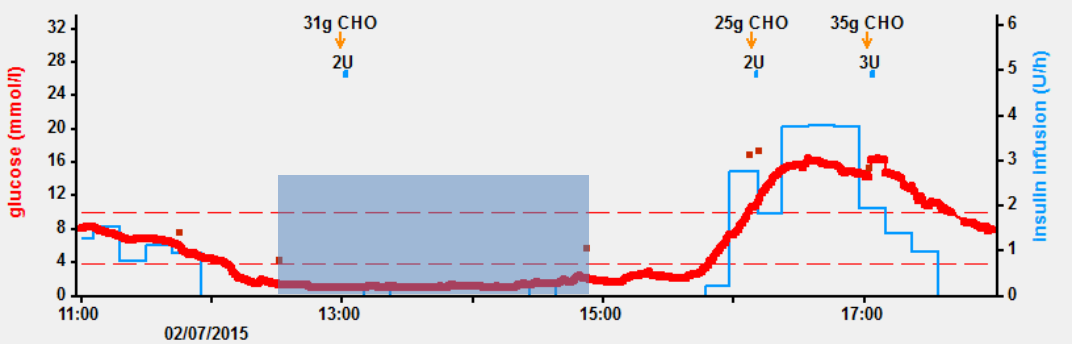

Figure 8.3. Subject 21, 02 July 2015: Sensor under-reading starting at 12:31 and ending at 14:52 (denoted by blue shaded area). Discrepancy noted between capillary blood glucose measurements (dark red squares) and sensor glucose levels (light red line) during this period (at 12:31 capillary glucose 4.4mmol/l vs. sensor glucose 1.4 mmol/l; at 14.52 capillary glucose 5.8 mmol/l vs. sensor glucose 2.2 mmol/l). A period of 02:21 hours was excluded during exploratory analysis.

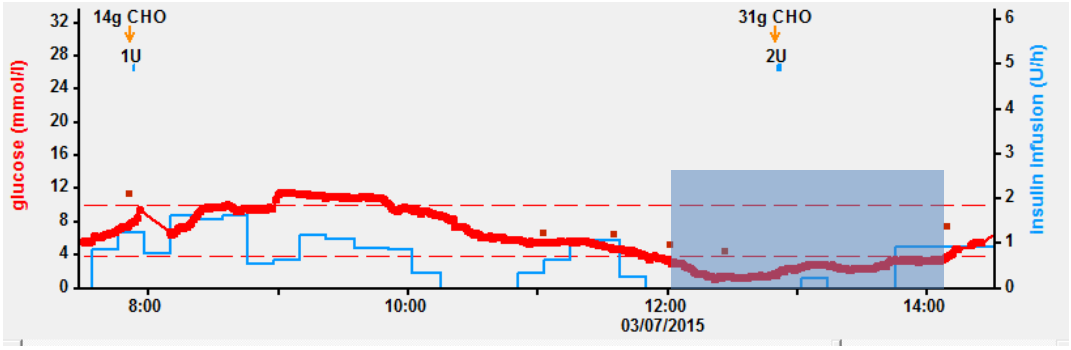

Figure 8.4. Subject 21, 03 July 2015: Sensor under-reading starting at 12:01 and ending at 14:09 (denoted by blue shaded area). Discrepancy noted between capillary blood glucose measurements (dark red squares) and sensor glucose levels (light red line) during this period (at 12:01 capillary glucose 5.3 mmol/l vs. sensor glucose 3.2 mmol/l; at 12.26 capillary glucose 4.4 mmol/l vs. sensor glucose 1.3 mmol/l; at 14.09 capillary glucose 7.5 mmol/l vs. sensor glucose 3.8 mmol/l). A period of 02:08 hours was excluded during exploratory analysis.

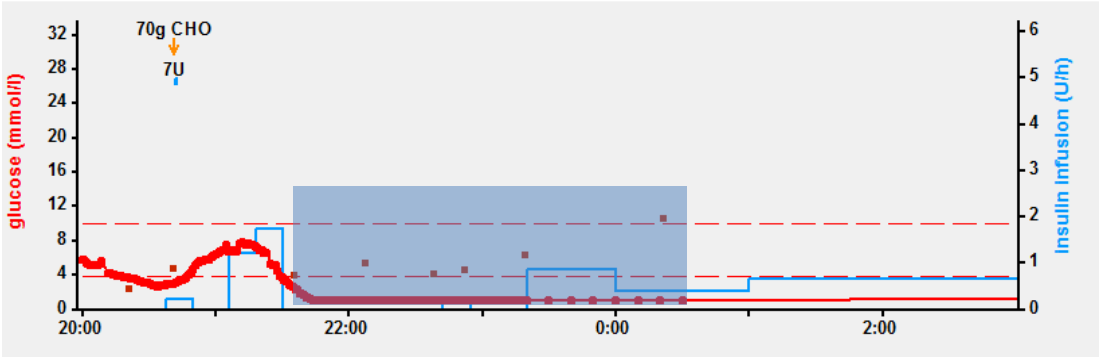

Figure 85. Subject 21, 05 July 2015: Sensor under-reading starting at 21:35 and ending at 00:30 (denoted by blue shaded area). Discrepancy noted between capillary blood glucose measurements (dark red squares) and sensor glucose levels (light red line) during this period (at 21.35 capillary glucose 4.0 mmol/l vs. sensor glucose 2.5 mmol/l; at 22:07 capillary glucose 5.4 mmol/l vs. sensor glucose 1.0 mmol/l; at 22:38 capillary glucose 4.1 mmol/l vs. sensor glucose 1.0mmol/l; at 22:52 capillary glucose 4.6 mmol/l vs sensor glucose 1.0 mmol/l; at 23:19 capillary glucose 6.7 mmol/l vs. sensor glucose 1.1 mmol/l; at 00:21 capillary glucose 10.7 mmol/l vs sensor glucose 1.1 mmol/l). A period of 02:55 hours was excluded during exploratory analysis.

8.5 APPENDIX E: APCAM11 STUDY SYNOPSIS

Title	Day and night closed-loop with pump suspend feature in sub-optimally controlled type 1 diabetes under free living conditions (APCam11)
Purpose of clinical trial	To determine whether day and night automated closed-loop glucose control combined with pump suspend feature will improve glucose control as measured by CGM time in range and reduce the burden of hypoglycaemia compared to sensor augmented insulin pump therapy.
Study objectives	1. EFFICACY: The objective is to assess efficacy of day and night automated closed-loop glucose control combined with pump suspend feature in maintaining CGM glucose levels within the target range from 3.9 to 10 mmol/l (70 to 180mg/dl), as compared to sensor augmented insulin pump therapy. 2. SAFETY: The objective is to evaluate the safety of day and night automated closed-loop glucose control combined with pump suspend feature, in terms of episodes of severe hypoglycaemia and other adverse events. 3. UTILITY: The objective is to determine the frequency and duration of the use of the automated closed-loop system. 4. PSYCHOSOCIAL: Subjects' and family members' perception in terms of life-style change, diabetes management and fear of hypoglycaemia will be assessed using validated questionnaires and semi-structured qualitative interviews.
Study design	An open-label, multi-centre, multi-national, randomised, single-period, parallel group study, contrasting day and night automated closed-loop glucose control combined with pump suspend feature with sensor augmented insulin pump therapy.
Primary endpoint	Time spent in the target glucose range (3.9 to 10mmol/l) (70 to 180mg/dl)

Secondary endpoint(s)	• Time spent below target glucose (3.9mmol/l)(70mg/dl) • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) • HbA1c levels at 12 weeks • Average, standard deviation, and coefficient of variation of glucose levels • Time with glucose levels < 3.5 mmol/l (63 mg/dl) and <2.8 mmol/l (50 mg/dl) • Time with glucose levels in significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) • Total, basal and bolus insulin dose • AUC of glucose below 3.5mmol/l (63mg/dl) • Number of pump suspend events (applicable to intervention arm) • Change in body weight from screening to end of study
Safety evaluation	Frequency of severe hypoglycaemic episodes. Frequency of severe hyperglycaemia (>16.7 mmol/l)(>300mg/dl) with significant ketosis (plasma ketones >0.6mmol/l) and nature and severity of other adverse events.
Utility evaluation	Assessment of the frequency and duration of use of the closed-loop system.
Psychosocial evaluation	Evaluation of subjects' response in terms of life-style change, daily diabetes management, fear of hypoglycaemia, and cognitive functions.
Sample size	84 participants randomised (42 youth and 42 adults). Each centre will aim to recruit between 05 and 20 participants
Summary of eligibility criteria	**Key inclusion criteria:** • The subject is at least 6 years or older with equal proportion of youth (6 to 21 years) and adults (22 years and older) • The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative • The subject/carer will have been an insulin pump user for at least 3 months, with good

knowledge of insulin self-adjustment as judged by the investigator
- The subject is treated with one of the U-100 rapid acting insulin analogues only (insulin Aspart, Lispro but not Glulisine)
- The subject/carer is willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements taken every day
- HbA1c ≥ 7.5% (58.5mmol/mol) and ≤ 10 % (86mmol/mol) based on analysis from local laboratory with equal proportion of subjects above and below HbA1c 8.5% (69mmol/mol)
- The subject is literate in English
- The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance

Key exclusion criteria:

- Non-type 1 diabetes mellitus including those secondary to chronic disease
- Subject is using real-time CGM on regular basis
- Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
- Untreated coeliac disease, adrenal insufficiency or hypothyroidism
- Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc.
- Known or suspected allergy against insulin
- Subjects with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator
- Total daily insulin dose ≥ 2 IU/kg/day
- Total daily insulin dose < 15 IU/day
- Pregnancy, planned pregnancy, or breast feeding
- Severe visual impairment
- Severe hearing impairment

	• Significantly reduced hypoglycaemia awareness in subjects 18 year and older (Gold score > 4) • Any episode of severe hypoglycaemia within the last 6 months • Subjects using implanted internal pace-maker • Random C-peptide > 100pmol/l with concomitant blood glucose >4 mmol/l (72 mg/dl) • Regular use of acetaminophen
Maximum duration of study for a subject	18 weeks
Recruitment	The subjects will be recruited through the paediatric and adult diabetes outpatient clinics at each centre.
Consent	Written consent/assent will be obtained from participants and/or guardians according to REC/IRB requirements.
Screening assessment	Eligible participants will undergo a screening evaluation where blood samples for full blood count, renal, liver, thyroid function and anti-transglutaminase antibodies with IgA levels will be taken (if not done in the previous 3 months). Random C-peptide, glucose and HbA1c will also be measured, and a urine pregnancy test in females of child-bearing potential. Questionnaires investigating participants' quality of life, psychosocial functioning and response to their current treatment will be distributed.
Study Training	Training sessions on the use of study CGM, insulin pump (and closed-loop system for those randomised to the intervention group) will be provided by the research team. Training session on the use of real-time CGM and on how to interpret real-time and retrospective stored data will be provided to all subjects/carers using written material.
Run-in Period	During a 4-week run-in period, subjects will use study CGM and insulin pump. The research team will contact subject once weekly during the run-in period,

	and subjects will also be able to contact the research team for support and treatment optimisation as necessary. For compliance and to assess the ability of the subject to use the CGM and study pump safely, at least 12 days of CGM data need to be recorded and safe use of study insulin pump demonstrated during the last 14 days of run-in period.
Competency assessment	Competency on the use of study insulin pump and study CGM will be evaluated using a competency assessment tool developed by the research team. Further training may be delivered as required.
Randomisation	Eligible subjects will be randomised using randomisation software to the use of real-time CGM and pump suspend feature combined with day and night closed-loop or to sensor augmented insulin pump therapy.
1. Automated day and night closed-loop insulin delivery (intervention arm) combined with pump suspend feature (interventional arm)	At the start, a blood sample will be taken for the measurement of HbA1c and a urine pregnancy test in females of child-bearing potential. A subset of participants will be interviewed to enable their historical diabetes management practices, everyday work and family lives, and their initial expectations of using closed-loop technology to be captured and explored in-depth. Subjects will be admitted to the clinical facility on Day 1. Training on the use of closed-loop and pump suspend feature will be provided by the research team. During the next 2-4 hours patient will operate the system under the supervision of the clinical team. Competency on the use of closed-loop system will be evaluated. Subjects will use closed-loop and pump suspend feature for 12 weeks.
2. Sensor augmented insulin pump therapy (control arm)	A blood sample will be taken for the measurement of HbA1c and a urine pregnancy test in females of child-bearing potential. Subjects will use sensor augmented insulin pump therapy without pump suspend feature for 12 weeks.

End of study assessments	A blood sample will be taken for measurement of HbA1c. - Validated questionnaires evaluating the impact of the devices employed on life change, diabetes management will be completed. - Follow-up interviews will be undertaken with the subset of participants/family members at the end of the closed-loop intervention.

8.6 APPENDIX F: CLOUD STUDY SYNOPSIS

Short title	Effect of closed-loop from onset on progression of T1D (CLOuD)
Purpose of clinical trial	To determine whether continued intensive metabolic control using closed-loop insulin delivery (CL) following diagnosis of type 1 diabetes can preserve C-peptide secretion as a marker of residual beta cell function compared to standard multiple daily injections (MDI) therapy

Study objectives	<u>Primary objective:</u>
	• To assess residual C-peptide secretion 12 months after diagnosis of type 1 diabetes in participants receiving either CL insulin delivery or standard MDI therapy
	<u>Secondary Objectives:</u>
	• Biochemical:
	  ○ To compare effects of study interventions on residual C-peptide secretion over 24 months following diagnosis
	  ○ To examine how intensive diabetes management using CL insulin delivery affects glucose control in terms of safety and efficacy over 24 months
	• Human Factors: To assess cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to closed-loop insulin delivery and clinical trial
	• Health economics: To perform cost utility analysis and inform reimbursement decision-making

Study design	An open-label, multi-centre, randomised, single period, two-arm parallel group study with internal pilot, contrasting closed-loop with MDI
Primary endpoint	Area under the meal stimulated C-peptide curve (AUC) during a mixed meal tolerance test (MMTT) at 12 months post diagnosis

Secondary endpoint(s)	• Mean stimulated C-peptide AUC at baseline, 6 and 24 months
	• Overall glucose control and glucose variability
	  ○ HbA1c levels
	  ○ Percentage of patients in each group with HbA1c <7.5% (58 mmol/mol)
	  ○ Percentage of time spent with sensor glucose readings in the target range (3.9 to 10mmol/l)
	  ○ Average, standard deviation, and coefficient of variation of sensor glucose levels
	• Hypoglycaemia
	  ○ Percentage of time spent below target glucose (3.9mmol/l)*
	  ○ Percentage of time with sensor glucose levels <3.5 mmol/l and <2.8 mmol/l
	  ○ AUC of sensor glucose below 3.5mmol/l
	• Hyperglycaemia
	  ○ Time spent with sensor glucose above target (10.0 mmol/l)
	  ○ Time with sensor glucose levels in significant hyperglycaemia (glucose levels > 16.7 mmol/l)
	• Insulin requirements
	  ○ Total, basal and bolus insulin dose (U/kg)
	• Weight
	  ○ Change in body mass index (BMI) standard deviation score

Safety evaluation	• Frequency of severe hypoglycaemic episodes • Frequency of diabetic ketoacidosis • Number, nature and severity of other adverse events
Utility evaluation	Assessment of the frequency and duration of use of the closed-loop system
Human factors assessment	Cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial will be assessed gathering both quantitative (validated surveys and tests) and qualitative data (interviews and focus groups).
Health economic evaluation	Cost utility analysis on the benefits of closed-loop insulin delivery to inform reimbursement decision-making

Sample size	96 participants randomised (48 per group); each clinical site will aim to recruit between 15 and 20 participants
Summary of eligibility criteria	Key inclusion criteria: 1. Diagnosis of type 1 diabetes within previous 10 working days 2. Age 10 to 16.9 years 3. Willingness to monitor blood glucose four or more times daily 4. Literate in English 5. Willingness to wear study devices Key exclusion criteria: 1. Physical or psychological condition likely to interfere with the normal conduct of the study 2. Current treatment with drugs known to interfere with glucose metabolism 3. Known or suspected allergy to insulin 4. Regular use of acetaminophen 5. Lack of reliable telephone facility for contact 6. Pregnancy, planned pregnancy, or breast feeding 7. Living alone 8. Severe visual impairment 9. Severe hearing impairment 10. Medically documented allergy towards the adhesive (glue) of plasters 11. Serious skin diseases located at places of the body, which potentially are possible to be used for localisation of the glucose sensor 12. Illicit drugs abuse 13. Prescription drugs abuse 14. Alcohol abuse 15. Sickle cell disease or haemoglobinopathy 16. Eating disorder such as anorexia or bulimia
Maximum duration of study for a subject	24 months
Recruitment	Recruitment will take place at Addenbrooke's Hospital, Cambridge, Leeds Teaching Hospital, Leeds, Alder Hey Children's Hospital, Liverpool, Nottingham Hospital, Nottingham, Oxford Children's Hospital, Oxford, Southampton

	Children's Hospital, Southampton and Royal Hospital for Sick Children, Edinburgh.
Screening and baseline assessment	Eligible participants will undergo a screening evaluation including the following activities: • medical (diabetes) history • body weight, height and blood pressure measurement • record of current insulin therapy • screening and baseline blood sampling During a baseline visit, the following assessments/ interventions will be carried out at the clinical research facility: • mixed meal tolerance test (MMTT) • blood sampling for lipid profile, centrally measured HbA1c, and subsequent immunological analyses • questionnaires • computerised cognitive testing • initiating blinded CGM to assess baseline glycaemic control
Run in period	Following consent/screening and baseline assessment, multiple daily injection therapy will be continued in all participants. All participants will receive non study related core diabetes training as per usual clinical practice for a period of up to three weeks. All subjects will be provided with 24 hour telephone helpline and will also be given written instructions about when to contact clinical team.
Randomisation	Eligible participants will be randomised in a 1:1 ratio using central randomisation software to either closed-loop or standard therapy i.e. MDI.
1. Closed-loop (interventional arm)	Following randomisation, participants in the closed-loop group will receive additional training sessions to cover key aspects of insulin pump use and CGM, prior to starting closed-loop insulin delivery.

	Once competent in the use of the study pump and CGM system, participants will receive training required for safe and effective use of the closed-loop system. During a 2-4 hour session participants will operate the system under the supervision of the clinical team. Competency on the use of closed-loop system will be evaluated. Thereafter, participants are expected to use closed-loop for 24 months without supervision or remote monitoring. The 24 hour support helpline will be available in case of problems.
2. Multiple daily injections (control arm)	Participants in the control group will receive additional training sessions following randomisation including a refresher on carbohydrate counting skills, and insulin dose adjustments. Standard therapy (i.e. MDI) will be applied for 24 months. Participants will be allowed to switch to insulin pump therapy if clinically indicated.
Follow up assessments **(3-, 6-, 9-, 12-, 15-, 18-, 21-months)**	*Both arms*. Follow up study visits will be conducted 3 monthly including data downloads/recording of insulin requirements, adverse event recording, and blood sampling (HbA1c). Participants will be fitted with blinded CGM systems at the end of each follow up visit. The sensors will be worn at home for up to 14 days and will be sent back to the research team. MMTTs will be performed at 6 month and 12 month follow up visit. Sleep will be assessed using a wristwatch device for 7 days following study visits at 6 and 12 months post diagnosis. Concomitantly, a sleep diary and sleep quality questionnaire will be distributed. Validated questionnaires evaluating the impact of the technology on quality of life, life change, diabetes management and fear of hypoglycaemia will be completed at the 12 month visit. At 12 months, participants will repeat the computerised cognitive tests first administered at baseline.

	Qualitative interviews will be conducted at month 12 in a subset of subjects and parents.
End of study assessments (24 months)	A MMTT will be performed. A blood sample will be taken for measurement of HbA1c, lipids and immunological analyses. Validated questionnaires evaluating the impact of the technology on quality of life, life change, diabetes management and fear of hypoglycaemia will be completed. Participants will repeat the computerised cognitive tests first administered at baseline. Sleep will be assessed using a wristwatch device for 7 days within the last month of the trial. Concomitantly, a sleep diary and sleep quality questionnaire will be distributed. Participants and families will be invited to attend focus group discussions.

8.7 APPENDIX G: DAN05 STUDY SYNOPSIS

Short title	Day and night closed-loop in young people with type 1 diabetes
Purpose of clinical trial	To determine whether 24/7 automated closed-loop glucose control will improve glucose control as measured by glycated haemoglobin and reduce the burden of hypoglycaemia compared to usual care (conventional or sensor-augmented insulin pump therapy)
Study objectives	**1. EFFICACY:** The objective is to assess efficacy of day and night automated closed-loop glucose control in improving glucose control as measured by glycated haemoglobin, as compared to insulin pump therapy alone. **2. SAFETY:** The objective is to evaluate the safety of day and night automated closed-loop glucose control, in terms of episodes of severe hypoglycaemia and other adverse events. **3. UTILITY:** The objective is to determine the frequency and duration of the use of the automated closed-loop system. **4. HUMAN FACTORS:** The objective is to assess cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial using validated surveys and focus groups. **5. HEALTH ECONOMICS**: The objective is to perform a cost utility analysis to inform reimbursement decision-making.
Study design	An open-label, multi-centre, randomised, single-period parallel study, contrasting day-and-night automated closed-loop glucose control with insulin pump therapy
Primary endpoint	The primary outcome is the centralised measurement of glycated haemoglobin (HbA1c) at 6 months.
Secondary endpoint(s)	• Time spent in the target glucose range (3.9 to 10mmol/l) (70 to 180mg/dl)

	• Time spent below target glucose (3.9mmol/l)(70mg/dl) • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) • Average, standard deviation, and coefficient of variation of glucose levels • The time with glucose levels < 3.5 mmol/l (63 mg/dl) and <3.0 mmol/l (54mg/dl) • Time with glucose levels in significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) • Total, basal and bolus insulin dose • AUC of glucose below 3.5mmol/l (63mg/dl) Secondary endpoints regarding glucose levels will be based on sensor glucose data.
Safety evaluation	Frequency of severe hypoglycaemic episodes, frequency of diabetic ketoacidosis (DKA) and nature and severity of other adverse events
Utility evaluation	Assessment of the frequency and duration of use of the closed-loop system
Human factors assessment	Cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial will be assessed gathering both quantitative (validated surveys) and qualitative data (focus groups)
Health economic evaluation	Cost utility analysis on the benefits of closed-loop insulin delivery to inform reimbursement decision-making
Sample size	130 participants randomised (equal proportion of those aged 6 to 12 years and 13 to 18 years, a minimum quota of 25% participants with baseline HbA1c >8.5%
Summary of eligibility criteria	Key inclusion criteria: 1. Age ≥ 6 and <19 years 2. Type 1 diabetes as defined by WHO for at least 1 year 3. Use of an insulin pump for at least 3 months, with good knowledge by subject or caregiver of insulin self-adjustment as judged by the investigator

4. Using U-100 rapid acting insulin analogues Aspart or Lispro only)
5. Willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements per day
6. HbA1c ≥ 7.5% (58 mmol/mol) and ≤ 10% (86mmol/mol) based on analysis from local laboratory
7. Literate in English
8. Willing to wear study devices
9. Access to WiFi
10. The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance

Key exclusion criteria:

1. Living alone
2. Current use of any closed-loop system
3. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
4. Untreated coeliac disease, adrenal insufficiency or thyroid disease
5. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc.
6. Known or suspected allergy against insulin
7. Clinical significant nephropathy, neuropathy or retinopathy as judged by the investigator
8. Recurrent incidents of severe hypoglycaemia during previous 6 months
9. Recurrent incidents of diabetic ketoacidosis during previous 6 months.
10. Unwilling to avoid regular use of acetaminophen
11. Lack of reliable telephone facility for contact
12. Total daily insulin dose ≥ 2 IU/kg/day
13. Total daily insulin dose < 15 IU/day
14. Pregnancy, planned pregnancy, or breast feeding
15. Severe visual impairment

	16. Severe hearing impairment 17. Seizure disorder 18. Medically documented allergy towards the adhesive 19. Serious skin diseases 20. Illicit drugs abuse 21. Prescription drugs abuse 22. Alcohol abuse 23. Use of pramlintide (Symlin), sulphonylureas, biguanides, DPP4-Inhibitors, , GLP-1 analogues, SGLT-1/ 2 inhibitors at time of screening 24. Shift work with working hours between 10pm and 8am 25. Sickle cell disease or haemoglobinopathy 26. Eating disorder such as anorexia or bulimia 27. Employed by Medtronic Diabetes or with immediate family members employed by Medtronic Diabetes
Maximum duration of study for a subject	8 months
Recruitment	The subjects will be recruited through the paediatric diabetes outpatient clinics at each centre
Screening and baseline assessment	Eligible participants will undergo a screening evaluation where blood samples for full blood count, liver, thyroid function and anti-transglutaminase antibodies (with IgA levels if not done within previous 12 months) will be taken. Non-hypoglycaemia C-peptide, glucose and HbA1c will also be measured, and a urine pregnancy test in females of child-bearing potential will be performed. Surveys investigating participants' quality of life, psychosocial and cognitive functioning, and response to their current treatment will be distributed. Participants will be fitted with a blinded continuous glucose monitoring (CGM) device to assess baseline glycaemic control. Instructions on how to safely use, remove and send back the device will be provided.

Run-in Period	During a 1-2 week run-in period, subjects will continue using their own insulin pump. Data obtained from blinded CGM and pump downloads may be utilised for therapy adjustment.
Randomisation	Eligible subjects will be randomised using randomisation software to the use of real-time CGM and low glucose feature combined with day and night closed-loop or to conventional insulin pump therapy alone. A blood sample for centralised analysis of HbA1c will be taken if screening and randomisation are >28 days apart. A urine pregnancy test in females of child-bearing potential will be performed.
1. Automated day and night closed-loop insulin delivery (intervention arm) combined with low glucose feature (interventional arm)	Participants in the closed-loop group will receive additional training sessions following randomisation covering the use of the study insulin pump and real-time CGM, prior to starting closed-loop insulin delivery. Once confident with the use of the study pump and CGM system, participants will receive training required for safe and effective use of the closed-loop system approximately 2-4 weeks after randomisation. During this 2-4 hour session participants will operate the system under the supervision of the clinical team. Competency on the use of closed-loop system will be evaluated. Thereafter, participants are expected to use closed-loop for 6 months without direct real-time remote monitoring.
2. Usual care (conventional or sensor-augmented pump therapy) **(control arm)**	Refresher training on key aspects of insulin pump therapy will be provided. Subjects will continue using their own insulin pump and CGM if a regular CGM user for 6 months.

3-month and 6-month assessments	A blood sample will be taken for measurement of HbA1c. A urine pregnancy test in females of child-bearing potential will be performed during the 3-month visit. Validated surveys evaluating the impact of the devices employed on quality of life, psychosocial and cognitive functioning, diabetes management and treatment satisfaction will be completed. Participants of both study arms will be fitted with blinded CGM systems at the end of each follow up visit. The sensors will be worn at home for up to 14 days and will be sent back to the research team. 6 months only: Subjects/guardians will be invited to join follow-up focus groups to gather feedback and reactions to their current treatment (closed-loop or insulin pump), the clinical trial, and quality of life changes.

9 References

1. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva. 2006.

2. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015;38 Suppl:S8-S16.

3. Todd JA. Etiology of type 1 diabetes. Immunity 2010;32:457-67.

4. Craig ME, Jefferies C, Dabelea D, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2014;15 Suppl 20:4-17.

5. Alberti G, Zimmet P, Shaw J, et al. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. Diabetes Care 2004;27:1798-811.

6. Haines L, Wan KC, Lynn R, Barrett TG, Shield JP. Rising incidence of type 2 diabetes in children in the U.K. Diabetes Care 2007;30:1097-101.

7. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005;146:693-700.

8. Diabetes Atlas. International Diabetes Federation, 2015. 7th edition, at http://www.diabetesatlas.org.)

9. Gale EA. The rise of childhood type 1 diabetes in the 20th century. Diabetes 2002;51:3353-61.

10. Patterson CC, Gyurus E, Rosenbauer J, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. Diabetologia 2012;55:2142-7.

11. Klein BE, Klein R, McBride PE, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Arch Intern Med 2004;164:1917-24.

12. Livingstone SJ, Levin D, Looker HC, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. JAMA 2015;313:37-44.

13. Steineck I, Cederholm J, Eliasson B, et al. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. BMJ 2015;350:h3234.

14. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997;20:22-5.

15. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study G. Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. Diabetes Care 2010;33:1004-8.

16. Cryer PE. Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. Endocrinol Metab Clin North Am 1999;28:495-500, v-vi.

17. Jones TW, Borg WP, Borg MA, et al. Resistance to neuroglycopenia: an adaptive response during intensive insulin treatment of diabetes. J Clin Endocrinol Metab 1997;82:1713-8.

18. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus. Arch Dis Child 1998;78:111-5.

19. Jones TW, Boulware SD, Kraemer DT, Caprio S, Sherwin RS, Tamborlane WV. Independent effects of youth and poor diabetes control on responses to hypoglycemia in children. Diabetes 1991;40:358-63.

20. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. Diabetes 2005;54:3592-601.

21. Clarke W, Jones T, Rewers A, Dunger D, Klingensmith GJ. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes 2009;10 Suppl 12:134-45.

22. Ly TT, Maahs DM, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes 2014;15 Suppl 20:180-92.

23. Jones TW, Group IHGW. Defining relevant hypoglycemia measures in children and adolescents with type 1 diabetes. Pediatr Diabetes 2018;19:354-5.

24. Group IHS. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2017;60:3-6.

25. Beregszàszi M, Tubiana-Rufi N, Benali K, Noël M, Bloch J, Czernichow P. Nocturnal hypoglycemia in children and adolescents with insulin-dependent diabetes mellitus: prevalence and risk factors. J Pediatr 1997;131:27-33.

26. Matyka KA, Wigg L, Pramming S, Stores G, Dunger DB. Cognitive function and mood after profound nocturnal hypoglycaemia in prepubertal children with conventional insulin treatment for diabetes. Arch Dis Child 1999;81:138-42.

27. Kaufman FR, Austin J, Neinstein A, et al. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. J Pediatr 2002;141:625-30.

28. Porter PA, Keating B, Byrne G, Jones TW. Incidence and predictive criteria of nocturnal hypoglycemia in young children with insulin-dependent diabetes mellitus. J Pediatr 1997;130:366-72.

29. Bulsara MK, Holman CD, Davis EA, Jones TW. The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes. Diabetes Care 2004;27:2293-8.

30. Cengiz E, Xing D, Wong JC, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes 2013;14:447-54.

31. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:298-305.

32. Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842-52.

33. Patterson CC, Dahlquist G, Harjutsalo V, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. Diabetologia 2007;50:2439-42.

34. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983;309:159-69.

35. Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am 2006;35:725-51, viii.

36. Wolfsdorf JI, Allgrove J, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes 2014;15 Suppl 20:154-79.

37. Hanas R, Lindgren F, Lindblad B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. Pediatr Diabetes 2009;10:33-7.

38. Rosilio M, Cotton JB, Wieliczko MC, et al. Factors associated with glycemic control. A cross-sectional nationwide study in 2,579 French children with type 1 diabetes. The French Pediatric Diabetes Group. Diabetes Care 1998;21:1146-53.

39. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. JAMA 2002;287:2511-8.

40. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990-96. Arch Dis Child 1999;81:318-23.

41. Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent trends in hospitalization for diabetic ketoacidosis in ontario children. Diabetes Care 2002;25:1591-6.

42. Decourcey DD, Steil GM, Wypij D, Agus MS. Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric diabetic ketoacidosis: an 11-year retrospective analysis of mortality*. Pediatr Crit Care Med 2013;14:694-700.

43. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.

44. Marcovecchio ML, Chiarelli F. Microvascular disease in children and adolescents with type 1 diabetes and obesity. Pediatr Nephrol 2011;26:365-75.

45. Maftei O, Pena AS, Sullivan T, et al. Early atherosclerosis relates to urinary albumin excretion and cardiovascular risk factors in adolescents with type 1 diabetes: Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). Diabetes Care 2014;37:3069-75.

46. Cho YH, Craig ME, Davis EA, et al. Cardiac autonomic dysfunction is associated with high-risk albumin-to-creatinine ratio in young adolescents with type 1 diabetes in AdDIT (adolescent type 1 diabetes cardio-renal interventional trial). Diabetes Care 2015;38:676-81.

47. Marcovecchio ML, Tossavainen PH, Dunger DB. Prevention and treatment of microvascular disease in childhood type 1 diabetes. Br Med Bull 2010;94:145-64.

48. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in

adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. J Pediatr 1994;125:177-88.

49. Rewers MJ, Pillay K, de Beaufort C, et al. ISPAD clinical practice consensus guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes 2014;15 Suppl 20:102-14.

50. Pihoker C, Forsander G, Fantahun B, et al. ISPAD Clinical Practice Consensus Guidelines 2014. The delivery of ambulatory diabetes care to children and adolescents with diabetes. Pediatr Diabetes 2014;15 Suppl 20:86-101.

51. American Diabetes Association. 11. Children and Adolescents. Diabetes Care 2016;39 Suppl 1:S86-93.

52. Wood JR, Miller KM, Maahs DM, et al. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. Diabetes Care 2013;36:2035-7.

53. Sherr JL, Hermann JM, Campbell F, et al. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. Diabetologia 2016;59:87-91.

54. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care 2015;38:971-8.

55. Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technol Assess 2004;8:iii, 1-57.

56. Hirsch IB. Insulin analogues. N Engl J Med 2005;352:174-83.

57. Jacobs MA, Keulen ET, Kanc K, et al. Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. Diabetes Care 1997;20:1279-86.

58. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643-53.

59. de Beaufort CE, Swift PG, Skinner CT, et al. Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes. Diabetes Care 2007;30:2245-50.

60. Paton JS, Wilson M, Ireland JT, Reith SB. Convenient pocket insulin syringe. Lancet 1981;1:189-90.

61. Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. Br Med J 1978;1:204-7.

62. Renard E. Insulin pump use in Europe. Diabetes Technol Ther 2010;12 Suppl 1:S29-32.

63. Szypowska A, Schwandt A, Svensson J, et al. Insulin pump therapy in children with type 1 diabetes: analysis of data from the SWEET registry. Pediatr Diabetes 2016;17 Suppl 23:38-45.

64. Zisser HC. The OmniPod Insulin Management System: the latest innovation in insulin pump therapy. Diabetes Ther 2010;1:10-24.

65. Leelarathna L, Roberts SA, Hindle A, et al. Comparison of different insulin pump makes under routine care conditions in adults with Type 1 diabetes. Diabet Med 2017;34:1372-9.

66. Ramotowska A, Golicki D, Dzygalo K, Szypowska A. The effect of using the insulin pump bolus calculator compared to standard insulin dosage calculations in patients with type 1 diabetes mellitus - systematic review. Exp Clin Endocrinol Diabetes 2013;121:248-54.

67. Jones SM, Quarry JL, Caldwell-McMillan M, Mauger DT, Gabbay RA. Optimal insulin pump dosing and postprandial glycemia following a pizza meal using the continuous glucose monitoring system. Diabetes Technol Ther 2005;7:233-40.

68. O'Connell MA, Gilbertson HR, Donath SM, Cameron FJ. Optimizing postprandial glycemia in pediatric patients with type 1 diabetes using insulin pump therapy: impact of glycemic index and prandial bolus type. Diabetes Care 2008;31:1491-5.

69. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med 2008;25:765-74.

70. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336-47.

71. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia 2008;51:941-51.

72. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab 2009;94:729-40.

73. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetol 2010;47 Suppl 1:77-81.

74. Pańkowska E, Błazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. Pediatr Diabetes 2009;10:52-8.

75. Bangstad HJ, Danne T, Deeb L, Jarosz-Chobot P, Urakami T, Hanas R. Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes 2009;10 Suppl 12:82-99.

76. Muller-Godeffroy E, Treichel S, Wagner VM. Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus--a large-scale multicentre pilot study. Diabet Med 2009;26:493-501.

77. Beato-Víbora P, Yeoh E, Rogers H, Hopkins D, Amiel SA, Choudhary P. Sustained benefit of continuous subcutaneous insulin infusion on glycaemic control and hypoglycaemia in adults with Type 1 diabetes. Diabet Med 2015;32:1453-9.

78. Joubert M, Morera J, Vicente A, Rod A, Parienti JJ, Reznik Y. Cross-sectional survey and retrospective analysis of a large cohort of adults with type 1 diabetes with long-term

continuous subcutaneous insulin infusion treatment. J Diabetes Sci Technol 2014;8:1005-10.

79. Orr CJ, Hopman W, Yen JL, Houlden RL. Long-term efficacy of insulin pump therapy on glycemic control in adults with type 1 diabetes mellitus. Diabetes Technol Ther 2015;17:49-54.

80. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia 2013;56:2392-400.

81. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA 2017;318:1358-66.

82. Lin MH, Connor CG, Ruedy KJ, et al. Race, socioeconomic status, and treatment center are associated with insulin pump therapy in youth in the first year following diagnosis of type 1 diabetes. Diabetes Technol Ther 2013;15:929-34.

83. Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. N Engl J Med 2012;366:1616-24.

84. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev 2010:Cd005103.

85. Bruttomesso D, Costa S, Baritussio A. Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. Diabetes Metab Res Rev 2009;25:99-111.

86. Heinemann L, Krinelke L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. J Diabetes Sci Technol 2012;6:954-64.

87. Haller MJ, Stalvey MS, Silverstein JH. Predictors of control of diabetes: monitoring may be the key. J Pediatr 2004;144:660-1.

88. Ziegler R, Heidtmann B, Hilgard D, et al. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatr Diabetes 2011;12:11-7.

89. Miller KM, Beck RW, Bergenstal RM, et al. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care 2013;36:2009-14.

90. Ziegler R, Cavan DA, Cranston I, et al. Use of an insulin bolus advisor improves glycemic control in multiple daily insulin injection (MDI) therapy patients with suboptimal glycemic control: First results from the ABACUS trial. Diabetes Care 2013;36:3613-9.

91. Vallejo Mora MDR, Carreira M, Anarte MT, Linares F, Olveira G, González Romero S. Bolus calculator reduces hypoglycemia in the short term and fear of hypoglycemia in the long term in subjects with type 1 diabetes (CBMDI study). Diabetes Technol Ther 2017;19:402-9.

92. Vallejo-Mora MD, Carreira-Soler M, Linares-Parrado F, et al. The Calculating Boluses on Multiple Daily Injections (CBMDI) study: A randomized controlled trial on the effect on metabolic control of adding a bolus calculator to multiple daily injections in people with type 1 diabetes. J Diabetes 2017;9:24-33.

93. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. Diabetes Technol Ther 2015;17:787-94.

94. Kropff J, Choudhary P, Neupane S, et al. Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial. Diabetes Care 2017;40:63-8.

95. Bergenstal RM. Continuous glucose monitoring: transforming diabetes management step by step. Lancet 2018.

96. DeSalvo D, Miller K, Hermann J, et al. *Continuous Glucose Monitoring (CGM) and Glycemic Control Among Youth with Type 1 Diabetes (T1D): International comparison from the T1D Exchange (T1DX) and the DPV Initiative*. 43rd Annual Conference of the International Society for Pediatric and Adolescent Diabetes. Innsbruck, Austria2017.

97. Bailey TS, Chang A, Christiansen M. Clinical accuracy of a continuous glucose monitoring system with an advanced algorithm. J Diabetes Sci Technol 2015;9:209-14.

98. Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: Results from two studies. Diabetes Technol Ther 2016;18 Suppl 2:S223-33.

99. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther 2017.

100. Kropff J, Bruttomesso D, Doll W, et al. Accuracy of two continuous glucose monitoring systems: a head-to-head comparison under clinical research centre and daily life conditions. Diabetes Obes Metab 2015;17:343-9.

101. Pleus S, Schoemaker M, Morgenstern K, et al. Rate-of-change dependence of the performance of two CGM systems during induced glucose swings. J Diabetes Sci Technol 2015;9:801-7.

102. Kovatchev BP, Patek SD, Ortiz EA, Breton MD. Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Diabetes Technol Ther 2015;17:177-86.

103. Aleppo G, Ruedy KJ, Riddlesworth TD, et al. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. Diabetes Care 2017;40:538-45.

104. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: A consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622-30.

105. Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017;40:1631-40.

106. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study G, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464-76.

107. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose:

meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805.

108. Langendam M, Luijf YM, Hooft L, Devries JH, Mudde AH, Scholten RJ. Continuous glucose monitoring systems for type 1 diabetes mellitus. The Cochrane database of systematic reviews 2012;1:CD008101.

109. Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. Eur J Endocrinol 2012;166:567-74.

110. Hoeks LB, Greven WL, de Valk HW. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabet Med 2011;28:386-94.

111. Golicki DT, Golicka D, Groele L, Pankowska E. Continuous glucose monitoring system in children with type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetologia 2008;51:233-40.

112. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes Care 2010;33:17-22.

113. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010;363:311-20.

114. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Sensor-augmented pump therapy for A1C reduction (STAR 3) study: results from the 6-month continuation phase. Diabetes Care 2011;34:2403-5.

115. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795-800.

116. Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155-62.

117. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 2017;317:371-8.

118. Fonseca VA, Grunberger G, Anhalt H, et al. Continuous glucose monitoring: A consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. Endocr Pract 2016;22:1008-21.

119. Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW, Network TDEC. Continuous Glucose Monitoring in Patients With Type 1 Diabetes Using Insulin Injections. Diabetes Care 2016;39:e81-2.

120. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. JAMA 2017;317:379-87.

121. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254-63.

122. Edge J, Acerini C, Campbell F, et al. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child 2017;102:543-9.

123. Ish-Shalom M, Wainstein J, Raz I, Mosenzon O. Improvement in glucose control in difficult-to-control patients with diabetes using a novel flash glucose monitoring device. J Diabetes Sci Technol 2016;10:1412-3.

124. Dover AR, Stimson RH, Zammitt NN, Gibb FW. Flash glucose monitoring improves outcomes in a type 1 diabetes clinic. J Diabetes Sci Technol 2017;11:442-3.

125. McKnight JA, Gibb FW. Flash glucose monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre. Diabet Med 2017;34:732.

126. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharaja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia. Diabet Med 2018;35:483-90.

127. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 2017.

128. Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464-76.

129. Hirsch IB, Abelseth J, Bode BW, et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technol Ther 2008;10:377-83.

130. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes Care 2009;32:2245-50.

131. Slover RH, Welsh JB, Criego A, et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. Pediatr Diabetes 2012;13:6-11.

132. Kordonouri O, Pankowska E, Rami B, et al. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. Diabetologia 2010;53:2487-95.

133. Kordonouri O, Hartmann R, Pankowska E, et al. Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study. Pediatr Diabetes 2012;13:515-8.

134. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The DCCT Research Group. Ann Intern Med 1998;128:517-23.

135. Mirouze J, Selam JL, Pham TC, Mendoza E, Orsetti A. Sustained insulin-induced remissions of juvenile diabetes by means of an external artificial pancreas. Diabetologia 1978;14:223-7.

136. Like AA, Biron CA, Weringer EJ, Byman K, Sroczynski E, Guberski DL. Prevention of diabetes in BioBreeding/Worcester rats with monoclonal antibodies that recognize T lymphocytes or natural killer cells. J Exp Med 1986;164:1145-59.

137. Gotfredsen CF, Buschard K, Frandsen EK. Reduction of diabetes incidence of BB Wistar rats by early prophylactic insulin treatment of diabetes-prone animals. Diabetologia 1985;28:933-5.

138. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 1989;320:550-4.

139. Buckingham B, Beck RW, Ruedy KJ, et al. Effectiveness of early intensive therapy on beta-cell preservation in type 1 diabetes. Diabetes Care 2013;36:4030-5.

140. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013;310:1240-7.

141. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224-32.

142. Weiss R, Garg SK, Bode BW, et al. Hypoglycemia reduction and changes in hemoglobin A1c in the ASPIRE in-home study. Diabetes Technol Ther 2015;17:542-7.

143. Danne T, Kordonouri O, Holder M, et al. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. Diabetes Technol Ther 2011;13:1129-34.

144. Choudhary P, Shin J, Wang Y, et al. Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk. Diabetes Care 2011;34:2023-5.

145. Agrawal P, Zhong A, Welsh JB, Shah R, Kaufman FR. Retrospective analysis of the real-world use of the threshold suspend feature of sensor-augmented insulin pumps. Diabetes Technol Ther 2015;17:316-9.

146. Maahs DM, Calhoun P, Buckingham BA, et al. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care 2014;37:1885-91.

147. Buckingham BA, Raghinaru D, Cameron F, et al. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. Diabetes Care 2015;38:1197-204.

148. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: A randomized controlled trial. Diabetes Care 2017;40:764-70.

149. Hovorka R. Closed-loop insulin delivery: from bench to clinical practice. Nature reviews Endocrinology 2011;7:385-95.

150. Bakhtiani PA, Zhao LM, El Youssef J, Castle JR, Ward WK. A review of artificial pancreas technologies with an emphasis on bi-hormonal therapy. Diabetes Obes Metab 2013;15:1065-70.

151. Peyser T, Dassau E, Breton M, Skyler JS. The artificial pancreas: current status and future prospects in the management of diabetes. Annals of the New York Academy of Sciences 2014;1311:102-23.

152. Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. Diabetes 2011;60:2672-82.

153. Kadish AH. Automation control of blood sugar. i.a. servomechanism for glycose monitoring and control. The American journal of medical electronics 1964;3:82-6.

154. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 2006;55:3344-50.

155. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934-9.

156. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743-51.

157. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010;33:1072-6.

158. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2:27ra.

159. Cobelli C, Man CD, Sparacino G, Magni L, De Nicolao G, Kovatchev BP. Diabetes: Models, signals, and control. IEEE Rev Biomed Eng 2009;2:54-96.

160. Hovorka R, Canonico V, Chassin LJ, et al. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physiol Meas 2004;25:905-20.

161. Hovorka R. The future of continuous glucose monitoring: closed loop. Curr Diabetes Rev 2008;4:269-79.

162. Haidar A, Smaoui MR, Legault L, Rabasa-Lhoret R. The role of glucagon in the artificial pancreas. Lancet Diabetes Endocrinol 2016;4:476-9.

163. Weinzimer SA, Sherr JL, Cengiz E, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:1994-9.

164. Renukuntla VS, Ramchandani N, Trast J, Cantwell M, Heptulla RA. Role of glucagon-like peptide-1 analogue versus amylin as an adjuvant therapy in type 1 diabetes in a closed loop setting with ePID algorithm. J Diabetes Sci Technol 2014;8:1011-7.

165. Sherr JL, Patel NS, Michaud CI, et al. Mitigating Meal-Related Glycemic Excursions in an Insulin-Sparing Manner During Closed-Loop Insulin Delivery: The Beneficial Effects of Adjunctive Pramlintide and Liraglutide. Diabetes Care 2016.

166. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. JAMA 2016;316:1407-8.

167. Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. Am J Med 1991;90:450-9.

168. Barnea-Goraly N, Raman M, Mazaika P, et al. Alterations in White Matter Structure in Young Children With Type 1 Diabetes. Diabetes Care 2013.

169. Marzelli MJ, Mazaika PK, Barnea-Goraly N, et al. Neuroanatomical correlates of dysglycemia in young children with type 1 diabetes. Diabetes 2014;63:343-53.

170. Elleri D, Acerini CL, Allen JM, et al. Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. Diabetes Technol Ther 2010;12:35-9.

171. O'Grady MJ, Retterath AJ, Keenan DB, et al. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:2182-7.

172. Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. Diabetes Care 2013;36:2909-14.

173. Nimri R, Danne T, Kordonouri O, et al. The "Glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. Pediatr Diabetes 2013;14:159-67.

174. Elleri D, Allen JM, Kumareswaran K, et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. Diabetes Care 2013;36:838-44.

175. Buckingham BA, Beck RW, Ruedy KJ, et al. The effects of inpatient hybrid closed-loop therapy initiated within 1 week of type 1 diabetes diagnosis. Diabetes Technol Ther 2013;15:401-8.

176. Dauber A, Corcia L, Safer J, Agus MS, Einis S, Steil GM. Closed-loop insulin therapy improves glycemic control in children aged <7 years: a randomized controlled trial. Diabetes Care 2013;36:222-7.

177. Hasan KS, Kabbani M. Mini-dose glucagon is effective at diabetes camp. J Pediatr 2004;144:834.

178. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368:824-33.

179. Ly TT, Breton MD, Keith-Hynes P, et al. Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. Diabetes care 2014;37:2310-6.

180. Ly TT, Buckingham BA, DeSalvo DJ, et al. Day-and-Night Closed-Loop Control Using the Unified Safety System in Adolescents With Type 1 Diabetes at Camp. Diabetes Care 2016;39:e106-7.

181. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery-the path to physiological glucose control. Adv Drug Deliv Rev 2004;56:125-44.

182. Ly TT, Keenan DB, Roy A, et al. Automated Overnight Closed-Loop Control Using a Proportional-Integral-Derivative Algorithm with Insulin Feedback in Children and Adolescents with Type 1 Diabetes at Diabetes Camp. Diabetes Technol Ther 2016;18:377-84.

183. Ly TT, Roy A, Grosman B, et al. Day and Night Closed-Loop Control Using the Integrated Medtronic Hybrid Closed-Loop System in Type 1 Diabetes at Diabetes Camp. Diabetes Care 2015;38:1205-11.

184. Del Favero S, Boscari F, Messori M, et al. Randomized Summer Camp Crossover Trial in 5- to 9-Year-Old Children: Outpatient Wearable Artificial Pancreas Is Feasible and Safe. Diabetes Care 2016.

185. DeBoer MD, Breton MD, Wakeman C, et al. Performance of an artificial pancreas system for young children with type 1 diabetes. Diabetes Technol Ther 2017;19:293-8.

186. Nimri R, Muller I, Atlas E, et al. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care 2014;37:3025-32.

187. Nimri R, Bratina N, Kordonouri O, et al. MD-Logic overnight type 1 diabetes control in home settings: A multicentre, multinational, single blind randomized trial. Diabetes Obes Metab 2016.

188. Hovorka R, Elleri D, Thabit H, et al. Overnight closed loop insulin delivery in young people with type 1 diabetes: A free-living randomised clinical trial. Diabetes Care 2014;37:1204-11.

189. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129-40.

190. Tauschmann M, Allen JM, Wilinska ME, et al. Day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes: A free-living, randomized clinical trial. Diabetes Care 2016;39:1168-74.

191. Tauschmann M, Allen JM, Wilinska ME, et al. Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with type 1 diabetes: A 3-week, free-living, randomized crossover trial. Diabetes Care 2016;39:2019-25.

192. Sharifi A, De Bock MI, Jayawardene D, et al. Glycemia, Treatment Satisfaction, Cognition, and Sleep Quality in Adults and Adolescents with Type 1 Diabetes When Using a Closed-Loop System Overnight Versus Sensor-Augmented Pump with Low-Glucose Suspend Function: A Randomized Crossover Study. Diabetes Technol Ther 2016;18:772-83.

193. Spaic T, Driscoll M, Raghinaru D, et al. Predictive Hyperglycemia and Hypoglycemia Minimization: In-Home Evaluation of Safety, Feasibility, and Efficacy in Overnight Glucose Control in Type 1 Diabetes. Diabetes Care 2017;40:359-66.

194. Kropff J, Del Favero S, Place J, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol 2015;3:939-47.

195. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129-40.

196. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014;371:313-25.

197. Russell SJ, Hillard MA, Balliro C, et al. Day and night glycaemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. Lancet Diabetes Endocrinol 2016;4:233-43.

198. Haidar A, Legault L, Matteau-Pelletier L, et al. Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial. Lancet Diabetes Endocrinol 2015;3:595-604.

199. Barnard KD, Wysocki T, Allen JM, et al. Closing the loop overnight at home setting: psychosocial impact for adolescents with type 1 diabetes and their parents. BMJ open diabetes research & care 2014;2:e000025.

200. Messer LH, Calhoun P, Buckingham B, et al. In-home nighttime predictive low glucose suspend experience in children and adults with type 1 diabetes. Pediatr Diabetes 2016.

201. Ziegler C, Liberman A, Nimri R, et al. Reduced Worries of Hypoglycaemia, High Satisfaction, and Increased Perceived Ease of Use after Experiencing Four Nights of MD-Logic Artificial Pancreas at Home (DREAM4). J Diabetes Res 2015;2015:590308.

202. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. Clin Chem 2001;47:153-63.

203. Ford ES, Cowie CC, Li C, Handelsman Y, Bloomgarden ZT. Iron-deficiency anemia, non-iron-deficiency anemia and HbA1c among adults in the US. J Diabetes 2011;3:67-73.

204. Nielsen LR, Ekbom P, Damm P, et al. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care 2004;27:1200-1.

205. Beck RW, Hirsch IB, Laffel L, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378-83.

206. Russell SJ, Beck RW. Design Considerations for Artificial Pancreas Pivotal Studies. Diabetes Care 2016;39:1161-7.

207. DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes 2013;62:1405-8.

208. Hirsch IB. Glycemic Variability and Diabetes Complications: Does It Matter? Of Course It Does! Diabetes Care 2015;38:1610-4.

209. Bergenstal RM. Glycemic Variability and Diabetes Complications: Does It Matter? Simply Put, There Are Better Glycemic Markers! Diabetes Care 2015;38:1615-21.

210. Service FJ. Glucose variability. Diabetes 2013;62:1398-404.

211. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. Diabetes Technol Ther 2009;11 Suppl 1:S55-67.

212. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155-63.

213. Castle JR, Pitts A, Hanavan K, et al. The accuracy benefit of multiple amperometric glucose sensors in people with type 1 diabetes. Diabetes Care 2012;35:706-10.

214. Kropff J, DeVries JH. Continuous glucose monitoring, future products, and update on worldwide artificial pancreas projects. Diabetes Technol Ther 2016;18 Suppl 2:S253-63.

215. Rodbard D. Continuous glucose monitoring: A review of successes, challenges, and opportunities. Diabetes Technol Ther 2016;18 Suppl 2:S23-S213.

216. Keenan DB, Mastrototaro JJ, Zisser H, et al. Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. Diabetes Technol Ther 2012;14:225-31.

217. Calhoun P, Lum J, Beck RW, Kollman C. Performance comparison of the medtronic sof-sensor and enlite glucose sensors in inpatient studies of individuals with type 1 diabetes. Diabetes Technol Ther 2013;15:758-61.

218. Gerritsen M, Jansen JA, Kros A, et al. Influence of inflammatory cells and serum on the performance of implantable glucose sensors. J Biomed Mater Res 2001;54:69-75.

219. Gifford R, Kehoe JJ, Barnes SL, Kornilayev BA, Alterman MA, Wilson GS. Protein interactions with subcutaneously implanted biosensors. Biomaterials 2006;27:2587-98.

220. Klueh U, Liu Z, Feldman B, et al. Metabolic biofouling of glucose sensors in vivo: role of tissue microhemorrhages. J Diabetes Sci Technol 2011;5:583-95.

221. Bailey TS, Ahmann A, Brazg R, et al. Accuracy and acceptability of the 6-day Enlite continuous subcutaneous glucose sensor. Diabetes Technol Ther 2014;16:277-83.

222. Luijf YM, Mader JK, Doll W, et al. Accuracy and reliability of continuous glucose monitoring systems: a head-to-head comparison. Diabetes Technol Ther 2013;15:722-7.

223. Hovorka R. Artificial Pancreas project at Cambridge 2013. Diabet Med 2015;32:987-92.

224. Elleri D, Allen JM, Tauschmann M, et al. Feasibility of overnight closed-loop therapy in young children with type 1 diabetes aged 3-6 years: comparison between diluted and standard insulin strength. BMJ Open Diabetes Res Care 2014;2:e000040.

225. Breton M, Farret A, Bruttomesso D, et al. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. Diabetes 2012;61:2230-7.

226. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010;33:1072-6.

227. Castle JR, Engle JM, El Youssef J, et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. Diabetes Care 2010;33:1282-7.

228. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER. Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. Diabetes Care 2012;35:2148-55.

229. Kovatchev BP, Renard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes care 2013;36:1851-8.

230. Thabit H, Lubina-Solomon A, Stadler M, et al. Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. Lancet Diabetes Endocrinol 2014;2:701-9.

231. Hovorka R, Elleri D, Thabit H, et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care 2014;37:1204-11.

232. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169-76.

233. Leelarathna L, Dellweg S, Mader JK, et al. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care 2014;37:1931-7.

234. Kovatchev BP, Renard E, Cobelli C, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 2014;37:1789-96.

235. Beck RW, Tamborlane WV, Bergenstal RM, et al. The T1D Exchange clinic registry. J Clin Endocrinol Metab 2012;97:4383-9.

236. Wood JR, Miller KM, Maahs DM, et al. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. Diabetes Care 2013;36:2035-7.

237. Acerini CL, Williams RM, Dunger DB. Metabolic impact of puberty on the course of type 1 diabetes. Diabetes Metab 2001;27:S19-25.

238. Burdick J, Chase HP, Slover RH, et al. Missed insulin meal boluses and elevated hemoglobin A1c levels in children receiving insulin pump therapy. Pediatrics 2004;113:e221-4.

239. Karges B, Rosenbauer J, Holterhus PM, et al. Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes. Eur J Endocrinol 2015;173:341-50.

240. Vanderwel BW, Messer LH, Horton LA, et al. Missed insulin boluses for snacks in youth with type 1 diabetes. Diabetes Care 2010;33:507-8.

241. Hofer SE, Heidtmann B, Raile K, et al. Discontinuation of insulin pump treatment in children, adolescents, and young adults. A multicenter analysis based on the DPV database in Germany and Austria. Pediatr Diabetes 2010;11:116-21.

242. Nimri R, Muller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatr Diabetes 2014;15:91-9.

243. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129-40.

244. Leelarathna L, Dellweg S, Mader JK, et al. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care 2014;37:1931-7.

245. Elleri D, Allen JM, Biagioni M, et al. Evaluation of a portable ambulatory prototype for automated overnight closed-loop insulin delivery in young people with type 1 diabetes. Pediatr Diabetes 2012;13:449-53.

246. Hovorka R, Shojaee-Moradie F, Carroll PV, et al. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. Am J Physiol Endocrinol Metab 2002;282:E992-1007.

247. Wilinska ME, Budiman ES, Taub MB, et al. Overnight closed-loop insulin delivery with model predictive control: assessment of hypoglycemia and hyperglycemia risk using simulation studies. J Diabetes Sci Technol 2009;3:1109-20.

248. Wilinska ME, Chassin LJ, Acerini CL, Allen JM, Dunger DB, Hovorka R. Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. J Diabetes Sci Technol 2010;4:132-44.

249. Kropff J, Del Favero S, Place J, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol 2015;3:939-47.

250. Blauw H, van Bon AC, Koops R, DeVries JH, PCDIAB Consortium. Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. Diabetes Obes Metab 2016;18:671-7.

251. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. N Engl J Med 2016;375:644-54.

252. Adolfsson P, Ziegler R, Hanas R. Continuous subcutaneous insulin infusion: Special needs for children. Pediatr Diabetes 2017;18:255-61.

253. Borot S, Franc S, Cristante J, et al. Accuracy of a new patch pump based on a microelectromechanical system (MEMS) compared to other commercially available insulin pumps: results of the first in vitro and in vivo studies. J Diabetes Sci Technol 2014;8:1133-41.

254. Mianowska B, Fendler W, Tomasik B, Młynarski W, Szadkowska A. Effect of insulin dilution on lowering glycemic variability in pump-treated young children with inadequately controlled type 1 diabetes. Diabetes Technol Ther 2015;17:605-10.

255. Ruan Y, Elleri D, Allen JM, et al. Pharmacokinetics of diluted (U20) insulin aspart compared with standard (U100) in children aged 3-6 years with type 1 diabetes during closed-loop insulin delivery: a randomised clinical trial. Diabetologia 2015;58:687-90.

256. Bally L, Thabit H, Kojzar H, et al. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 2017;5:261-70.

257. Forlenza GP, Raghinaru D, Cameron F, et al. Predictive hyperglycemia and hypoglycemia minimization: In-home double-blind randomized controlled evaluation in children and young adolescents. Pediatr Diabetes 2017.

258. Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. Diabetes Obes Metab 2012;14:780-8.

259. Garg SK, Voelmle M, Gottlieb PA. Time lag characterization of two continuous glucose monitoring systems. Diabetes Res Clin Pract 2010;87:348-53.

260. Basu A, Dube S, Veettil S, et al. Time lag of glucose from intravascular to interstitial compartment in type 1 diabetes. J Diabetes Sci Technol 2015;9:63-8.

261. Setji TL, Hong BD, Feinglos MN. Technosphere insulin: inhaled prandial insulin. Expert Opin Biol Ther 2016;16:111-7.

262. Cengiz E, Weinzimer SA, Sherr JL, et al. Acceleration of insulin pharmacodynamic profile by a novel insulin infusion site warming device. Pediatr Diabetes 2013;14:168-73.

263. Hompesch M, Muchmore DB, Morrow L, Vaughn DE. Accelerated insulin pharmacokinetics and improved postprandial glycemic control in patients with type 1 diabetes after coadministration of prandial insulins with hyaluronidase. Diabetes care 2011;34:666-8.

264. Stenerson M, Cameron F, Wilson DM, et al. The Impact of Accelerometer and Heart Rate Data on Hypoglycemia Mitigation in Type 1 Diabetes. J Diabetes Sci Technol 2014;8:64-9.

265. Jackson MA, Caputo N, Castle JR, David LL, Roberts CT, Ward WK. Stable liquid glucagon formulations for rescue treatment and bi-hormonal closed-loop pancreas. Curr Diab Rep 2012;12:705-10.

266. O'Keeffe DT, Maraka S, Basu A, Keith-Hynes P, Kudva YC. Cybersecurity in artificial pancreas experiments. Diabetes Technol Ther 2015;17:664-6.

267. Barnard KD, Venkat MV, Close K, et al. PsychDT Working Group: Report Psychosocial Aspects of Artificial Pancreas Systems. J Diabetes Sci Technol 2015;9:925-8.

268. Barnard KD, Hood KK, Weissberg-Benchell J, Aldred C, Oliver N, Laffel L. Psychosocial assessment of artificial pancreas (AP): commentary and review of existing measures and their applicability in AP research. Diabetes Technol Ther 2015;17:295-300.

269. Lewis D, Leibrand S, Community O. Real-world use of open source artificial pancreas systems. J Diabetes Sci Technol 2016;10:1411.

270. Malek R, Davis SN. Novel methods of insulin replacement: The artificial pancreas and encapsulated islets. Rev Recent Clin Trials 2016;11:106-23.

271. Rege NK, Phillips NFB, Weiss MA. Development of glucose-responsive 'smart' insulin systems. Curr Opin Endocrinol Diabetes Obes 2017;24:267-78.