Clinical evaluation of a novel adaptive bolus calculator and safety system in Type 1 diabetes

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Thesis submitted for the degree of Doctor of Philosophy
CID: 974665

i. Abstract

Bolus calculators are considered state-of-the-art for insulin dosing decision support for people with Type 1 diabetes (T1D). However, they all lack the ability to automatically adapt in real-time to respond to an individual's needs or changes in insulin sensitivity. A novel insulin recommender system based on artificial intelligence has been developed to provide personalised bolus advice, namely the Patient Empowerment through Predictive Personalised Decision Support (PEPPER) system. Besides adaptive bolus advice, the decision support system is coupled with a safety system which includes alarms, predictive glucose alerts, predictive low glucose suspend for insulin pump users, personalised carbohydrate recommendations and dynamic bolus insulin constraint.

This thesis outlines the clinical evaluation of the PEPPER system in adults with T1D on multiple daily injections (MDI) and insulin pump therapy. The hypothesis was that the PEPPER system is safe, feasible and effective for use in people with TID using MDI or pump therapy. Safety and feasibility of the safety system was initially evaluated in the first phase, with the second phase evaluating feasibility of the complete system (safety system and adaptive bolus advisor). Finally, the whole system was clinically evaluated in a randomised crossover trial with 58 participants.

No significant differences were observed for percentage times in range between the PEPPER and Control groups. For quality of life, participants reported higher perceived hypoglycaemia with the PEPPER system despite no objective difference in time spent in hypoglycaemia.

Overall, the studies demonstrated that the PEPPER system is safe and feasible for use when compared to conventional therapy (continuous glucose monitoring and standard bolus calculator). Further studies are required to confirm overall effectiveness.

ii. Declaration of Originality

During the PEPPER clinical trials, I was the principal recruiter of participants in the UK at Imperial College London. I was a key part of the trial study group (full list below) and met weekly by teleconference to liaise with the engineering and technical teams, as well as the clinicians in Spain. I provided the clinical and technical support for the participants at Imperial, except where specified. I wrote the data analysis plan for the Phase 3 randomised control trial (Appendix 2). I analysed data for the three clinical phases presented in this thesis, including the combined study results for participants in UK and Spain. I wrote the first draft of the submitted manuscript (on which I am joint first author) that reports the main trial outcomes and the key findings reported in Chapter 5.

Information used from third parties has been referenced accordingly. To clarify collaboration and assistance, this has been outlined below:

Chapters 2

The architecture of the PEPPER clinical system described has been created by the PEPPER Consortium.

Chapters 3, 4 and 5

Screening participants, blood sampling and equipment logging during clinical studies at Imperial College London were performed with assistance from Ms Narvada Jugnee (Research Nurse) and Ms Maria Thomas (Project Officer).

Participants recruited in Girona and clinical data were collected and recorded by Dr Marzena Wos and Dr Yenny Leal. With their permission, these data have been combined with data collected in UK for analysis.

Data from Phase 1 participants on multiple daily injections were analysed by BSc student (Kumuthine Sivasithamparam) under mine and Prof Nick Oliver's supervision.

The engineering team - Dr Pau Herrero and Dr Chengyuan Liu provided technical support during the clinical studies and wrote the coding scripts for Matlab for analysing the safety system outcomes. Data from Table 4.3 on Case-based reasoning outcomes were kindly analysed by Dr Quim Massana.

The PEPPER Study Group:

Imperial College London – Prof Nick Oliver (Principal Investigator), Dr Monika Reddy (Co-Investigator), Dr Pau Herrero, Dr Chengyuan Liu, Miss Narvada Jugnee, Miss Maria Thomas

Girona Biomedical Research Institute (IDIBGI) – Dr Mercè Fernández (Principal Investigator), Dr José Manuel Fernández-Real (Principal Investigator), Dr Yenny Leal, Dr Marzena Wos

Oxford Brookes University – Dr Clare Martin (Project Coordinator)

University of Girona – Dr Beatriz López, Dr Joaquim Massana

Cellnovo – Mr Julian Shapley, Mr Javaid Massoud, Mr Ben Marshall, Mr Andy Burns

RomSoft – Mr Lucian Nita

iii. Copyright Declaration

iv. Acknowledgements

First and foremost, I would like to express my sincere thanks to my supervisors, Professor Nick Oliver, Dr Monika Reddy and Professor Desmond Johnston, for their continued guidance, support and encouragement throughout my PhD. It has been a great research opportunity.

It has been a huge privilege to work with Professor Nick Oliver and Dr Monika Reddy over the last 3 years, who have inspired, enthused and supported along every path of this journey.

My clinical research project has been a close collaboration with the PEPPER Consortium, and without their hard work put into the technology for clinical testing, this project would not have existed. In particular, special thanks to Dr Pau Herrero, for all his help and support during the entire PEPPER project. I am also very grateful to Dr Clare Martin (Oxford Brookes University), for steering this project successfully through some challenging times.

Miss Narvada Jugnee and Miss Maria Thomas have been wonderful and supportive throughout the clinical trials; I would like to thank them for their hard work and dedication. Thank you to my friends and colleagues who have been incredibly supportive.

I would like to especially thank my parents for always believing in me and encouraging me to achieve my goals. Huge thanks to my sister, Parin, and brother

in law, Eddie, for their support and always being there; and my gorgeous nephew Rian who fills me with so much joy as I write this thesis.

Finally, I would like to express my love and gratitude to my husband Jehangir for being my sounding-board during the challenges of this project and for his unwavering support.

The work outlined in this thesis was funded by an EU H2020 grant.

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vi. Abbreviations

ADA	American Diabetes Association
ADRR	Average daily risk ratio
AI	Artificial intelligence
ALPHA	Adaptive learning postprandial hypoglycaemia prevention algorithm
ANN	Artificial neural networks
AUC	Area under the curve
BMI	Body mass index
BOB	Bolus insulin on board
BST	British summer time
CBG	Capillary blood glucose
CBR	Case based reasoning
CDSS	Clinical decision support systems
CE Mark	Certification Mark
CGM	Continuous glucose monitoring
CHO	Carbohydrate
CI	Confidence interval
COB	Carbohydrates on board
CONGA	Continuous overlapping net glycaemic action
COPD	Chronic obstructive pulmonary disease
CR	Carbohydrate recommendations
CSF	Carbohydrate sensitivity factor
CSII	Continuous subcutaneous insulin infusion
CV	Coefficient of variation
DAFNE	Dose Adjustment for Normal Eating
DBIC	Dynamic bolus insulin constraint
DCCT	Diabetes Control and Complications Trial
DPP-4	Dipeptidyl peptidase-4
DIA	Duration of insulin action
DKA	Diabetic ketoacidosis
DL	Deep learning
DPV	Diabetes Patienten Verlaufsdokumentation registry
DQOL	Diabetes Quality of Life
DSS	Decision support system
DTSQ	Diabetes treatment satisfaction questionnaire
DTTP	Diabetes Teaching and Treatment Programme
EASD	European Association for the Study of Diabetes
ECAI	European Conference on Artificial Intelligence
EDIC	Epidemiology of Diabetes Interventions and Complications

EGA	Error grid analysis
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FFA	Free fatty acids
FL	Fuzzy Logic
GAD	Glutamic acid decarboxylase
GMT	Greenwich Mean Time
GRADE	Glycaemic risk assessment diabetes equation
GLP	Glucagon-like peptide
GOx	Glucose oxidase
GV	Glycaemic variability
GVP	Glycaemic variability percentage
HBGI	High blood glucose index
ICHNT	Imperial College Healthcare NHS Trust
ICL	Imperial College London
ICR	Insulin to carbohydrate ratios
IDIBGI	Institut d'Investigacio Biomedica de Girona
IGC	Index of glycaemic control
IHD	Ischaemic heart disease
IHSG	International Hypoglycaemia Study Group
IOB	Insulin on board
ISF	Insulin sensitivity factor
isCGM	Intermittently scanned continuous glucose monitoring
ITT	Intention-to-treat
LBGI	Low blood glucose index
LGS	Low glucose suspend
LI	Lability index
LSM	Least squares mean
MAG	Mean absolute glucose
MAGE	Mean amplitude of glucose excursions
MARD	Mean absolute relative difference
MBR	Model-based reasoning
MDI	Multiple daily injections
ML	Machine learning
MMR	Multi-modal reasoning
MODD	Mean of daily differences
MPC	Model Predictive Control
NB	Naive Bayes
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NLP	Natural language processing
NNPG	Neural network for predicting glucose
OS	Operating system

PAID	Problem Areas in Diabetes
PGS	Personal glycaemic status
PID	Proportional Integral Derivative
PLGS	Predictive low glucose suspend
R2R	Run-to-run
RCT	Randomised controlled trial
RMSE	Root mean square error
RR	Rate ratio
SD	Standard deviation
SGLT	Sodium-glucose cotransporter
SMBG	Self monitoring blood glucose
TAR	Time above range
TBR	Time below range
TDD	Total daily dose
TEDDY	The Environmental Determinants of Diabetes in the Young
TIR	Time in range
TSH	Thyroid stimulating hormone
UK	United Kingdom
US	United States
USAID	US Agency for International Development

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1 Introduction

1.1 Type 1 Diabetes and Background

Type 1 diabetes (T1D) is an autoimmune condition, resulting in the destruction of pancreatic beta-cells, required for maintaining glucose homeostasis. The burden of diabetes management is significant; with approximately 300,000 people in the United Kingdom having T1D. Worldwide, there is an annual increase in incidence of about 2-3% per year (1,2), although there are indications of geographic differences (3). Lifetime risk varies widely by country and geographical region, but overall is about 1 in 250 people (4). T1D is slightly more common in men and boys, than in women and girls (5).

In a person with a fully functioning endocrine pancreas gland, insulin production is primarily regulated by glucose concentrations in the blood and by glucagon, a hormone produced by the α-cells in the pancreas. The destruction of the pancreatic β-cells within the islets of Langerhans results in an inability of the pancreas to produce insulin in response to a glucose stimulus.

At diagnosis, people with T1D may present with hyperglycaemia and osmotic symptoms such as polydipsia, polyuria, weight loss and blurred vision. The relative or absolute deficiency of insulin results in increased activity of hormone-sensitive lipase, which converts triglycerides to fatty acetyl-CoA (fatty acid β-oxidation), facilitating ketogenesis and leading to diabetic ketoacidosis (DKA) (6). DKA can be life-threatening if not treated promptly.

No cure has been discovered for T1D. However, an increased understanding of the pathogenesis, as well as the identification of predisposing genetic and environmental factors, aid potential theoretical targets for disease process modification. Moreover, the various interplay of factors may also partly explain significant heterogeneity observed in responses to insulin management, and potential for personalised, adaptive systems.

1.1.1 An interplay of genetic, immune and environmental influences

The pathogenesis of T1D is complex, with interactions occurring between pancreatic B-cells and the innate and adaptive immune system. T-cell mediated autoimmune destruction within the islets of Langerhans results in an inability of the pancreas to produce insulin in response to a glucose stimulus. CD8+ T cells are predominantly associated within the insulitis lesion, followed by macrophages (CD68+), CD4+ T cells, B lymphocytes (CD20+) and plasma cells (CD138+) (7).

A key distinguishing feature between Type 1 and Type 2 diabetes is the presence of autoantibodies against B-cell autoantigens. In the ADDRESS-2 study of 1778

participants aged ≥ 5 years, 85% of individuals with newly diagnosed T1D (within 6 months of diagnosis) have ≥1 autoantibody at onset of diagnosis against glutamic acid decarboxylase (GAD), islet-cell antigen (IA2) and zinc transporter (ZnT8) (8). Insulin autoantibodies were not tested as majority of participants had received insulin therapy prior to study entry and may have developed antibodies to exogenous insulin (8). Tetraspanin-7 antibodies have also been identified in T1D, but are unlikely to account for large numbers (8,9).

T1D is a heritable polygenic disease; identical twins have concordance of 30-70%, siblings have a risk of 6-7% and for children with a parent with T1D the risk is 1-9% (4). To date, approximately 40 genetic loci have been known to affect disease susceptibility, supporting that the risk of T1D is polygenic (7). The HLA region of chromosome 6 (i.e. the IDDM1 locus) provides approximately one-half of the genetic susceptibility that leads to the risk of T1D (7).

Despite the links with genetic susceptibility, the incidence of T1D differs substantially in genetically similar people that are separated by socioeconomic borders (10). This suggests that environmental risk factors play a role in the development of T1D regardless of genetic background (4). A plethora of such environmental influences have been alleged to be involved, including infections (particularly viral), diet, and toxins that affect children in-utero, perinatally, or during early childhood (11). The Environmental Determinants of Diabetes in the Young (TEDDY) Study is the largest prospective observation cohort study following 8676 children from birth, and is an effort to better identify environmental factors (12). Vehik *et al* (2019) reported that frequencies of enterovirus B infection

did not differ between children with or without islet autoimmunity, but instead prolonged duration of viral infection (rather than independent, short lived infections) was observed with islet autoimmunity (13).

Despite known genetic underpinnings and various environmental influences postulated, attempts at primary prevention remain difficult and a cure for T1D remains elusive. Teplizumab, an anti-CD3 monoclonal antibody, has been shown to have potential in delaying progression of T1D in high-risk individuals (14). However, the study cohort was relatively small, with limited power. More importantly, development of antibodies to teplizumab has not been fully assessed, with previous reports reporting approximately 20% to 55% participants treated with teplizumab developing antibodies after their first course (14–16). Long-term immunologic effects or clinical outcomes are unclear. In therapeutic treatment of T1D, teplizumab failed to meet the primary end-point in the Protégé trial; showing no difference in percentage (%) of people with insulin use < 0.5 units/kg/day and HbA1C <6.5% at 1 year (17).

One of the major limitations in conducting studies targeting a cure is that majority of people with T1D already have significant β-cell destruction at diagnosis. Hence, aiming for maintenance or improvement of remaining functional β-cell mass may be a more realistic goal. Significant evidence suggests intensification of glycaemia early after diagnosis plays a major role in preserving β-cell function, which is likely to be beneficial in the long-term (6, 7). In the Diabetes Control and Complications Trial (DCCT) persistent C-peptide secretion was associated with reduced development of retinopathy, neuropathy and hypoglycaemia (18,19). Additionally,

the persistence of C-peptide secretion in people with long-term T1D could improve glucagon responses to hypoglycaemia (20).

1.1.2 Complications associated with Type 1 diabetes

In 1922, the discovery of insulin transformed T1D from a terminal to a treatable condition. However, despite advances in care (as discussed below), the condition continues to be associated with substantial medical, psychological and financial burden. Hypoglycaemia and diabetic ketoacidosis are persistent potentially life-threatening complications.

The burden of hypoglycaemia in adults with T1D is significant and is associated with mortality and morbidity (21). In adults, severe hypoglycaemia is defined as any episode of hypoglycaemia requiring the assistance of a third party to actively administer carbohydrate, glucagon, or take other corrective actions. On average, people with T1D have 1-2 self-treated incidences of hypoglycaemia per week, and 0.2–3.2 episodes of severe hypoglycaemia annually (22). However, this may well be under-reported by individuals. In a real-world non-interventional, multi-country questionnaire-based survey of 1631 people with T1D, 65% of respondents reported either rarely or never reporting hypoglycaemic events (23). Reasons for this may include fear of losing their job or driving licence, or some individuals may deliberately under-report events so that they are perceived as being in control of their diabetes (24). Additionally, hypoglycaemic episodes may go unnoticed by individuals themselves or their families (24).

Severe hypoglycaemia has the ability to provoke major vascular events, including adverse effects on cognitive function, and causing neurological disability (25). Between 4 - 10% of deaths in people with T1D are attributed to hypoglycaemia (26) and the risk of severe hypoglycaemia increases 6-fold in people with impaired awareness of hypoglycaemia (27,28).

Nocturnal hypoglycaemia accounts for approximately half of severe hypoglycaemic events, and is a source of hypoglycaemia fear (11). Recurrent hypoglycaemia results in an increased likelihood of impaired awareness of hypoglycaemia, affecting approximately 20% of adults with T1D (27). Furthermore, a preceding episode of severe hypoglycaemia is a powerful predictor of subsequent episodes of hypoglycaemia, independent of treatment intensity (29), as well as 5 year mortality, with nearly 3.4-fold higher risk of death (21).

The impact of hypoglycaemia on health systems is widespread and includes both, acute and chronic complications. In the United Kingdom (UK), diabetes accounts for greater than 10% of the National Health Service (NHS) budget (30) and in the USA relatively more is spent on type 1 compared with type 2 diabetes (8.6% of the diabetes budget compared with 5.6% of diabetes prevalence) (31).

Mean costs per hospital admission for hypoglycaemia in England is estimated to be greater than £1000, with approximately £13million spent each year relating to the total direct cost of severe hypoglycaemic episodes (32–34). Whilst hospital admissions represent only a small proportion of emergency department visits for hypoglycaemia, they have substantial resource implications (35).

Other complications related to hyperglycaemia in type 1 (and type 2) diabetes can be classified as macrovascular or microvascular. Cardiovascular disease is becoming the most common macrovascular complication and remains a major cause of morbidity and mortality. Microvascular complications of the condition primarily manifest as retinopathy, neuropathy and nephropathy. The degree and length of exposure to hyperglycaemia is believed to be the primary risk factor for microvascular disease, and reducing HbA1c through intensive diabetes management, particularly during early disease, is associated with a striking (about 70%) reduction in incidence and slower progression of microvascular and macrovascular complications (4).

Compared to the general population, the higher mortality observed in T1D results almost exclusively from higher rates of diabetes related acute and chronic complications (36). The absence of microalbuminuria appears to minimise this risk and such individuals may have a normal life expectancy (36).

It has been shown that diabetes is associated with reduced quality of life and an increased risk of developing depression (37). Adults with T1D commonly experience psychosocial problems and coping difficulties, with worry about developing complications and loss of functional abilities being a source of major distress (38). Acute fluctuations in blood glucose, particularly hypoglycaemia, can be disruptive and burdensome, negatively impacting relationships, work performance, relationships and emotional health (39).

1.2 Insulin is Key: Devices in Insulin Management

1.2.1 Multiple daily injection and Insulin Pumps

Most individuals with T1D receive insulin either through injections or through continuous subcutaneous insulin infusion (CSII; commonly known as insulin pump therapy). Intensive insulin therapy through multiple daily injections (MDI) is achieved with a long acting insulin to keep glucose levels within target in fasting condition (basal insulin) and rapid acting insulin to lower the blood glucose levels after each meal (bolus insulin). This is to mimic the natural insulin secretion of the pancreatic ß-cells. The majority of people worldwide, with T1D, are still using MDI.

Novel insulins continue to be developed to improve outcomes or quality of life, particularly for those on MDI. Since the early days of human insulin use, newer insulin analogues have been developed to optimise glycaemia, whilst minimising hypoglycaemia. Analogue insulins are similar to human insulin, but additions in free fatty acid chains to the parent molecule or modifications in amino acid sequencing, result in changes to the pharmacokinetic profile; predominantly by altering absorption through subcutaneous tissue (40).

Compared to human insulin, rapid acting insulin analogues (aspart, lispro and glulisine) dissociate faster in the subcutaneous space, enabling more rapid onset and a less protracted duration of insulin action (40). This enables insulin analogues to be injected closer to mealtimes, with greater flexibility in daily life, as well as lowering hypoglycaemia risk post-meals, particularly late evenings and in the

night. Despite these advances, limitations include that the insulin is required to be taken in advance of the meal, to coincide with glucose excursions (ideally at least 15 minutes before eating).

Newer short-acting insulin aspart (Fiasp; Novo Nordisk) has shown 23% faster onset of action than conventional insulin aspart (NovoRapid; Novo Nordisk) with a 74% greater glucose-lowering effect in the first 30 min post injection (41). The ONSET 1 trial in adults with T1D on MDI regimen showed improved glycaemia with Fiasp vs NovoRapid at 52 weeks (HbA1c levels −0.08% and +0.01% respectively with estimated treatment difference significantly favouring Fiasp (−0.10% [95% confidence interval {CI} −0.19 to −0.00]) (42). Despite this, the ONSET 5 study in adults on CSII over 16 weeks did not show improvements in HbA1c, with a statistically significant small difference in favour of insulin aspart. However, Fiasp was superior to NovoRapid for 30mins, 1 hour and 2 hours postprandial glucose measurements (43).

In 2020, novel ultra-rapid lispro (URLi; Liumjev, Eli Lilly) was approved for use. It contains treprostinil, a prostacyclin analogue, resulting in increased local vasodilation to enhance absorption of insulin lispro, and citrate, which speeds up insulin absorption through increased local vascular permeability (44,45). In adults on MDI regimen, the PRONTO-T1D study showed superior postprandial glycaemia with mealtime dosing, as well as improved daytime time in target range (least squares mean (LSM) difference = +43.6min; p=0.020) and reduced time in nocturnal hypoglycaemia (LSM difference ≤ 3.9mmol/l = -11.5min; p=0.009) (46). At 26 weeks, URLi demonstrated non-inferiority to conventional lispro (Humalog;

Eli Lilly) for HbA1c with mealtime and post-meal URLi, although there was a significantly higher endpoint HbA1c for post-meal URLi vs Humalog (47).

In a Phase 1 randomized, double-blinded, four-period, crossover study with 68 participants by Heise *et al* (2020), URLi had significantly faster insulin absorption compared to Fiasp and the conventional insulins (Novorapid and Humalog) (48). The early half-maximal drug concentration was reached in 12.8 minutes of administration with URLi. Least square mean differences showed URLI was 5.9 (4.1 to 7.7) minutes faster than Fiasp, 12.5 (10.8 to 14.3) minutes faster than Humalog and 13.9 (12.1 to 15.7) minutes faster than NovoRapid (all $p < 0.0001$). The maximum postprandial glucose at 1 and 2 hours post-meal was significantly reduced with URLi compared to Humalog and NovoRapid ($p<0.05$) (48). It is important to note, however, that the main study limitation was the use of a liquid test meal, which is not a typical meal for people. Further evaluation in larger, long-term clinical studies is warranted. It is likely any advantages of rapid onset of action with faster short-acting insulin analogues, will need to be offset against the potential disadvantages of earlier cessation of action.

Amongst the long acting insulins, new insulin degludec (Tresiba; Novo Nordisk) is an ultra-long acting insulin lasting >24hours, with a relatively stable profile, low intra-individual variability and minimal peaks/troughs in pharmacodynamic studies (40). In a meta-analysis comparing insulin degludec and glargine (Lantus; Sanofi-Aventis) in T1D, no difference in glycaemia were seen, but hypoglycaemia was less probable with degludec, including nocturnal hypoglycaemia (rate ratio

(RR) = 0.68, 95% CI 0.56 to 0.81) (49). Between degludec and detemir (Levemir; Novo Nordisk), no differences were observed in people with T1D (49).

Another newer insulin is glargine U300 (Toujeo; Sanofi-Aventis), which is more slowly released and lasts longer than Lantus, the U100 formulation (40). A meta-analysis comparing insulin glargine U300 to U100, found reductions in clinically significant nocturnal hypoglycaemia (RR = 0.64, 95% CI 0.42 to 0.97) in T1D (50).

Overall, the repertoire of available insulins is ever increasing and is important for people with T1D. Newer analogues have more stable profiles and less variability in glucose-lowering, which may be clinically useful, with some potential additional benefit in the reduction of nocturnal hypoglycaemia and severe hypoglycaemia events (40). The challenge is establishing who would benefit the most from these newer insulin analogues and whether they are cost-effective. Further studies will help to establish this.

An inhaled insulin preparation (Afrezza, Mannkind, Westlake City, CA, USA) is an ultrarapid-acting insulin that mimics the time action of physiological insulin more closely than subcutaneous insulin, but is currently used sparingly. The “ultra-short” duration of insulin exposure can lead to late post-meal hyperglycaemia, necessitating the use of a second dose of Afrezza in approximately 20-40% of individuals (51). Further limitations include the need for fixed dosing (multiples of 4 unit increments only), issues with cost and need for pulmonary function tests (52). As a result, insulin administered subcutaneously remain the mainstay of treatment.

New “Smartpen” insulin systems integrate additional features to the standard insulin pen. For example, the Eli Lilly Memoir insulin pen was one of the first to track administered doses and log the last 16 doses through its Digital Log. The InPen system (Companion Medical) not only tracks administered doses, provides bolus advice in 0.5 U increments, but can also transmit these data via Bluetooth (53).

CSII provides an alternate modality of insulin therapy via a pump, with the advantage of delivering variable basal rates throughout the day and fewer injections. One of the other advantages of insulin pump therapy, is the ability of the bolus infusion to be varied to adjust for the composition of food (e.g. glycaemic index) or duration of a particular meal (including spread of different courses i.e. starter, main and/or dessert). There are various different bolus subtypes, including square and dual/combination bolus (Figure 1.1). The aim of extending a bolus with an insulin pump, manipulates the insulin action to match the extended absorption of glucose from low glycaemic index foods or foods with protein and fat (54).

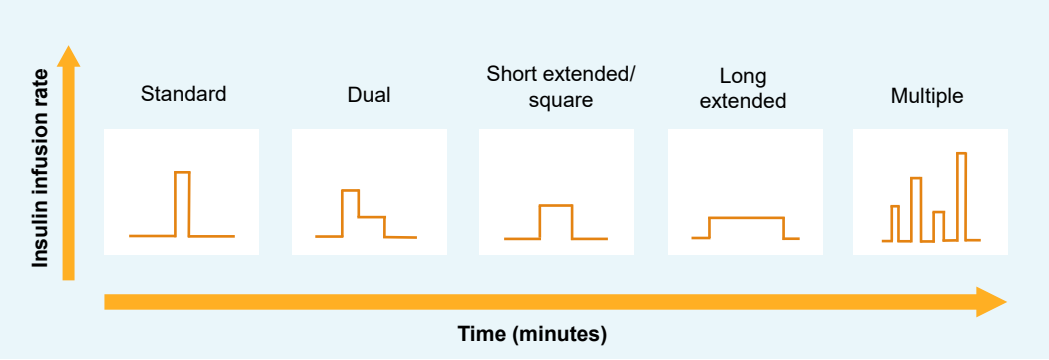

Figure 1.1: Subtypes of insulin bolus dosing through insulin pump therapy

Insulin pumps can deliver meal bolus insulin through various subtypes of bolus dosing. These include standard bolus, where the insulin is delivered immediately; short or long extended/ square wave bolus, where the insulin delivery is spread over longer period of time; and dual wave bolus, where a percentage of the insulin is delivered as a rapid bolus and the remainder is delivered as an extended bolus.

Previously, the overall effectiveness of CSII has been debated due to the heterogeneity of participants at baseline and their glycaemic control, inclusion of studies with short duration, use of obsolete pump technology and differing psychological factors, such as non-adherence and lack of motivation (55). Furthermore, some initial meta-analyses comparing outcomes with MDI vs. CSII were reported to be misleading due to poor trial selection and over-reliance on summary mean effect size as evidence of effectiveness (56).

Strict glycaemic control is achievable for both MDI and CSII users without hypoglycaemia in some people with T1D, especially those who are motivated, have had structured education and have ongoing input from healthcare professionals (56). However, a beneficial effect of CSII has been shown in a meta-regression analysis of mean effect size (HbA1c difference or severe hypoglycaemia rate ratio) on reducing HbA1c, particularly in those with baseline suboptimal glycaemia, and reducing hypoglycaemic frequency, especially in those with frequent, severe hypoglycaemia (57). Best outcomes in CSII use are therefore observed in those motivated to use insulin pumps and with continued elevated HbA1c and/or disabling hypoglycaemia on MDI (56).

1.2.2 Adjuvant Pharmacotherapies to Insulin

In addition to insulin therapy, the inclusion of other pharmacological agents have been explored for use in T1D to improve glycaemia. Pramlintide (Symlin; AstraZeneca) is an amylin analogue. Amylin is a polypetide co-secreted with insulin by pancreatic β-cells, and acts by suppressing postprandial glucagon

secretion and slowing gastric emptying (58). In a meta-analysis comparing pramlintide vs placebo, a reduction in HbA1c was observed, as well as a reduction in total daily and mean insulin doses, body weight and postprandial glucose levels (59). Pramlintide is FDA approved for adjunctive use in Type 1 diabetes in the US, however its clinical use has been limited by cost, gastrointestinal side effects, and frequency of administration (requires 3 to 4 additional pre-meal injections per day being impractical on a daily basis) (58). Pramlintide is not available in Europe.

Glucagon-like peptide-1 (GLP-1) is an incretin secreted by intestinal enteroendocrine L-cells in response to a meal stimulus and stimulates insulin secretion in a glucose-dependent manner (60). It suppresses glucagon secretion, inhibits gastric emptying and reduces appetite and food intake through early satiety (60). In a meta-analysis of adjunctive GLP-1 receptor agonist use, there was a statistically significant but only minimal reduction in HbA1c levels (-0.2 (-0.40 to 0.02)%), decrease in body weight (-3.53 (-4.86 to 2.19) kg), and weight-adjusted-bolus insulin doses (61). Its use was associated with increased gastrointestinal side effects but not with hypoglycaemia (62).

The enzyme dipeptidyl peptidase-4 (DPP-4) rapidly degrades physiological GLP-1, therefore DPP-4 inhibitors enhance the action of endogenous incretins by inhibiting their degradation (62). In a meta-analysis with pooled data from 5 randomized controlled trials (RCTs), the additional use of DPP-4 inhibitors in T1D had no significant impact on HbA1c, weight, daily insulin requirement, hypoglycaemia incidence (63). Neither DPP-4 inhibitors, nor GLP-1 receptor agonists, are currently licenced for adjunctive use in T1D in the UK.

Another group of adjunctive agents include sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which primarily work by increasing excretion of glucose in the urine secondary to blocking reabsorption of glucose in the proximal renal tubule (64). Dual SGLT-1/2 inhibitor additionally blocks SGLT-1, a major transporter of intestinal glucose and decreases reabsorption of glucose in the intestine as well (62). In a meta-analysis of 13 RCTs, SGLT inhibitors reduced HbA1c, fasting plasma glucose and total daily insulin dose (65). However, higher risks of diabetic ketoacidosis, urinary tract and genital infections were associated with SGLT inhibitors. SGLT inhibitors did not increase overall hypoglycaemia risk (65). Both sotagliflozin (SGLT-1/2 inhibitor; Lexicon Pharmaceuticals) and dapagliflozin (SGLT-2 inhibitor; AstraZeneca) have been licensed in the UK for adjunctive use in people with T1DM with a body mass index (BMI) > 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy (66,67).

1.2.3 Techniques for glucose monitoring

Glucose monitoring methods have significantly improved since urine testing before the 1980s, to portable glucose meters for self-monitoring in 1978, to present day use of continuous glucose monitoring, introduced in 1999 (68). For most people, blood glucose levels are determined by intermittent capillary blood glucose measurements using glucose meters. The National Institute of Clinical Excellence (NICE) recommends people with T1D to test at least 4 times a day, and up to 10 times daily (69). The commercial market for blood glucose meters accounts for

approximately 85% of the total biosensor market (70). In 2015, the global market for glucose sensors was estimated at US$15.3 billion, and is anticipated to reach US$ 31.0 billion by 2022 (71).

Current day commercially available real-time continuous glucose monitoring (rtCGM) devices use subcutaneous needle type sensors, which employ a sensor inserted beneath the skin to detect glucose concentrations within the interstitial fluid. There are three generations of enzyme-based glucose sensors, with the fourth-generation being non-enzymatic. These have been summarised in Figure 1.2. Most currently used systems for CGM are first-generation enzyme-based, with the exception of Abbott Freestyle Libre (intermittently scanned continuous glucose monitoring; isCGM), which uses osmium as a mediator (72).

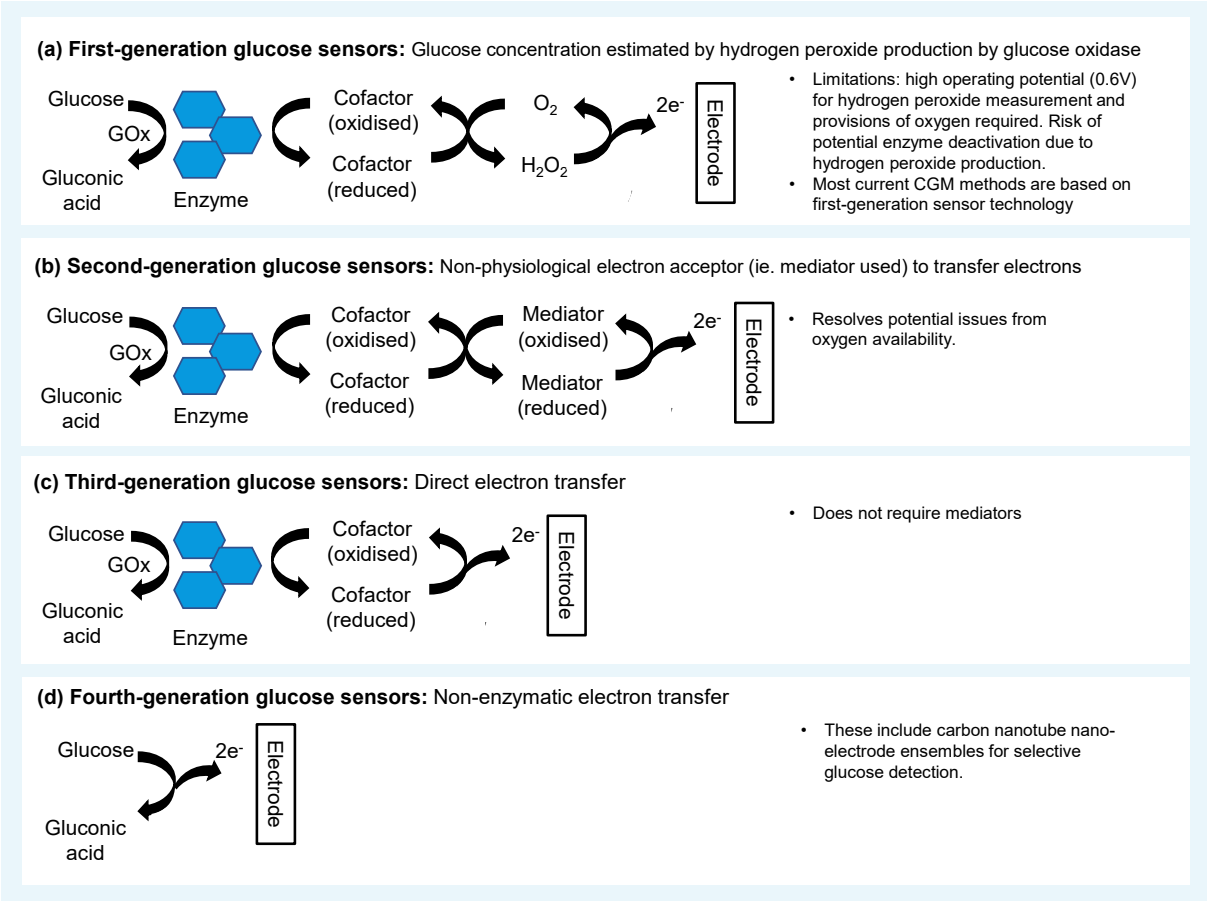

Figure 1.2: Methods of glucose sensing technology

(a) First-generation glucose sensors based on hydrogen peroxide production by glucose oxidase (GOx). (b) Second-generation glucose sensors based on redox mediators. (c) Third-generation glucose sensors based on direct electron transfer, without artificial mediators. (d) Fourth-generation glucose sensors using non-enzymatic electron transfer (e.g. carbon nanotubes and alloy nanostructures containing lead, palladium, gold and rhodium) enable direct electro-oxidation of glucose to gluconic acid. Reproduced with permission from Avari *et al* (72)**.**

RtCGM systems support optimal insulin dosing by providing continuous real-time glucose values and trends. Additionally, it provides alerts and alarms for impending hypo- and hyperglycaemia, and in times of rapid glucose change. Freestyle Libre does not provide real-time data with alerts and alarm, but users are able to review preceding 8 hours of continuous data when the reader is swiped over the sensor. At the time of writing, FreeStyle Libre 2, a hybrid CGM device with

optional high and low glucose alarms has obtained Certification (CE) Mark and US Food and Drug Administration (FDA) approval, but is yet not widely available.

The use of rtCGM has been associated with improved glycaemic control, reduced HbA1c (73), and reduced exposure to hypoglycaemia (74), in people using CSII and MDI regimens (75–77). Reduced fear of hypoglycaemia (78), improvements in quality of life (79), and cost-effectiveness (80) have also been associated with rtCGM use. Moreover, rtCGM can be particularly beneficial in people with T1D at higher risk of hypoglycaemia, for example, those with recurrent severe hypoglycaemia and hypoglycaemia unawareness (81,82).

However, despite the advances in technology and established benefits, there are barriers to device uptake, which include person-related, health-care system related and environmental factors. Data from the T1D Exchange Registry in 2016-2018 with 22,697 participants indicate that rtCGM uptake in the United States (US) was only 30%, increased from 7% in 2010–2012 (83). One of the most commonly endorsed reasons for discontinuation of rtCGM was cost (84).

In the UK, rtCGM funding is available to individuals meeting the NICE criteria, with remaining users self-funding. The criteria include: >1 episode of severe hypoglycaemia/year; complete loss of awareness of hypoglycaemia; hypoglycaemia that is causing problems with daily activities; extreme fear of hypoglycaemia; and HbA1c ≥ 75mmol/mol IFCC (≥ 9.0% DCCT) despite testing ≥10 times/day (69).

However, even within a reimbursed healthcare system, there are barriers to rtCGM use, which limit uptake. These include concerns about accuracy and reliability, alarm fatigue, and physical discomfort. Current rtCGM devices are susceptible to 5-15 minutes lag behind blood glucose owing to diffusion of glucose to interstitial fluid (85). Another important factor for device uptake is age. Younger users (18–25 years) in the T1D Exchange Registry in the United States have the lowest uptake, but are also associated with highest levels of diabetes distress and HbA1c compared to older individuals (72,84). Younger users are also more likely to worry about others' perception and dislike wearing devices (72,84). In contrast, in the German/Austrian Diabetes Patienten Verlaufsdokumentation (DPV) registry, since 2015, there has been an exponential increase of rtCGM use amongst young adults aged 18 – 26 years in Germany and Austria, with relatively slower uptake in other age groups.

For many years, huge research efforts have gone in to developing alternative modalities of glucose sensing, including non-invasive sensors using optical and transdermal approaches. However, despite non-invasive techniques having been developed, no commercial device has, to date, been successful (72).

Currently available glucose monitoring technologies that can be used by people with T1D are summarised in Table 1.1.

System	Guardian Connect (Sensor 3)	Enlite Sensor	Dexcom G6	Eversense	Freestyle Libre	Medtrum S7 EasySense
Sensor life	7 days	6 days	10 days	90 days / 180 days (Eversense XL)	14 days	14 days
Sensor method	Subcutaneous	Subcutaneous	Subcutaneous	Implantable (within the subcutaneous tissue)	Subcutaneous	Subcutaneous
Transmitter life	12 months	12 months	3 months	12 months (rechargeable)	3 years (reader life-span)	3 months
Calibration	Yes, every 12h	Yes, every 12h	No, factory-calibrated (user may self-calibrate if required)	Yes, every 12h	No, factory-calibrated	Yes, every 12h
Frequency of readings	5 minutes	5 minutes	5minutes	5 minutes	When sensor is scanned. Glucose data stored every 15minutes	2 minutes
CE Mark	2018	2011	2018	2017	2014	2014
FDA approval date	2018	2013	2018	2017	2017	Awaiting
Company	Medtronic	Medtronic	Dexcom	Senseonics	Abbott	Medtrum
Sensing technology	Enzyme electrode	Enzyme electrode	Enzyme electrode	Optical Fluorescence	Enzyme electrode	Enzyme electrode
MARD	10.6% in abdomen; 9.1% in arm (86)	13.6% (87)	9.0% calibrated once daily (88); 10.0% without calibration (89)	8.8% (90)	11.4% (91)	9.1% (92)

Table 1.1: Currently available glucose monitoring systems and their accuracy

The mean absolute relative difference (MARD) is a metric of glucose sensor accuracy (i.e. how close the sensor glucose measurement is to blood glucose). A MARD of <10% represents sufficient accuracy for CGM device readings to make insulin dosing decisions. Reproduced with permission from Avari *et al* (72).

1.2.4 State-of-the-art innovation: Automated insulin delivery systems

With insulin pump and rtCGM improving diabetes care, these two technologies are now being used together as sensor augmented pump therapy. Insulin pumps combined with rtCGM integrated with computer algorithms (i.e. closed-loop systems or artificial pancreas) are now available.

Initial systems, also known as low glucose suspend (LGS) pumps, suspend basal insulin delivery if a low glucose concentration threshold is reached (Medtronic 630G; Medtronic diabetes, Northridge, CA, USA). Subsequent systems are able to suspend or reduce insulin delivery by algorithms which predict when hypoglycaemia is likely to occur (known as predictive low glucose suspend (PLGS) system; Medtronic 640G system (Medtronic diabetes, Northridge, CA, USA) and Tandem Basal-IQ (Tandem Diabetes Care, San Diego, CA, USA). Both LGS and PLGS have been shown to be efficacious in reducing hypoglycaemia without deterioration in glycaemic control (93–97).

The latest state-of-the-art technologies that are commercially available include the Medtronic 670G system (Medtronic diabetes, Northridge, CA, USA), Tandem X2 insulin pump with Control-IQ technology (Tandem Diabetes Care, San Diego, CA, USA), and the Dana RS pump compatible-CamAPS FX (Cambridge University, Cambridge, UK). In addition to PLGS, these systems are able to increase insulin delivery in response to hyperglycaemia or predictive hyperglycaemia. The system is not fully automated as a closed-loop “artificial pancreas”, and is therefore known as a hybrid closed-loop automated system. The user is required to announce when

a meal will be eaten and provide the planned carbohydrate intake information to activate an appropriate insulin bolus.

Future hybrid closed-loop systems due to be available soon, include Diabeloop (Grenoble, France; CE mark 2018), which uses the Kaleido patch pump (Kaleido, Utrecht, Netherlands). Initial studies appear to be promising (98,99), however long-term studies on clinical and cost-effectiveness of hybrid closed-loop systems are required, as well as studies of which populations derive meaningful benefits. Lal *et al* published decreasing use of Medtronic 670G over 12 months (despite increased time in range (TIR) when used), with the % time in auto mode (i.e. hybrid CL) decreasing from median of 83% after a week, to 2% median after a year of use (100).

In a closed-loop system, the control engineering algorithm enables integration of the parts of these technologies for glucose control (Figure 1.3). Several control algorithms have been developed and studied, including Model Predictive Control (MPC), Proportional Integral Derivative (PID) and Fuzzy Logic (FL), with the two former approaches most widely used. MPC is a control method which predicts future glucose concentrations using an individualised mathematical model of glucose regulation based on inputs such as insulin delivery. The model-predicted glucose concentration is compared with measured glucose levels, and the model is updated, calculating future insulin delivery rates to minimise the difference between model-predicted glucose concentration and target glucose levels (101). PID is a reactive control algorithm that adjusts insulin delivery rate from determining three key perspectives: deviation from target glucose (proportional

component), area under the curve between measured and target glucose (integral component) and rate of glucose change (derivative component) (102). The use of FL has increased over the recent years and the algorithm modulates insulin delivery based on rules that replicate diabetes clinicians (103).

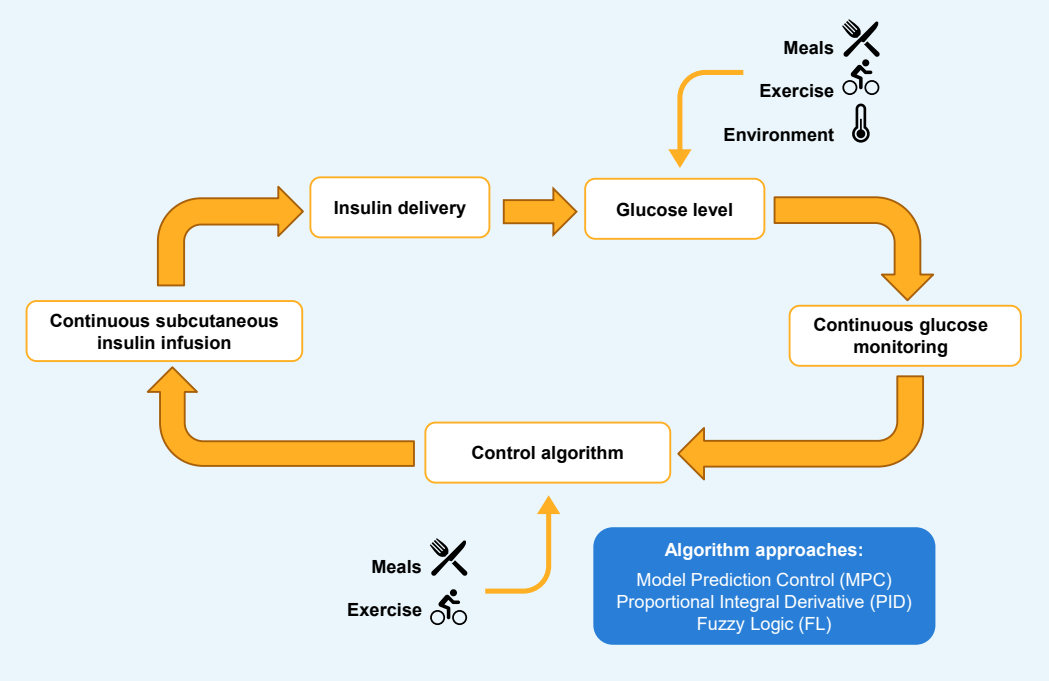

Figure 1.3: Illustration of a closed-loop automated artificial pancreas system

A closed-loop insulin delivery system consists of continuous glucose monitoring, an insulin pump, and a glucose control algorithm. These algorithms are a set of programmed rules which enable the glucose controller to make automated insulin adjustments based on real-time CGM data. Current hybrid closed-loop control algorithms used in clinical practice also require meal-announcement and in some, exercise-announcement as well, to influence the algorithm's response.

Barriers remaining to full automation include the slow pharmacokinetics of subcutaneous insulin, sensor accuracy and the impact of other factors such as activity. Further developments including the addition of glucagon, better accuracy of rtCGM and the availability of insulins with more rapid onsets of action have the potential to improve current AP systems (101). In terms of clinical practice,

questions remain regarding adoption of closed-loop systems and whether it will be cost-effective for health care systems with adequate training and infrastructure.

Intriguingly despite the advances in technology, results from the recent T1D Exchange clinical registry show that although there is increased use of insulin pumps from 57% in 2010–2012 to 63% in 2016–2018 and use of rtCGM from 7% to 30%, the adjusted mean HbA1c increased from 7.8% to 8.4% ($p < 0.001$ adjusted for age, diabetes duration, self-monitoring blood glucose (SMBG), and use of rtCGM) (83). It remains unclear on why glycaemia worsened despite increased use of technology, although Rodbard speculated this may be due to changes in population at study groups, racial/ ethnic groups and income status (104). The overall findings also suggest that use of technology does not automatically result in improved glycaemia, but that interpretation and subsequent action is also required. Structured education and decision support systems may be key to "getting the dose right" (Section 1.3).

1.2.5 Measures of glycaemia

HbA1c, has traditionally been the standard for assessing glycaemia and reflects average blood glucose levels over 1 to 3 months prior to testing. Its utility was established by the DCCT trial (105,106) and the Stockholm Diabetes Intervention Study (107,108) as a predictor of diabetes complications. For example, for every 10% reduction in HbA1c, the risk of progression of retinopathy reduced by 44%, microalbuminuria by 25%, macroalbuminuria by 44% and of confirmed clinical neuropathy by 30% (105). Furthermore, the Epidemiology of Diabetes

Interventions and Complications (EDIC) study established that mortality increased significantly with increasing HbA1c (109,110).

HbA1c does, however, have its limitations with its validity compromised in people with iron deficiency anaemia, haemoglobinopathies, and renal disease.

With increasing use of glucose monitoring technologies, latest consensus guidelines identify percentage times in glucose range as a metric of glycaemia that enables actionable information (111). The recommended times in ranges metrics for rtCGM include the following: time per day within target glucose range (time in range [TIR]: 3.9-10.0 mmol/l), time below target glucose range (TBR: <3.0 and <3.9 mmol/l), and time above target glucose range (TAR: >10.0 mmol/l). Validity of %TIR using seven-point SMBG testing has been demonstrated with a clear association with the risk of development of, or progression of retinopathy and development of microalbuminuria in the DCCT study data (68). The adjusted hazard ratios for developing retinopathy and microalbuminuria were 1.64 (1.51–1.78) and 1.40 (1.25–1.56), respectively, for each 10% decrease in % time spent between 3.9-10 mmol/l.

Glycaemic variability (GV) is also being increasingly recognised as a potential contributory factor for developing diabetes related complications (112). GV reflects hypo- and hyperglycaemic excursions, and can define within- and between day glucose variability.

Animal and human studies *in-vitro* suggest hypo- and hyperglycaemic excursions may be associated with mitochondrial oxidative stress, accelerated atherosclerosis, secondary endothelial damage, impaired quality of life, as well as mortality (113–116). A higher incidence of severe hypoglycaemia in people with T1D has been associated with increased glycaemic variability (117). Furthermore, *in-vitro* and *in-vivo* data suggest glycaemic variability is as an independent risk factor for total mortality and death due to cardiovascular disease in both type 1 and type 2 diabetes (118–120).

One of the main limitations of GV is that a gold standard measurement has yet not been identified, leading to heterogenous study designs and reported study outcome measures (116). As a result, the "International Consensus on Use of Continuous Glucose Monitoring" published in 2017, recommend the coefficient of variance (CV) should be considered as the primary measure of variability (119,121). The advantage of CV is that it is more descriptive of hypoglycaemic excursions than standard deviation (SD) alone, as SD is dependent on the mean. A threshold %CV of 36% is used to distinguish between stable and unstable glycaemia in people with diabetes, because the frequency of hypoglycaemia is significantly increased beyond this limit (122).

Using discriminant ratios, Moscardo *et al* (2020) showed that the mean absolute glucose (MAG) may be the optimal index to differentiate glucose variability, and may be a complementary therapeutic monitoring tool in addition to HbA1c and a measure of hypoglycaemia (116). The data supported percentage TIR reported at

3.9-10.0 mmol/l (70-180 mg/dL) to be the optimal range for discriminating between individuals (116).

Overall, GV can be subdivided into glycaemic measures (i.e. based on glucose distribution), and measures based on risk and quality of glycaemic control, which are associated with frequency and severity of hypoglycaemia (74). Table 1.2 reports definitions of the various GV metrics that exist and glucose control indices. (123)

Metric	Definition	Computational Formula	Clinical interpretation
Glycaemic measures based on glucose distribution			
Standard deviation (SD)	Shows how much variation or dispersion there is from the average	$SD = \sqrt{\sum_{i=1}(G_i - \bar{G})^2/(N-1)}$ G = glucose reading N = the number of observations I = the sample index	
Coefficient of variation (%CV)	Measure of dispersion of data points around the mean	$\%CV = SD/\bar{G} \cdot 100$ SD = standard deviation G = glucose reading	Target %CV <36% Lower %CV targets (<33%) may provide additional protection against hypoglycaemia for those receiving insulin (111)
Mean amplitude of glycaemic excursions (MAGE) (124)	The mean of the glycaemic excursions of glucose peaks and nadirs encountered in a day (greater than 1 SD)	$MAGE = \sum_{i=1}^{x} \lambda_i/x \; if \; \lambda > v$ λ = blood glucose change from peak to nadir (or nadir to peak) x = total number of valid observations ν = 1 SD of mean glucose for a 24h period.	
Continuous overlapping net glycaemic action (CONGA) (125)	A composite index of the amount of time spent in glycaemic excursions and the degree of glycaemic variation	$CONGA_n = \sqrt{\sum_{t=1}^{k}(D_t - \bar{D})^2 \Big/ (k-1)}$ $D_t = G_t - G_{t-m}$ k = number of observations where there is an observation nx60 min ago m = nx60 G_t = the glucose reading at time *t* min after start of observations.	
Mean of daily differences (MODD) (126)	Metric of intraday variability: the average of the difference between values on different days but at the same time	$MODD = \sum_{t=t_1}^{tk} \lvert G_t - G_{t-24h} \rvert \Big/ k$ k = number of observations with an observation 24h ago	
Lability Index (LI) (127)	The formula processes three glucose values to calculate a lability value and then moves to the next three glucose values, and so on. The LI is the mean of these values (128)	$M = \sum_{i=1}^{N} \lvert 10 \cdot log_{10}(G_i/IGv) \rvert^3 \Big/ N$ G = glucose measured IGv = ideal glucose value (default: 100mg/dL)	

		N = the total number of readings	
Glycaemic variability percentage (GVP) (116)	A quantitative measurement of GV over an interval of time by analysing the length of the CGM temporal trace normalized to the duration under evaluation.	$GVP = 100 \cdot (L \,/\, L_0 - 1)$ $L = \sum_{i=1}^{n} \sqrt{dx_i{}^2 + dy_i{}^2}$ L_0 = the ideal length for a given temporal duration *dx* = the decomposition of the temporal line into horizontal component *dy* = the decomposition of the temporal line into vertical component n = the total number of glucose recordings	
Mean absolute glucose change per unit time (MAG) (121)	Calculates the sum of the differences between successive glucose values divided by the total time measured in hours	$MAG = \sum_{i=1}^{N=1} (G_i - G_{i+1}) \Big/ T$ G_i = the glucose measured N = the number of measurements T = the total time (in hours)	
Measures based on risk and quality of glycaemia			
Glycaemic Risk Assessment in Diabetes Equation (GRADE) (129)	An integrated risk score based on use of the mean value and the relative percent contribution to the weighted risk score from the hypoglycaemic, euglycaemic, hyperglycaemic range, respectively, e.g. GRADE (hypoglycaemia%, euglycaemia%, hyperglycaemia%)	$GRADE = median(425\ x\ \{\log[log(Gn)] + 0.16\}^2)$ G = glucose measured	Median GRADE < 5 is good control with values corresponding to euglycaemia
M-VALUE (130)	A measure of the stability of glucose excursions in comparison with an "ideal" glucose value, which can be decided by the investigator Calculated on each glucose value using a formula and then divided by the total number of values to produce a mean (131)	$M = \sum_{i=1}^{N} \lvert 10 \cdot log_{10}(G_i/IGV) \rvert^3 \Big/ N$ G = glucose measured IGV = the ideal glucose value (default: 100mg/dL) N = the total number of readings	M-value is zero in healthy controls, rising with increasing glycaemic variability or poorer glycaemic control (131) Defined for T2D: 0≤M≤18 is good control; 19≤M≤31 is fair control; and M≥32 is poor control (128)

Low blood glucose index (LBGI)/ High blood glucose index (HBGI) (132)	Measures of risk of hypoglycaemia (LBGI) and hyperglycaemia (HBGI) Calculated by transforming each glucose value by the formula and then attributing a risk value to the transformed point	$$LBGI = \left(\sum_{i=1}^{N} rl(x_i)\right)\Big/N$$ $$HBGI = \left(\sum_{i=1}^{N} rh(x_i)\right)\Big/N$$ $$rl(x_i) = 22.77 \cdot f(x_i)^2 \; if \; f(x_i) \leq 0, and \; 0 \; otherwise$$ $$rh(x_i) = 22.77 \cdot f(x_i)^2 \; if \; f(x_i) > 0, and \; 0 \; otherwise$$ $$f(x_1) = ln(x_i)^{1.084} - 5.381$$ x_i = the glucose recording N = the total number of recordings.	If the glucose risk score is below 0, then the risk is labelled as LBGI, and if it is above 0, then it is labelled as HBGI (128)
Average daily risk ratio (ADRR) (133)	A risk assessment of the total daily BG variation in risk space; i.e. the sum of the peak risks of hypoglycaemia and hyperglycaemia for the day	$$ADRR = \left(\sum_{j=1}^{M} LR^j + HR^j\right)\Big/M$$ $$LR^j = max\big(rl(x_1), \cdots rl(x_n)\big)$$ $$HR^j = max\big(rh(x_1), \cdots rh(x_n)\big)$$ j = the day index M = total number of days x_i = the glucose recording n = total number of recordings per day	
Personal glycaemic status (PGS) (134)	A composite index based on rtCGM data only that assesses four domains of glycaemic control: mean glucose, glycaemic variability, time in range and frequency and severity of hypoglycaemia	$$PGS = F(GVP) + F(MG) + F(PTIR) + F(H)$$ $$F(GVP) = 1 + 9 \,/\, 1 + e^{-0.049 \cdot (GVP - 65.47)}$$ $$F(MG) = 1 + 9/1 + e^{-0.1139 \cdot (MG - 72.08)}$$ $$F(PTIR) = 1 + 9 \,/\, 1 + e^{-0.0833 \cdot (PTIR - 55.04)}$$ $$F(H) = F_{54}(H) + F_{70}(H)$$ $$F_{54}(H) = 0.5 + 4.5 \cdot (1 - e^{-0.81093 \cdot N_{54}})$$ $$F_{70}(H) = \begin{cases} 0.5714 \cdot N_{70} + 0.625 & N_{70} \leq 7.65 \\ 5 & N_{70} > 7.65 \end{cases}$$ MG = the mean glucose PTIR = the %TIR (70-180mg/dL) N_{54} = number of hypoglycaemic events per week below the low threshold (≤54mg/dL) N_{70} = number of hypoglycaemia events per week below the higher threshold (≤70mg/dL)	

Index of glycaemic control (IGC) (135)	Sum of hyperglycaemia index and hypoglycaemia index	$IGC = Hypo\ Index + Hyper\ Index$ $Hypo\ Index = \left(\sum_{1=1}^{k_{hypo}} \left(LLTR - G_{hypo_i}\right)^b\right) \Big/ (N \cdot d)$ $Hyper\ Index = \left(\sum_{1=1}^{k_{hyper}} \left(G_{hyper_i} - ULTR\right)^a\right) \Big/ (N \cdot c)$ LLTR = the Lower Limit of Target Range (default= 80mg/dL) b = an exponent in the range [1.0, 2.0] (default= 2.0) d = a scaling factor to weigh hypoglycaemia and hyperglycaemia values (default= 30) ULTR is the upper Limit of Target Range (default= 140mg/dL) a = an exponent in the range [1.0, 2.0] (default=1.1) c = a scaling factor (default=30)	
J-Index (136)	Combination of information from mean and SD of all glucose values Sensitive to hyperglycaemia; but rarely sensitive to hypoglycaemia (135)	$J = 0.001 \cdot (\bar{G} + SD)^2$ G = glucose reading (mg/dL) $J = 0.324 \cdot (\bar{G} + SD)^2$ G = glucose reading (mmol/L)	Defined for T2D: $10 \leq J \leq 20$ is ideal control; $20 \leq J \leq 30$ is good control; $30 \leq J \leq 40$ is poor control; $J > 40$ is lack of control

Table 1.2: List of measures of glycaemic variability

Abbreviations: AUC, area under the curve; CV, coefficient of variation; CONGA, continuous overlapping net glycaemic action; G, glucose; GRADE, glycaemic risk assessment in diabetes equation; GVP, glycaemic variability percentage; HBGI, high blood glucose index; IGC, index of glycaemic control; LI, lability index; LBGI, low blood glucose index; MAG, mean absolute glucose change; MAGE, mean amplitude of glycaemic excursions; MODD, mean of daily differences; PGS, personal glycaemic status; SD, standard deviation.

1.3 Getting the Dose Right

For maintaining glucose physiology, a balance is required between the two main driving forces i.e. insulin requirements and dietary intake. Besides optimising basal insulin, it is therefore necessary to ensure insulin dosing at mealtimes and correction doses are appropriate to avoid postprandial hypo- or hyperglycaemia.

1.3.1 Structured education and carbohydrate counting

Structured education has been shown to be effective for self-management of T1D, by empowering individuals with self-monitoring capillary blood glucose (CBG), carbohydrate counting, and insulin dose adjustment (137,138). Adjusting insulin meal bolus doses according to carbohydrate content enables flexibility to manage glycaemia, but requires knowledge of individualised insulin to carbohydrate ratios (ICR) and insulin sensitivity factor (ISF).

NICE recommends that structured education should be offered to all adults diagnosed with T1D with the aim of supporting self-management (69). The Dose Adjustment for Normal Eating (DAFNE) programme, derived from the German Diabetes Teaching and Treatment Programme (DTTP), provides an evidence-based training course for adults with T1D in the UK. Participation in DAFNE has been associated with a reduction in HbA1c (137) and GV (139), as well as being cost-effective (140). An observational analysis of 687 people demonstrated significant reduction in median HbA1c of −3.5 mmol/mol (−0.3%) at 12 months, with a significant reduction of −1.5 mmol/mol (−0.1%) still seen at 5 years of follow-up ($p<0.001$) (139). DAFNE is also associated with significant reductions

in diabetic ketoacidosis and severe hypoglycaemia, as well as restoring hypoglycaemia awareness (141), reducing psychosocial distress and improvement in perceived well-being (142). Another evidence-based structured education course delivered in the UK for T1D, includes the Bournemouth Type 1 Intensive Education (BERTIE) (143).

However, despite structured education, in the UK, only 7.5% of people with T1D achieve a treatment target of HbA1c below 48mmol/mol and only 27% of people were found to have achieved a HbA1c below 58mmol/mol (144). Barriers to optimal glucose control include fear of hypoglycaemia, the time commitment required from each individual, inadequate support, and the complexity of calculating meal boluses, which involves a combination of arithmetic addition, subtraction and division. Low numeracy skills are common amongst people with diabetes and can be a significant problem in diabetes self-management (145,146). One study found approximately 25% of people were unable to determine what blood glucose values were within the normal range, 56% of participants were unable to calculate the total carbohydrate content in a pre-packaged snack, and 59% could not accurately calculate the insulin dose based on glucose level and carbohydrate intake (146,147).

1.3.2 Insulin bolus advisors for clinical decision support

To assist people with calculating meal insulin boluses and improve post-meal glucose excursions, bolus advisors (also known as bolus calculators) are simple decision support systems to calculate prandial and corrective bolus insulin doses.

Clinical decision support systems (CDSS) are computerised systems to assist clinicians and patients in assessing disease status and facilitating one or more aspects of the therapy or management. Individualised characteristics of patients are matched to a computerised knowledge base, with software algorithms using communication or processing technology (feedback, advice, reinforcement, rewards, patient decision support, goal setting and reminders) to provide a tailored response (148).

The first bolus calculator was patented by Medtronic in 1999 (#6554798) and implemented within an insulin pump (Deltec Cozmo) in 2002 (12). Now, bolus calculators are incorporated into many commercially available blood glucose monitors (13) and insulin pumps (14). The incorporation of bolus calculators into standard glucose meters (e.g. AccuCheck Aviva Expert and FreeStyle Insulinx) enabled use in individuals who are not on insulin pumps, but using MDI basal-bolus regime. The widespread availability of smartphones has also led to a rapid increase in the availability of bolus calculators and other decision support software.

A standard bolus calculator uses a generic formula taking into account the target glucose level, current glucose level, carbohydrate content of a meal, insulin:carbohydrate ratio (ICR), insulin sensitivity factor (ISF) and insulin on board (IOB). This formula is described as follows:

$$B = \frac{CHO}{ICR} + \frac{G_c - G_{sp}}{ISF} - IOB$$

B = recommended dose of insulin (units)
CHO = total amount of carbohydrate in the meal (grams)
ICR = insulin-to-carbohydrate ratio i.e. how many grams correspond to one unit fast acting insulin (g/U)
G_c = the current capillary BG level (mmol/l)
G_{sp} = the target blood glucose level (mmol/l)
ISF = insulin sensitivity factor (mmol/l/U) i.e. a personal relation describing drop in blood glucose after one unit of insulin
IOB = insulin-on-board i.e. the amount of insulin still in the body from previous injections

1.3.2.1 Insulin-Carbohydrate Ratio

The ICR denotes the amount of carbohydrates covered by one unit of insulin. A commonly used formula to estimate the initial ICR is based on the total daily dose (TDD) of insulin, where the ICR is determined by dividing the TDD from a factor of 300, 450 or 500 (i.e. 300/450/500 rule).

Another formula proposed by Davidson and colleagues, is based on the retrospective analysis of 167 adults on insulin pump that incorporated the weight (lb) of the individual:

$$ICR = \frac{2.8 \times Weight(lb)}{TDD} \quad (149)$$

In 2010, the formula was later adjusted by Walsh *et al* following analysis of data from 1020 pumps downloaded to:

$$ICR = \frac{2.6 \times Weight(lb)}{TDD} \quad (150)$$

Estimated ICR values often need to be adjusted for different times of the day and regularly re-adjusted to compensate for changes in insulin sensitivity.

1.3.2.2 Insulin Sensitivity Factor

Insulin sensitivity factor (ISF) is used to determine the insulin dose needed to correct for glucose levels outside the target range. More specifically it describes how much glucose levels drop for one unit of insulin given. Similar to ICR values, rules or guidelines exist based on the experience of clinical experts to determine the starting point of ISF for an individual. Most rules are based on factors, which are divided by the TDD. Commonly used factors in the literature are 1700 (149), 1800 (151) and 1960 (sometimes rounded to 2000 (150)) for mg/dL and 94, 100 and 110 for mmol/l, respectively.

1.3.2.3 Insulin on Board

Bolus advisors are also able to factor in active “insulin on board” (IOB). The IOB insulin is estimated by the individual’s duration of insulin action (DIA), with adjustments based on mathematical modelling of insulin kinetics for insulin that has been injected subcutaneously. Modifying the DIA, therefore, regulates how aggressive or conservative subsequent insulin bolus recommendations are after previous dosing. IOB estimations are designed to prevent “stacking” of multiple insulin boluses, which can result in hypoglycaemia.

Different formulae may be used by different manufacturers to estimate the IOB (i.e. linear or curvilinear). The linear estimation is the simplest formula used and is described as:

$$IOB = B_{k-1}, 1 - \frac{t - T_B}{T_{IOB}}$$

where B_{k-1} is the previously administered bolus, T_B is the time of bolus administration, t is the time that IOB wants to be estimated, and T_{IOB} is a predefined interval during which the administered insulin is supposed to be active (e.g. 4 hours) (15).

1.3.3 Factors affecting blood glucose

In addition to carbohydrate content of a meal, there are many other variables that may impact the glucose regulatory system and insulin requirements. These factors can often be challenging to address and have been listed below:

Fat/ Protein Content and Glycaemic index: Principals of carbohydrate counting assume carbohydrates are the nutrient component with greatest impact on postprandial glucose excursions. There is evidence, however, that dietary fat and protein can delay gastric emptying and therefore delay carbohydrate digestion and glucose absorption. Another mechanism postulated is that free fatty acids (FFA) directly induce insulin resistance, and therefore FFA-induced insulin resistance with increased hepatic glucose output, may be the cause for delayed hyperglycaemia (152).

Caffeine: Caffeine intake alters blood glucose metabolism, however the results from studies remain varied (153). In few studies, glucose levels increased more following caffeine intake with, compared to just, carbohydrate intake. However, acute caffeine consumption in T1D may not raise glucose levels alone (153,154).

Alcohol Consumption: Alcohol consumption has been shown to reduce gluconeogenesis by approximately 45% and hepatic glucose output by 12% (155). Furthermore, the relationship between alcohol and insulin sensitivity is J-shaped, with increased insulin resistance in both abstainers and in heavy drinkers (156,157). Moderate intake has been associated with increased insulin sensitivity in young adults (158).

For people with T1D, alcohol is recognised as a risk factor for hypoglycaemia, particularly the following morning after consumption the evening before (159,160). Whilst there is a general paucity of clinical trials with several studies and meta-analyses failing to identify any acute changes in glucose or insulin concentration (161–163), caution about potential dangers of excessive alcohol is deemed the safest course (163).

Physical Activity: Basal plasma insulin concentrations have been known to drop as a result of physical activity. In addition, glucose uptake is amplified by working tissue and there is an increase in hepatic glycogenolysis (164). Physical exercise has both immediate (acute) and longer-term effects on insulin sensitivity. The immediate effects are directly resultant from the episode of activity and may be

evident up to 72 hours post exercise. If repeated regularly, physical activity can produce additional long-term chronic improvements in insulin sensitivity (165).

Hormone cycle: Women may face additional challenges with their diabetes care due to metabolic influences on glycaemia during the menstrual cycle (166,167). During the perimenstrual phase, many women experience luteal phase hyperglycaemia that remains consistent between cycles (168,169). In addition, significant alterations in insulin doses are required during pregnancy and in the post-partum period (170), as well as later in life through menopause (171).

Hormones may in part account for these changes; oestrogen which is highest in the luteal phase, has been associated with reduced insulin sensitivity, whilst progesterone has been implicated in insulin resistance (168).

Stress and Illness: Stress and illness are important contributors to glycaemia, due to several hormonal changes that can affect glucose homeostasis in both healthy people and in those with diabetes. The hormones released during stress include norepinephrine, epinephrine, cortisol, β-endorphin and growth hormone, which can reduce insulin sensitivity and lead to elevated glucose levels (172,173).

Environmental temperature and season: Ambient temperature levels have been noted to affect glycaemic profiles and variability in people with T1D. Tsujimoto *et al* (2014) found lower HbA1c levels in the summer or warmer seasons and increased HbA1c in the winter or cold season (174). Additionally, severe

hypoglycaemia occurred significantly more often in the summer than in the winter. By contrast, Moscardo *et al* (2018) observed an increasing trend in glycaemic mean with increasing temperatures, with varying influences on glycaemic measures (175).

Insulin timing and absorption:

The timing of insulin injection given in relation to the meal can affect postprandial glycaemia and is dependent on the type of insulin used and its variables (such as onset, peak, and duration). Studies have shown superiority and safety of injecting rapid acting insulins 15–20 minutes pre-meal, resulting in almost 30% lower postprandial glycaemia, lower area under the curve (AUC) for hyperglycaemia and less post-meal hypoglycaemia when the pre-meal glucose levels are in range (176). Mistiming of insulin bolus and eating within a few minutes after (or before) injecting rapid-acting insulins may substantially reduce the ability of that insulin to prevent a rapid rise in blood glucose (177). Fear of hypoglycaemia, the practicality of injecting 15–20 minutes prior to mealtimes and individual circumstances may prevent individuals from following this advice (176). Ultrarapid insulins (Fiasp and URLi) with faster onset of action, but shorter duration of action, can potentially support insulin administration closer to meal-times but will need to be offset against earlier cessation of action.

1.3.4 Review of standard bolus calculators to date

Overall, standard bolus calculators have been associated with improved postprandial glucose values, reduced dosing errors, a reduction in hypoglycaemia fear, and improved confidence in diabetes self-management (178–180). Clinical outcomes related to HbA1c, however, have been mixed with some studies showing improved HbA1c (181–183), whilst other studies have shown no impact on HbA1c, but improved treatment satisfaction (180). Furthermore, some studies have shown improved glycaemic control, but at the expense of increased hypoglycaemia (184).

The BolusCal study in 2012 of 51 adults with baseline HbA1c 8.0 – 10.5% were randomised to three groups: control, carbohydrate counting and carbohydrate counting with an automated bolus calculator (AccuCheck Aviva Expert). Reduction in HbA1c in the carbohydrate counting groups was significantly lower than in the control group. No difference in HbA1c was reported in those using the bolus calculator, however treatment satisfaction was greater in this group (180).

The ABACUS trial was a 26-week prospective, multi-centred, randomised controlled trial evaluating the Aviva Expert in 193 adults with T1D and T2D. Significantly more people in the bolus calculator group achieved >0.5% HbA1c reduction ($p<0.01$), without increased hypoglycaemia and improved treatment satisfaction (181).

Newer bolus calculators have incorporated additional features to aid the user. For example, VoiceDiab analyses input from voice description by the user to estimate amount of carbohydrate, protein, and fat in a meal (185). The %TIR for postprandial glycaemia (2h from the beginning of eating) was 58.6 ± 18.2 vs 46.6 ± 17.4 in the VoiceDiab group compared to control respectively (p=0.03). No significant differences were observed for %TIR; %TBR and %TAR. Whilst the application itself was designed in Polish, the system can be translated into other languages. It would also require customisation of the food products database.

In 2015, Huckvale et al. assessed 46 bolus calculators available for iOS and Android. Of these, 59% contained a clinical disclaimer, but only 30% documented the calculation formulae used, 91% lacked numeric input validation, 59% allowed calculation with missing inputs, 48% used ambiguous terminology, 9% lacked numeric precision, and 4% did not reliably store parameters. Critically, 67% of the apps carried a risk of inappropriate dose recommendation. As per the author's criteria, only one app (for iOS) was issue free (186).

With majority of bolus calculators largely untested and rendering individuals at risk of hypoglycaemia or hyperglycaemia (187), it has highlighted the requirements for greater scrutiny and standards for medical apps and decision support systems in the field.

As a result of the need for greater clinical evidence and real-world performance/outcomes by 'digital health technology', the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA)

have introduced and implemented a new regulatory framework in 2020 to provide clarity on medical device software (188).

Table 1.3 summarises current FDA approved/ CE marked standalone bolus calculators available on the market.

Name/ Platform	FDA/ CE marked	Author Sample Size Type of Diabetes	Trial Design	Comparator	Evidence in literature/ Main Results
Accu-Chek Connect *(Roche Diagnostics, Indianapolis, IN, USA*) **Platform: Glucometer and app**	FDA (recalled in 2019 (189))	**Zeigler *et al*** (181) n=193 T1D (93%) + T2D Adults; MDI	Multi-centred RCT 26weeks HbA1c >7.5% (58 mmol/mol)	Standard therapy	**ABACUS Trial** Improvement in HbA1c (56.0% participants in intervention group achieved >0.5% HbA1c reduction compared to 34.4% in control, p<0.01). Improvement in GV (MAGE) and treatment satisfaction No difference in hypoglycaemia
Aviva Accu-Chek Expert *(Roche Diagnostics*) **Platform: Glucometer and app**	FDA	**Mora *et al*** (190,191) n=85 T1D Adults; MDI **Schmidt *et al*** (180) n= 51 T1D Adults; MDI	Randomised prospective parallel-arm (n=85) 4-months + 4-months extension HbA1c >7.0% (53 mmol/mol) Randomised, open-label, three-arm parallel study 16-weeks Poorly controlled (HbA1c 8.0–10.5%)	Standard therapy	**CBMDI Study** At 4 months (190): No significant differences in HbA1c or hypoglycaemia fear. At 8 months (191): Reduction in fear of hypoglycaemia and greater treatment satisfaction; no change in HbA1c. **BolusCal Study** No improvement in HbA1c; Improvement in treatment satisfaction
Dario (NASDAQ) **Platform: Glucometer and app**	FDA + CE				None
Diabeo **Platform: Smartphone app**	CE (France)	**Charpentier *et al*,** 2011 (182) n = 180 Adults T1D; MDI and CSII Further multicentre, randomised, open-label, three parallel–arms study in approximately	Open-label parallel-group, multicentre study 6 months Poorly controlled (HbA1c ≥8%) Diabeo software with basal and prandial insulin bolus advisor +/- telemonitoring and phone consultations providing motivational support.	Group1: Standard therapy **Vs** Group2: Bolus calculator with quarterly caregiver visits **vs** Group 3: Bolus calculator with teleconsultations every 2 weeks (no caregiver visits till end of study)	**TeleDiab 1 Study** Improvement in HbA1c (0.91% (0.60-1.21)% HbA1c reduction in Group 3 with teleconsultations vs 0.67% (0.35-0.99)% reduction in Group 2 without teleconsultations). No difference in hypoglycaemia or QOL Sub-analysis of the TeleDiab Study (above) to determine high and low users of system.

		100 centres in France (NCT0228753; TELESAGE Study) (192).			Improved glycaemia in both high and low users using Diabeo, although greatest improvement seen in low users having motivational teleconsultations support
Diabetes Diary **Platform: Smartphone app**	CE (Norway)	**Skrovseth *et al***, 2015 (193) N=30 Adults T1D; MDI and CSII	Randomised stepped-wedge trial with two groups 23 weeks Diastat modules: (1) Glucose periodicity graph (2) Glucose trends (3) Situation matching (i.e. presents situations most similar to the current one)	4 weeks run-in period (basic Diabetes Diary without Diastat), then Group 1 served as intervention group (with Diastat), and Group 2 served as a control group for 8 weeks. Subsequently, Group 1 was dismissed, and Group 2 served as intervention group for 10 weeks (with Diastat).	No differences between groups in HbA1c or out of range events
Diabetes Insulin Guidance System (Hygieia) **Platform: Glucometer app**	CE (Italy)	**Bergenstal *et al*,** 2012 (194) n = 46 Adults T1D (43%) + T2D; MDI	Open-label, single-arm feasibility study 16 weeks HbA1c ≥7.5%	Run-in period (standard therapy + weekly diary keeping)	No differences in HbA1c or out of range episodes between control and intervention groups All participants had reduction of 0.6% in mean HbA1c ($p<0.001$)
Diabetes Interactive Diary **Platform: Glucometer app**	CE	**Rossi *et al*, 2010** (195) n=130 Adults T1D; MDI and CSII **Rossi *et al*, 2013** (196) n=127 Adults T1D; MDI	Multicentre, randomised, parallel-group study HbA1c levels≥7.5% Multicentre RCT; 6 months HbA1c levels≥7.5%	Standard therapy Structured educated	No reduction in HbA1c Improved perceived frequency of hyperglycaemic episodes; improved treatment satisfaction ($p=0.04$) No reduction in HbA1c or GV between groups (HbA1c decrease of 0.5% in both groups) Lower mean basal insulin in the intervention group ($p=0.04$)
Freestyle InsuLinx (Abbott)	FDA + CE	**Sussman *et al* 2012** (197) n=205	Multicentre observational study 1 day	Manual calculation	Primary outcome = frequency of insulin dosing errors

Platform: Glucometer app		>13years old T1D (48%) + T2D; MDI	Opinion surveys completed after to doses determined using the FreeStyle InsuLinx or manual calculation		63% of manually calculated doses were incorrect; 10 times fewer errors (i.e. 6% of same dose determinations) using the meter ($p<0.0001$)
Glooko *(Mountain View, CA, USA)* **Platform: Phone app**	FDA + CE	**Clements *et al*,** 2017 (198) N= 81 Youth + young adults T1D; MDI and CSII **Offringa *et al*,** 2018 (199) n=1,788 Adults T1D + T2D	Retrospective multicentre study Retrospective multicentre study	Compared to clinic population (n= 2294)	Improvement in SMBG frequency (2.3 fold increase; $p<0.01$); No reduction in HbA1c Improvement in SMBG frequency ($p<0.001$); Reduction in average glucose by 3.5% after 2 months ($p<0.001$) Reduction in probability of hyperglycaemic events after 2 months ($p<0.001$)
Go Dose (Eli Lily) *(Companion Medical Inc.)* **Platform: Phone app**	FDA				None
InPen **Platform: Phone app**	FDA + CE				None
MySugr *(AccuChek, Roche Diagnostics*) **Platform: Phone app**	FDA + CE	***Debong et al, 2019*** N=2104 Adults T1D ***Secher et al, 2020*** Adults T1D	Retrospective observational study Highly engaged users (logging ≥5 days/week for ≥6 months)		Improvement in blood glucose at 6 months ($p < 0.01$) Reduction of eA1c of ~0.3% in an already well-controlled population (from 7.3% to 7.0%) Four groups to compare: standard care, bolus calculator, isCGM or bolus calculator + isCGM.

Table 1.3: FDA approved or CE marked standalone bolus calculators for T1D

Abbreviations: CSII, continuous subcutaneous insulin infusion; FDA, Food and Drug Administration; isCGM, intermittently scanned continuous glucose monitoring; MDI; multiple daily injections of insulin; SMBG, self-monitoring blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes; QOL, quality of life.

1.3.5 Limitations and sources of error of standard bolus calculators

Bolus calculators are considered state-of-the-art for insulin dosing decision support. However, besides the requirements for greater scrutiny, they suffer from several other key limitations. Firstly, whilst bolus calculators may have potential, their overall effectiveness is limited by the requirement for adaptation over time, which necessitates frequent review of ICR and ISF settings. In clinical practice, this can be impractical as diabetes clinic appointments are generally scheduled twice a year.

Secondly, bolus calculators require accurate carbohydrate counting skills (200), and structured education amongst people with T1D remains limited (201). Inaccurate or non-physiological settings of ICRs or ISF can introduce errors into bolus recommendations. Another common error is to select a DIA time that is too short, in order to increase the size of the recommended bolus doses (202). In an online discussion, pump wearers were questioned about what their DIA setting was. Nineteen respondents reported a median DIA time of 3 hours and an average time of 3.4 hours (range 2.5 – 5.0 hours) (203). Selection of short DIA times may result in unexplained hypoglycaemia (203). The inappropriate selection of the most commonly used DIA time setting of 3 hours, masks active bolus insulin on board (BOB), leading to insulin stacking (187).

Third, current commercially available calculators limit the estimation of required bolus insulin at mealtimes to the amount of carbohydrate consumption. As discussed previously, additional parameters that are required to be taken into account include glycaemic index, fat or protein content of meals, altered digestion

(i.e. in individuals with gastroparesis) and concomitant use of a glucagon-like peptide agonist (187).

Finally, whilst some bolus calculators additionally consider parameters such as exercise, all lack the ability to automatically adapt over time to respond to individual needs or changes in insulin sensitivity. It is hypothesised that a personalised and adaptive insulin advisory system will provide better glycaemic control than state-of-the-art standard bolus calculators. This brings us to the frontier of artificial intelligence and adaptive decision support systems, which can help rapidly analyse large datasets and provide recommendations to adjust bolus/basal insulin in real-time.

1.4 Artificial Intelligence Powering Innovation in Healthcare

Over the last few years, artificial intelligence (AI) has brought a paradigm shift to healthcare management, much of which is powered by increasing availability of healthcare data and rapid progress of analytic techniques. AI has been defined in many ways. One such accepted definition quoted by Forbes, is “the theory and development of computer systems to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages” (204).

It is reported that each person will generate more than 1 million gigabytes of health-related data in their lifetime, which is equivalent to approximately 300

million books (205). The promise of machines (computers) to therefore learn and identify patterns using biostatistics by handling massive datasets (big data) through layered mathematical models (algorithms), offers the potential to power innovation in healthcare. Correcting algorithm mistakes (training) adds to AI predictive model confidence (206). It is anticipated that AI has the potential to help healthcare move from traditional "one-size-fits-all" medical solutions towards personalised therapies, targeted treatments and uniquely composed drugs i.e. precision medicine.

In the literature, intelligent algorithms are widely used to support advanced analysis and provide individualised medical aid. Successful applications for AI include image analysis in radiology, pathology (207) and dermatology (208), with diagnostic speed exceeding, and accuracy paralleling, medical experts. Additionally, an increasing number of health care companies are using these techniques (209). Examples of large corporations using AI, range from mining medical records (Google Deepmind and IBM Watson (210)), identifying therapies (Zephyr Health), genomics (Deep Genomics (211) to supporting diagnostic imaging (Enlitic, Arterys, 3Scan).

The US Agency for International Development (USAID) has several key areas of healthcare to which AI techniques may be applied (Figure 1.4; (212)). At an individual health level, care services can broadly be divided into applications for prevention, diagnosis (both data-driven and image-based), acute treatment (i.e. clinical decision support, monitoring and AI-facilitated care) and follow-up and chronic care.

Despite the huge promise of AI, there are many challenges to be faced for its use in healthcare and in diabetes (i.e. apps, devices and systems). Firstly, the biggest challenge will be governance, with physician cooperation, expensive up-front and ongoing costs being some of the initial challenges starting up. Technical interoperability between systems to exchange and use information, and the limitation of sharing algorithms and codes in published studies, make reproducing results challenging. From a survey of 400 algorithms presented at two AI conferences, only 6% of presenters shared codes, with only half sharing a "pseudocode" and limited summary (213).

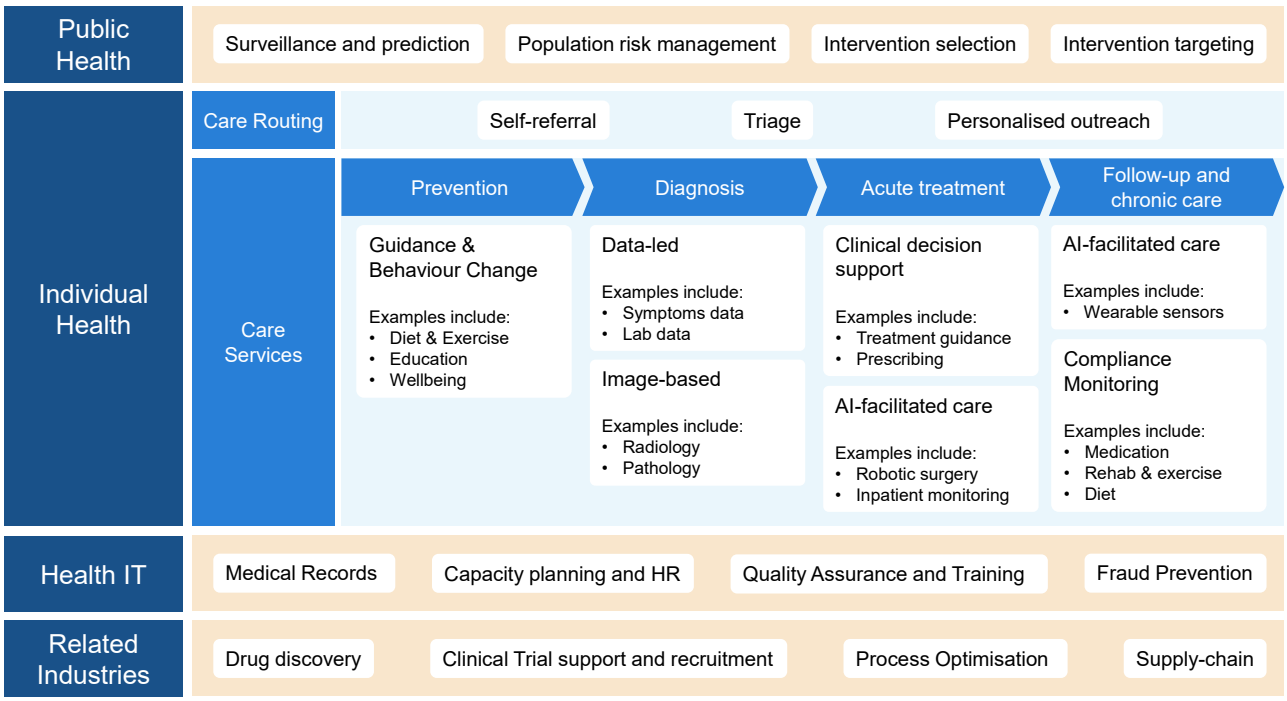

Figure 1.4: Potential use-cases for AI use in Healthcare

AI has the potential to transform medical care at multiple levels of healthcare provision, including at a population level (e.g. surveillance and intervention targeting), or by targeting individual health, (e.g. through information technology), and other related industries. The classification is based on key areas identified by the US Agency for International Development (212) with examples provided in each of the key areas. Abbreviations: AI, artificial intelligence; IT, information technology; HR, human resources.

1.4.1 Artificial intelligence techniques

This section provides a short overview of several well-known AI techniques and methodologies. Historically, the dominant approach to AI was inspired by logic or "reasoning systems" (214). However, over the past decade, significant research has been invested into "learning systems", especially machine learning and its compute intensive offspring, deep learning. Each AI technique has strengths and weaknesses. When selecting an AI technique, it is important to consider the features that are critical to the particular problem (215). Figure 1.5 provides a framework for AI techniques, categorized by learning and reasoning systems. Table 1.4 describes the key algorithms and their limitations in AI processes.

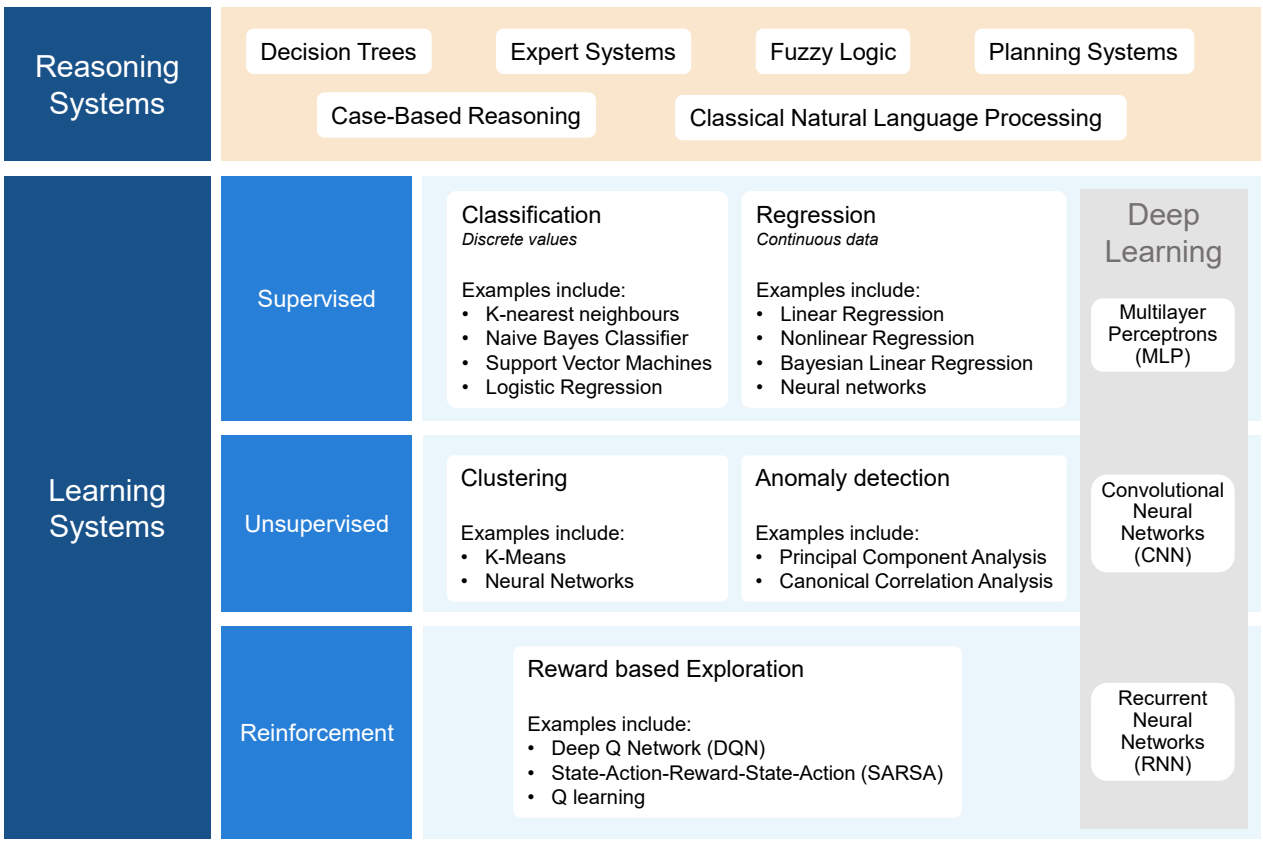

Figure 1.5: Framework of artificial intelligence (AI) techniques

AI techniques can be categorized into learning and reasoning systems. Current day learning systems include supervised, unsupervised and reinforcement learning. Reasoning systems (or knowledge-based or logic-based systems) involve the use of logical techniques to generate conclusions, through deduction and induction from available knowledge.

Learning systems

Learning from data is commonly referred to as machine learning, which is characterised by the ability to learn over time without explicitly being programmed. Geoffrey Hinton and colleagues renewed interest within this field of research in their 1986 seminal paper on backpropagation, published in Nature (216). Current day machine learning can be divided into three main categories, namely, supervised learning, unsupervised learning and reinforcement learning. Table 1.4 summarises these methods.

Reasoning systems

Reasoning systems, also referred to as knowledge-based or logic-based systems, involve the use of logical techniques to generate conclusions, through deduction and induction from available knowledge. For example, knowledge engineers extract the logic by interviewing or observing human experts. Such systems commonly apply heuristics and are based on three key components. Firstly, a *knowledge acquisition system* gathers information and collect inferences that can be used for further development. Second, a *knowledgebase* is used for problem solving. This is characterised by rules and information. Finally, the *inference engine* links the knowledge base with the gathered information (215). These facilitate the process of reasoning, enabling the system to recognise an anticipated solution. Examples include rule-based reasoning, expert systems, case-based reasoning and planning systems.

Method	How it works	Limitations and examples
Machine learning (ML)		
Supervised ML	The user trains the algorithm to generate an answer based on a known and labelled data set	Problems encountered with data preparation and pre-processing include: missing values; impossible/unlikely values inputted; irrelevant input features present in the data. This leads to many research areas where labelled data is elusive or too expensive (217) Examples: logistic regression, linear regression, k-nearest neighbour, support vector machine
Unsupervised ML	The algorithms generate answers on unlabelled data. Techniques are useful in exploratory situations and are used to find undefined patterns or clusters within datasets	Algorithmic outcomes may not be easily interpretable (i.e. black boxes) Examples: K-means, hierarchical clustering, probabilistic clustering
Reinforcement learning	An iterative process, where the learning algorithm is set a goal which it tries to solve by adapting its previously used actions or series of actions when confronted with same problem	Typically these algorithms make a lot of mistakes during early iterations, but over time become more successful at achieving their set goals
Reasoning systems		
Expert systems	These are based on collections of 'if-then' rules and were the dominant technology for AI in the 1980s and are still in wide use today Expert systems require human experts and knowledge engineers to construct a series of rules within the knowledge domain (218)	When the number of rules are large (usually over several thousand) and rules begin to conflict with each other, they may tend to break down If the knowledge domain changes, changing rules can be difficult and time-consuming Examples: rule-based reasoning, case-based reasoning
Fuzzy logic	A form of multi-valued logic dealing with reasoning that is approximate rather than precise. The truth value may range between completely true and completely false, and fuzzy logic is able to handle values between with an appropriate degree of fuzzification (219)	Determining the exact fuzzy rules and membership functions can be time-consuming
Classical natural language processing (NLP)	NLP algorithms analyse large amounts of natural language data to include text and speech processing and voice recognition Classical NLP from the 1950s were designed with heuristic methods, using rules of syntax and grammar. This approach is deeply rooted in using logic to create a sense of meaning	Rules for classical NLP need to be well-crafted and are often numerous and time-consuming. Do not handle colloquial text well Classical NLP has now given way to deep learning NLP, based on ML, for improved accuracy

Table 1.4: Examples of AI techniques

1.4.2 Diabetes care powered by artificial intelligence

Diabetes is attracting increased attention of AI and its applications due to the large amount of data that can be drawn and exploited from the newer technologies, such as rtCGM and wearable health monitors (e.g. Fitbit wrist watches).

Diabetes care may be transformed over the forthcoming years with AI systems deployed within this specialist field. Key areas where AI has been successfully used include: 1) Screening and predicting risk; 2) Minimising diabetes related complications; 3) Personalising glycaemic control through monitoring and insulin recommender systems.

Screening and predicting risk: Population-based intervention may be facilitated through machine learning algorithms for more targeted screening and prevention programmes in diabetes. For example, in predicting type 2 diabetes risk, machine learning-based predictive modelling can mine vast numbers of various genetic and metabolic combinations to identify at risk populations (220).

Another example includes the use of machine learning for causal inference in identifying important heterogeneous treatment effects hidden amongst large datasets within existing trials, even in trials reporting average negative effects. The Action for Health in Diabetes (Look AHEAD) trial of 5145 people investigating whether weight loss intervention resulted in reduced long-term cardiovascular disease morbidity and mortality in type 2 diabetes, found no significant reductions (221). However, post-hoc analysis using causal forest modelling (type of machine learning) identified participant subgroups where weight loss was indeed beneficial

(222). As a result, more personalised intervention could be provided to both subgroups.

Diabetes related complications: Deep learning using neural networks can be used to predict the onset of diabetic retinopathy from retinal image evaluation. To build the model, large image datasets (annotated retinal images) can be collected and the algorithm can "self-rate" severity from pixel intensity, 'learning' to predict the consensus grade of the raters (clinicians). Findings demonstrated comparable specialist level proficiency compared to a panel of ophthalmologists, with high sensitivity and specificity in detecting referable diabetic retinopathy (223). Tested in an-outpatient clinic setting, this has been feasible and well-accepted by patients (224). In 2018, the FDA approved the first autonomous AI diagnostic system in any field of medicine - without the need for a clinician to also interpret the results or image. The device, called IDx-DR (IDx LLC, Coralville, IA) uses an AI algorithm to analyse images of the eye taken with retinal camera called Topcon NW400 (Topcon Medical Systems, Inc, Oakland, NJ). The pivotal trial of 900 participants at 10 clinical sites concluded a sensitivity of 87.2% (95% CI 81.8–91.2%), specificity of 90.7% (95% CI 88.3–92.7%), and imageability rate of 96.1% (95% CI 94.6–97.3%) (225).

Other promising research includes advanced computer vision algorithms to help in the detection and monitoring of diabetic foot pathologies. FootSnap captures standardised photographs of diabetic feet in relation to the distance from the foot and the orientation of the camera relative to the foot (226). This system may be used for longitudinal follow-ups in diabetic feet, as a potential for monitoring

pathology. Approaches such as this may lead to people at higher risk of foot complications benefitting from quicker referral times, and reducing specialist referrals for those at low risk (227).

Glucose monitoring and insulin recommender systems: Various strategies using AI techniques and algorithms are being adopted to improve glycaemic control. GoCARB is a computer vision-based smartphone system, which employs computer vision, machine learning, and smartphone technologies to estimate the carbohydrate content on plated meals for individuals with T1D. Comparing GoCARB and dietitians on 64 plated meals, both achieved comparable accuracies (228). Using technologies such as these may offer individuals easy, accurate, and real-time estimation of carbohydrate content in their meals, thus enhancing diabetes self-management (228,229).

Zeevi et al. from Weizmann Institute of Science, use a machine learning algorithm to predict personalised postprandial glycaemic responses to real-life meals. Inputs into the algorithm included blood parameters, dietary habits, anthropometrics, physical activity and gut microbiota. Subsequently, they were able to tailor dietary interventions based on these predictions to significantly improve post-meal glucose levels (230).

AI has also been successful in enabling short to medium-term glucose forecasting for up to 15mins-2hours (231,232). With machine learning, glucose forecasting is now further extended to predict quality of glycaemia over the overnight period

(01.00 – 05.00hrs), thereby allowing the user to take the appropriate preventive action (snack or change in basal insulin) (233).

Adaptive bolus calculators, for example, the 'Advanced Bolus Calculator for Diabetes Management' (ABC4D) which uses case-based reasoning (CBR) to support individuals with T1D, have been discussed in greater depth in the following sections (234,235).

1.5 Innovations in Bolus Calculators

Bolus calculators are considered state-of-the-art for insulin dosing decision support. However, as outlined previously, they suffer from several key limitations. The main drawback is that standard bolus calculators are based on clinical algorithms, which remain constant over time. However, parameters (such as ISF and ICR) are usually not constant and can vary depending on parameters such as circadian rhythms, physical activity levels, hormone cycles, psychological stress, alcohol consumption, and recurrent illness. To address this, an ideal bolus calculator should be able to automatically adapt over time and respond to an individual's needs and changes in insulin sensitivity. It is therefore hypothesised that a personalised and adaptive insulin advisory system will provide better glycaemic control than state-of-the-art standard bolus calculators.

Over the recent years, there has been growing interest in developing algorithms using AI to guide insulin therapy adjustments. Bolus calculators are one such

proposed area. Whilst rtCGM and insulin pump data have revolutionised decision support and the way in which clinicians and individuals are able to analyse glucose trends and patterns, incorporation of new physiological variables (e.g. heart rate, hours of sleep and physical activity) will be particularly helpful when analysed with AI applications.

The predominant methods of reasoning, which have been integrated in adaptive bolus calculators have been reviewed below.

1.5.1 Rule-based reasoning

During the 1970s and 1980s, one of the most visible developments in AI research was the emergence of rule-based expert systems. Rule-based reasoning stores the knowledge of experts directly into a rule base and uses inference to solve the problem. Skyler *et al* (236) and Jovanovic and Peterson (237) were among the first to introduce heuristic algorithms, using rules based on practical experience to adjust insulin dosing.

An example of such rules may be expressed in IF−THEN format:
IF fasting glucose is <5mmol/l → **THEN** reduce evening basal insulin by 2units.

Algorithm may differ in inputs, for example, Skyler *et al* used only pre-prandial blood glucose measurements, whilst the algorithm by Jovanovic and Peterson used pre- and postprandial measurements (238).

However, despite the success of rule-based systems in various sectors, there were several pertinent problems (239):

1. Construction of the intended knowledge base can be difficult and time-consuming. This was particularly the case for topics covering a broad range of knowledge.
2. Challenge of dealing with problems not anticipated by rules, and require exact matching (of antecedents).
3. Lack of learning, creativity and common sense. Traditional rule-based expert systems do not have the ability to learn or be creative, and therefore require expert intervention/programmer to facilitate any addition to the existing system.

1.5.2 Run-to-Run control

Run-to-Run (R2R) is a control engineering algorithm designed to exploit the repetitive nature of a process being controlled (240). The algorithm learns from one run so that variables in the next run can be changed, thereby converging upon a set target within a set time period or number of runs (241).

R2R was first proposed in a bolus calculator by Owens *et al* in 2006 (238). Both insulin dosing and basal insulin delivery can be classified as being repetitive, and thus R2R control can be used to exploit the repetitive nature of insulin therapy regimen in an individual with diabetes. The ICR can be corrected for the following day, based on a performance metric evaluating post-meal glucose excursions. Efficacy of the R2R algorithm (on its own) in individuals with T1D has been

investigated in pilot clinical studies (241,242). Zisser *et al* tested glucose 60 and 90 mins postprandially to adjust the dose and timing of the insulin bolus. Whilst, majority of the people converged to or maintained good glycaemia, several diverged in their responses (241).

There are several key limitations to R2R. Firstly, R2R assumes that the insulin therapy regime of the individual with T1D is repetitive, which is in most cases is unrealistic. Furthermore, the R2R algorithms are useful for dealing with intra-day variability but are not able to deal with inter-day variability due to other factors such as exercise, alcohol, stress, and menstrual cycle (243).

1.5.3 Case-based reasoning

Case-based reasoning (CBR) is an AI technique (235), that addresses the task of solving newly encountered problems by applying the solutions learnt from solving similar problems encountered in the past (i.e. cases). CBR stores the related cases that are used in the past into a case base, and each case is defined by three components: the problem description, the problem solution and the outcome. For example, the problem may be described by parameters that could affect glucose levels (e.g. exercise or alcohol consumption), the solution can be defined by the parameters of a bolus calculator (i.e. ISF and ICR) and the outcome can be the glycaemic metric assessing glucose excursions.

The foundations of CBR have been established in the work conducted by Kolodner based on the idea of dynamic memory modelling proposed by Schank (244).

Several applications were developed to demonstrate the capabilities of CBR for solving real-world problems, notable seminal examples include CHEF for meal dish planning, MEDIATOR for conflict resolution, and CASEY for diagnosing heart problems and JULIA for meal designing (245,246). Since then, the applications of CBR have been widely used by more than 130 major companies worldwide till 1997 (247). One widely adopted CBR cycle model, proposed by Aamodt and Plaza (248), consists of a four cycle approach (Figure 1.6):

- Retrieve: Retrieve the most similar case or cases;
- Re-use: the information in that case to solve the problem;
- Revise: the proposed solution;
- Retain: experiences retained are likely to be useful for future problem solving.

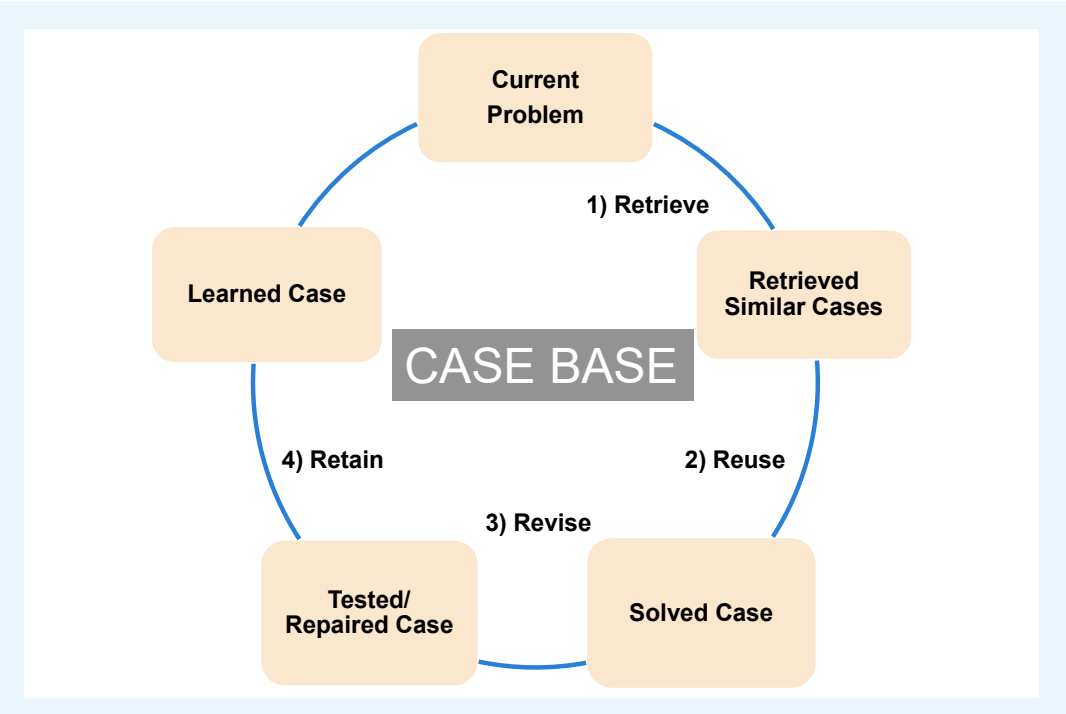

Figure 1.6: The Case-based reasoning (CBR) cycle model

The CBR cycle (adapted from Aamodt and Plaza) learns through solving new problems when a "learned" case is created from the current case, which is revised, and its confirmed solution is retained as a new case within the case base.

In general, as a major advantage, the CBR approach can be applied to problem domains that are only partially understood, and can provide solutions when no algorithmic or rule-based method is available. The main advantages of CBR over rule-based models include the following (249):

1. CBR systems can be built where a model of the problem does not exist;
2. Implementation is made easy by identifying relevant case features;
3. CBR systems can be rolled out using only a partial case base, and the case base will continue to grow due to its cyclic nature;
4. CBR systems are efficient in avoiding the need to infer answers from first principles each time;
5. Retrieved cases can be used to provide satisfactory explanations as to why the given solution is produced (i.e. is not a "black-box");
6. The case-based nature of the learning system makes maintenance easier.

Main disadvantages include memory requirements and time-consuming execution for handling large case bases, although this is less of an issue as hardware technology is becoming faster and cheaper. Dynamic problems which lead to a shift in the way problems are solved, may result in an outdated case base.

The first use of CBR combined with rule-based reasoning (i.e. multimodal reasoning; MMR) within decision support for diabetes was first coined by Montani and Bellazzi in 2002 within the telemedicine EU-funded project M^2DM (250,251). The system was an aid for doctors to aid modifications to the individual's therapy regime, later giving rise to the T-IDDM project (see Section 1.5.5).

CBR combined with the R2R control framework has been shown to have better outcomes in-silico and is better in managing intra-subject and inter-subject variability (252).

1.5.4 Model-based reasoning

Model-based reasoning (MBR) is based on a model of the structure and behaviour of the system aiming to simulate or control.

Observed behaviour (what the system is actually doing) is compared with predicted behaviour (what the system should do). Assuming the models are correct, any discrepancy between these processes is defined as defaults on the system (e.g. rtCGM or pump fault) (253).

Within the context of diabetes technology, MBR techniques have been proposed to predict episodes of hypoglycaemia (254), detect rtCGM and insulin pump faults (255), and to constrain insulin delivery by an artificial pancreas (256).

1.5.5 Review of studies on adaptive bolus advisors to date

To date, there are limited trials on adaptive bolus calculators assessing clinical outcomes in people with T1D. Reasons for the limited clinical research in this field are unclear, but it is likely to be related to the primary focus of research being on closed-loop systems, the limited use of clinical diabetes apps in the real-world setting, and the lack of Bluetooth enabled insulin pens to fully support insulin inputs in to an automated system (213). There are few studies in an artificial

pancreas setting, which are adaptive for both basal and bolus insulin (99,257,258), however, in these studies it is difficult to evaluate whether the net benefit is due to basal or bolus adaptation, or both.

The first clinical project to use CBR to aid decision support in the management of T1D was the Telematic Management of Insulin-Dependent Diabetes Mellitus (T-IDDM) project in 2002 (259). Designed as an "intelligent" web-based telemedicine system, this integrated rule-based reasoning with CBR and a probabilistic model of insulin effects on blood glucose levels. Participants in the study used standard MDI therapy. The system, however, was not intended for self-management use, but rather as a tool for doctors to aid modifications to the individual's therapy regime.

In 2010, the 4 Diabetes Support System (4DSS) project used CBR as the primary reasoning modality for decision support in participants on insulin pump therapy. Several factors were included into the calculations, for example, life events that may influence blood glucose fluctuations. Within the feasibility study, the system identified twelve distinct types of clinical problems and offered learning solutions as decision support to the physician (260). No glycaemic outcomes were reported.

The first automated decision support system approved by the FDA in June 2018 is the DreaMed Advisor Pro (DreaMed Diabetes Ltd, Petah Tikva, Israel). This system is approved as a decision support software to provide basal and bolus insulin therapy adjustment recommendations to physicians for people with T1D using an insulin pump (does not include hybrid closed-loop). The system uses the

AI technique, fuzzy logic (named Medical Doctor-Logic; MD-Logic). Nimri *et al* evaluated the system with healthcare professionals, and found physicians only were in full agreement with Advisor Pro in basal 41.5 ± 8%, ICR 48 ± 11% and ISF 43.4 ± 11% of cases (261). However, the Advisor Pro provided similar directional agreement to that of clinicians, with the magnitude of dosing change equal or less than that recommended by clinicians for safety reasons (261). The study also found there was only 41-45% agreement amongst physicians for the trend of adjustment of basal rates, ICR and ISF. These findings confirm that insulin dosing adjustment is both an art and science, with a range of different recommendations given to single situation. The Advisor Pro has also been tested clinically in a single centre feasibility study with 15 participants. Participants were randomly assigned to the group with insulin pump adjustments made by a physician (control group) or a group guided by Advisor Pro (intervention group). No difference was observed for time spent in range or hypoglycaemia between the two groups (262). The algorithm effectiveness is being tested in a randomised controlled clinical (NCT03003806) with publications of results awaited.

One of the key limitations of these projects is that they have been intended to aid clinicians with therapy adjustments as opposed to the individual directly. It is an important aspect to consider whether decision support systems are directed towards providing recommendations to patients, providers (i.e. healthcare professionals) or both. Meta-analyses suggest that providing recommendations to both users and providers improves adherence and is more effective than providing decision support to providers only (263). In the management of diabetes, providing support

to the user directly, not only facilitates more patient centred care, but empowers users in real-time.

The Advanced Bolus Calculator for Diabetes (ABC4D) project has been one of the most relevant clinical studies in this field. The decision support system provides real-time insulin advice through a smartphone application with CBR. For the retrieval process of the CBR, ABC4D uses the k-nearest neighbour (k-NN) classifier to retrieve the most similar case when compared to the current meal scenario. Reddy *et al* published results from a 6-week prospective non-randomised single arm pilot study with 10 adult participants. More than a two-fold reduction in the number of postprandial hypoglycaemic episodes was observed, however the study was not sufficiently powered to show significance (234). No significant differences were observed for percentage TIR (55% at baseline vs 60.9% at endpoint; p=0.9) or time in hypoglycaemia (5.0% vs 3.6%; p=0.7). The study concluded ABC4D is safe for use as a decision support tool. Currently, a randomised controlled trial over 8 months with 40 participants is underway (NCT03963219).

There are many promising studies conducted in-silico. Cappon *et al* uses a neural network approach to optimise and personalise meal bolus calculation using rtCGM data (264). The system was testing in-silico using 100 meals, with its use significantly decreasing the blood glucose risk index after meals. Reselat *et al* incorporate an adaptive learning postprandial hypoglycaemia prevention algorithm (ALPHA) that adjusts the insulin delivery after meals within a hybrid closed-loop system where meals are announced. ALPHA combined with an insulin sensitivity

adaptation algorithm significantly reduced time spent in hypoglycaemia by 71.7% and the total number of rescue carbs by 67.8% to 0.37% events/day/patient (123). Further studies in-silico have been outlined in Table 1.5.

Although there are a significant number of in-silico studies, these algorithms need to be ideally tested in-humans to assess the associated risk of hypoglycaemia. Within experimental fully closed-loop systems, there is still a strong compromise between the aggressiveness of the control algorithm within a closed-loop system and the postprandial excursion. If the controller is too aggressive, there is a higher risk of insulin overdosing and consequently, postprandial hypoglycaemia (265). On the other hand, if the controller is not aggressive enough to an administered meal, there is a higher risk of insulin underdosing (266). Similar principles are likely to apply in bolus calculators for differing algorithms.

Several systems adapt both bolus and basal insulin. Breton *et al* conducted a prospective crossover study with 24 adults using either MDI or CSII. Participants were randomised to either usual care or the University of Virginia Decision Support System (UVA DSS), which provided automated basal insulin titration, bolus calculation and carbohydrate treatment advice. The UVA DSS significantly reduced hypoglycaemia without increasing the mean rtCGM values, as well as reduced GV (267).

Dassau *et al* investigated the use of decision support to optimise parameters within a hybrid closed-loop (268). 30 adults with T1D participated in a single arm 12-week feasibility study. The system uses MPC, a control engineering algorithm,

combined with the Health Monitoring System hypoglycaemia prediction algorithm. Compared with SAP run-in, %time spent in hypoglycaemia improved during the day from 5.0 to 1.9% (-3.1, 95% CI -4.1 to -2.1, p< 0.001) and overnight from 4.1 to 1.1% (-3.1, 95% CI -4.2 to -1.9, P < 0.001) (268). 10% of adaptation recommendations were manually overridden. Larger, randomised control trials are required to evaluate overall efficacy.

In summary, the number of clinical trials facilitating adaptive bolus calculators are limited. Furthermore, clinical studies in humans and outcomes involving AI for automated real-time adaptation to people with T1D remain in the primitive stage. At present, there are no large randomised control trials assessing outcomes in adaptive bolus calculators for people using MDI and CSII. Results from small trials or in-silico data are promising and it is likely we are at the start of a new era where the potential of AI and technology will enable personalised management of T1D. Further large-scale clinical studies are required to evaluate the efficacy of many algorithms being proposed. Table 1.5 summarises current adaptive systems.

Author, Year	Algorithm	Methods/ Population	Bolus/Basal adaptation	Study duration	Population/ Study design	Main Results	Comments/ Limitations
ADAPTIVE BOLUS ADVISORS							
Marling *et al.* 2009 (269)	CBR	In-vivo; Adults; CSII	Bolus rtCGM (3 occasions x 3 days) + SMBG 6-15 x daily	6 weeks	N=20 T1D	No glycaemic outcomes reported Feedback on automated problem detection: 77.5% reported correct identification of problem; 15% having mixed feelings. 87.5% usefulness to bring to attention of patient Feedback on case retrieval: 70% felt applying matching case's solution to the original problem would be beneficial; 23% felt neither beneficial nor detrimental	Only 10/ 352 problem detections randomly selected for evaluation by panel Clinicians review/revise cases on weekly basis
Schwartz *et al*. 2010 (270) **The 4 Diabetes Support System (4DSS)**	CBR + run-to-run	In-vivo; Adults; CSII	Bolus rtCGM + SMBG 6-15 x daily	5 weeks	N=23 T1D	No glycaemic outcomes reported	
Reddy *et al.* 2016 (234)/ Pesl *et al.* 2017 (235) **ABC4D project**	CBR (k-nearest neighbour for case retrieval)	In-vivo; Adults; MDI	Bolus rtCGM data	6 weeks home study	N=10 T1D Non-randomised single arm study	No difference in %TIR (55% vs 60.9%; p=0.9) No difference in % time in hypoglycaemia <3.9 (5.0% vs 3.6%; p=0.7) More than two-fold reduction in number of postprandial hypoglycaemic episodes, but not statistically significant	Exercise and alcohol were the most frequently used parameters 11.6 ± 3.5 cases were created by end of study which is half the maximum possible number of cases (i.e., 24). Majority created were within first week of use, with subsequent user attrition
Bell *et al.*. 2016 (271)	Model-based	In-vivo; Adults; CSII	Bolus	Single meal	N=10 T1D	Reduced glucose incremental area under the curve (27,092 ± 1,709 mg/dL/min to 11,712 ± 3,172 mg/dL/min; p= 0.001) Reduced incremental change in blood glucose concentration (73 ± 4mg/dL to 24 ± 11 mg/dL; p= 0.001) For high fat high protein diet, the insulin dose needed to be increased by 65% +/- 10% and delivered as a combination bolus with a 30%/70% split over 2.4h	Limited study as only evaluated for a single meal For high fat high protein diet

IN-SILICO STUDIES							
Boiroux *et al.* 2017 (272)	Bergman minimal model with Kalman filter	In-silico	Bolus/Basal	-	N=9 simulated. T1D	Significant improvement with nonlinear adaptive basal-bolus calculator compared to the conventional bolus calculator ($p<0.01$) No hypoglycaemia (glucose <3.0 mmol/l)	If no meal announced to the controller within previous 3hours, the filter will only estimate the insulin sensitivity If a meal announced within 3 previous hours, the filter will only estimate the second meal compartment, and the mealtime constant. The insulin sensitivity is not estimated
Cappon *et al.* 2018 (273)	Neural Networks	In-silico;	Bolus	-	N=100	Reduction in blood glucose risk index by 0.37 with neural networks compared to standard formula ($p<0.001$)	NN was trained to learn the optimal insulin dose using the standard formula parameters, rate of change of glucose, body weight, insulin pump basal infusion rate and insulin sensitivity as features
Oviedo *et al.* 2018 (274)	Neural Networks	In-silico	Bolus	-	N=10	Reduction in postprandial episodes of hypoglycaemia (<3.9mmol/l and <3.0mmol/l) by 37% and 44%, respectively Percentage of time <3.9mmol/l and <3.0mmol/l decreased ($p<0.05$) Increase by 9% increase in postprandial peak, 10% increase in mean CGM, and a 35% increase in the %time above range ($p<0.05$)	Different machine learning algorithms: artificial neural networks, support vector machines (SVMs), Gaussian naïve Bayes (NB), AdaBoost (AB) used. Postprandial hypoglycaemia predicted using retrospective data from 10 real patients
Toffanin *et al.* 2018 (275)	Run-to-run	In-silico	Bolus/basal	-	N=100	Time in range after 8 weeks during the day and night increased from 82.0% to 91.3%, and the time spent above 10mmol/l is reduced from 15.1% to 7.8%	In-silico only
Resalat *et al.* 2019 (123)	Adaptive learning postprandial hypoglycaemia prevention algorithm + insulin sensitivity adaptation	In-silico	Bolus/Basal	-	N=99 T1D	Reduced time spent in hypoglycaemia by 71.7% Reduced total number of rescue carbs by 67.8% to 0.37% events/day/patient	In-silico only
BOLUS AND BASAL ADAPTATION							
Peters *et al.* 1991 (276)	Rule-based with algorithms	In-vivo; Adults	Bolus/basal SMBG data	32 days	N=40 T1D	No difference in HbA1c (%) between groups (9.0 ± 1.2 vs 9.2 ± 1.2)	Short study with data input SMBG only

	modified with control engineering theory					Reduction in day to day standard deviation (2.6 ± 0.8 vs 2.8 ± 0.9; p<0.05) Reduction in MAGE (7.1 ± 1.4 vs 8.1 ± 2.0; p<0.05) Reduction in time in hyperglycaemia ≥11.1mmol/l (16.8% ± 0.8% vs 28.0% ± 2.0; p<0.01)	
Ambrosiadou *et al*, 1996 (277) **DIABETES expert system**	Rule-based	Cases of 600 adults reviewed	Bolus/basal SMBG		N=600 cases (chosen from 600 participants) T1D/ T2D	65% of cases was graded by medical expert as 0 or 1 degree (Scale = 0 indicating full agreement and 5 full disagreement)	Evaluation of system compared to medical experts. Glycaemic outcomes not evaluated in real-world setting
Holman *et al* 1996 (278) **Patient-oriented insulin regimen optimizer (POIRO)**	Rule-based	In-vivo Adults	Bolus/basal SMBG	7 weeks	N=6 T1D RCT 3 weeks	Pre-prandial blood glucose levels lower with decision support (7.5 (0.4) versus 8.9 (0.4) mmol/l; p = 0.015) No change in hypoglycaemia	Small numbers; short study duration
Bellazzi *et al.* 2002 (259) **T-IDDM project**	Rule-Based Reasoning + CBR	In-vivo; Children and Adults	Bolus/basal	415 days	N=17 T1D	In paediatric cohort (n=6) using INTRAnet: No significant reduction of HbA1c Reduced insulin requirements (p<0.03) In adults using INTERnet (n=11): No significant changes	Small numbers; feasibility study Assistance on dose adjustments provided by the system considered acceptable only by 3 participants. A negative opinion provided by one patient on the user interface The medical unit assists the physician in the definition of the basal insulin regimen through a periodic evaluation of patient's data, whilst the patient unit helps tpatients in their self-monitoring activity, by suggesting insulin dose adjustments

Schwartz *et al.* 2008 (260)	CBR	In-vivo Adults; CSII	Bolus/Basal rtCGM (3 occasions for 72hours) + SMBG	6 weeks	N = 12	No glycaemic outcomes reported The prototypical system detected 12 distinct types of clinical problems: Hypoglycaemia; Awakening; Pre-meal; Post-meal; Over-correction for low glucose; Over-bolus with meal; Pre-waking; Exercise-induced Hyperglycaemia: Awakening; Pre-meal; Post-meal; Over-correction for high glucose; Possible pump or infusion set malfunction	Overall description of cases provided only
Wong *et al.* 2009 (279)	Model-based + rule-based for basal insulin titration	In-silico	Bolus/Basal SMBG		N=40 T1D	Adaptive protocol significantly reduced HbA1c for SMBG frequencies ≥6/day compared with controls and the conventional intensive insulin therapy protocol. With adaptive control for basal insulin, mild and severe hypoglycaemia reduced by 86–100% for all SMBG frequencies	The basal insulin dosing regimen used to optimise the single, daily insulin glargine dose based on the forced-titration regimens. This regimen incorporates a dose decrement if hypoglycaemia occurs Adaptive protocol prescribes 1–2 boluses per meal, a conservative initial bolus, and an aggressive second bolus to restore basal glycaemia, administered 90min after the start of the meal and first bolus. The first bolus is dosed according to the conventional insulin protocol
Dassau *et al.* 2017 (268)	MPC + the Health Monitoring System hypoglycaemia prediction algorithms (University of California, Santa Barbara/Harvard University) – run on DiAs.	In-vivo; Adults; AP	Bolus/Basal rtCGM	12 weeks	N=30 T1D	HbA1c 7.0 +/- 0.8% at the start of AP use, improved to 6.7 +/- 0.6% after 12 weeks (-0.3, 95% CI -0.5 to -0.2, p=0.001). Compared with the SAP run-in, %time spent in hypoglycaemia improved during the day from 5.0 to 1.9% (-3.1, 95% CI -4.1 to -2.1, P< 0.001) and overnight from 4.1 to 1.1% (-3.1, 95% CI -4.2 to -1.9, p < 0.001) compared with the last week No protocol-related serious adverse events	Single arm, uncontrolled study 10% of adaptation recommendations were manually overridden

Bode *et al.* 2018 (280)	Proportional integral derivative model	In-vivo; Adults; MDI	Bolus/Basal SMBG	90 days training period + 11 months	N=46 T1D + T2D	Reduced HbA1C 10.2% vs 7.2% at 12 months (p <.00001) – No control group	Retrospective analysis with no control group Adaptive advice provided to clinicians only. Changed doses communicated to participants by email, telephone, text messages.
Breton *et al.* 2018 (267) **UVA decision support system**	Kalman filter with glucose-insulin dynamics	In-vivo; Adults; MDI / CSII	Bolus/Basal	2x 48hr visits	N=24 T1D RCT	Reduced glycaemic variability (primary outcome); CV: 0.33 ± 0.06 vs 0.36 ±0.08; p=0.045 LBGI: 1.6 ±1.3 vs 2.5± 2.1; p= 0.042 Reduced TBR <3.3mmol/l 1.59 (± 1.27) vs 2.49(± 2.08); p=0.042 No change in TIR and TAR	Decision support system consists of two real-time advisors (CGM-Informed Bolus Advisor, and Exercise Advisor), and a retrospective insulin titration tool - generates ad hoc behavioural advice to avoid hypoglycaemia during an imminent exercise bout n=2 met stopping criteria (1 for high ketones; 1 for use of glucagon) 5 adverse events –unrelated to system High drop-out rate: visit availability (n=11), study-related stress (n=4), unable to complete data collection (n=2)
Nimri *et al.* 2018 (261) **Advisor Pro (DreaMed, Petah Tikva, Israel)**	MD-Logic	In-Vivo Children and Adults; CSII	Bolus rtCGM and SMBG participants		N=15 T1D	Full agreement by physicians with Advisor Pro for basal, ICR and ICF plans were 41.5 ± 8%, 48 ± 11% and 43.4 ± 11%	Evaluation of system compared to medical experts
Biester *et al.* 2019 (257) **DREAM5 Study**	MD-Logic	In-vivo; Children and Adults; CSII (hybrid closed-loop)	Bolus/Basal rtCGM	60 hours	N=48 T1D RCT SAP vs MD-Logic closed-loop system (DreaMed GlucoSitter)	Increased TIR range (3.9 – 10mmol/l) 66.6% vs 59.9% (p= 0.002) observed with the closed-loop system vs control Reduced time in hyperglycaemia > 10mmol/l 28.3% vs 36.3 (p=0.01) No change in hypoglycaemia	Short study duration High rate of communication errors between tablet computer running algorithm and insulin CSII. Most commonly due to miscommunication from the communication device: USB plugged ComLink

							MD-Logic algorithm into the CSII itself this could be alleviated
Tyler *et al.* 2020 (281)	Machine learning: K-nearest-neighbours	In-vivo; Children and Adults MDI	Bolus/Basal rtCGM	4 weeks	N=25 T1D	Improved TIR 47.7% to 58.7% (p<0.001). No reduction in hypoglycaemia over 24hr period (p=0.051) or during the day Reduction in serious hypoglycaemia (<3.0mmol/l) by 76% overnight (from 0.48% to 0.11%; p = 0.03) No reduction in hypoglycaemia for prandial mealtime dosing during the daytime was observed.	Small numbers; feasibility study not powered Weekly recommendations suggested by the KNN- decision support system were provided to clinicians (rather than in real-time to the user).

Table 1.5: Review of adaptive bolus and basal decision support systems in T1D

Abbreviations: CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; KNN, k-nearest neighbours; LBGI, low blood glucose index; MAGE, mean amplitude of glucose excursion; MDI, multiple daily injections of insulin; RCT, randomised control trial; rtCGM, real-time continuous glucose monitoring; SAP, sensor augmented pump therapy; SMBG, self-monitoring blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes; TAR, time above range; TBR, time below range; TIR, time in range; QOL, quality of life.

2 System Architecture and Study Design

2.1 Introduction

The PEPPER (**P**atient **E**mpowerment through **P**redictive **PER**sonalised decision support) project is a personalised decision support system for self-management of T1D, which includes an AI-derived insulin bolus recommender and a safety system. The project has been funded by a €3.8million H2020 grant with several European collaborators namely: Imperial College London (UK); Oxford Brookes University (UK); Institut d'Investigacio Biomedica de Girona (IDIBGI; Spain); University of Girona (Spain); Romsoft (Romania) and Cellnovo (UK).

In this chapter, the architecture for the PEPPER system has been described and is based on the work of the multi-partner consortium of clinicians, software engineers and academics. During the clinical trial, my involvement in the system architecture has been to provide feedback to de-bug the software system described, as well as provide clinical input for settings and criteria devised. During clinical testing, I

contributed in regular teleconference meetings held once weekly with the Consortium, as well as maintained a clinical and technical log of issues faced by participants. A further action log to include software fixes and testing of each component was maintained by the Consortium. More than 25 software versions were released across the period of the full clinical trial, each software update performed manually on each participant handset by me. Parts of this chapter have been published in Liu*, Avari* *et al* (282), as well as in the final Phase 3 manuscript (in revision).

2.2 PEPPER Architecture

PEPPER, as shown in Figure 2.1, offers dual architecture to serve both MDI or CSII users, the latter via the Cellnovo patch pump (Cellnovo Ltd., UK). In both cases, the user wears rtCGM (Dexcom G5, CA, US) which communicates to the handheld device via xDrip+, an open source software (283,284). An activity monitor (MiBand 1s, Xiaomi, China) is used to determine physical activity.

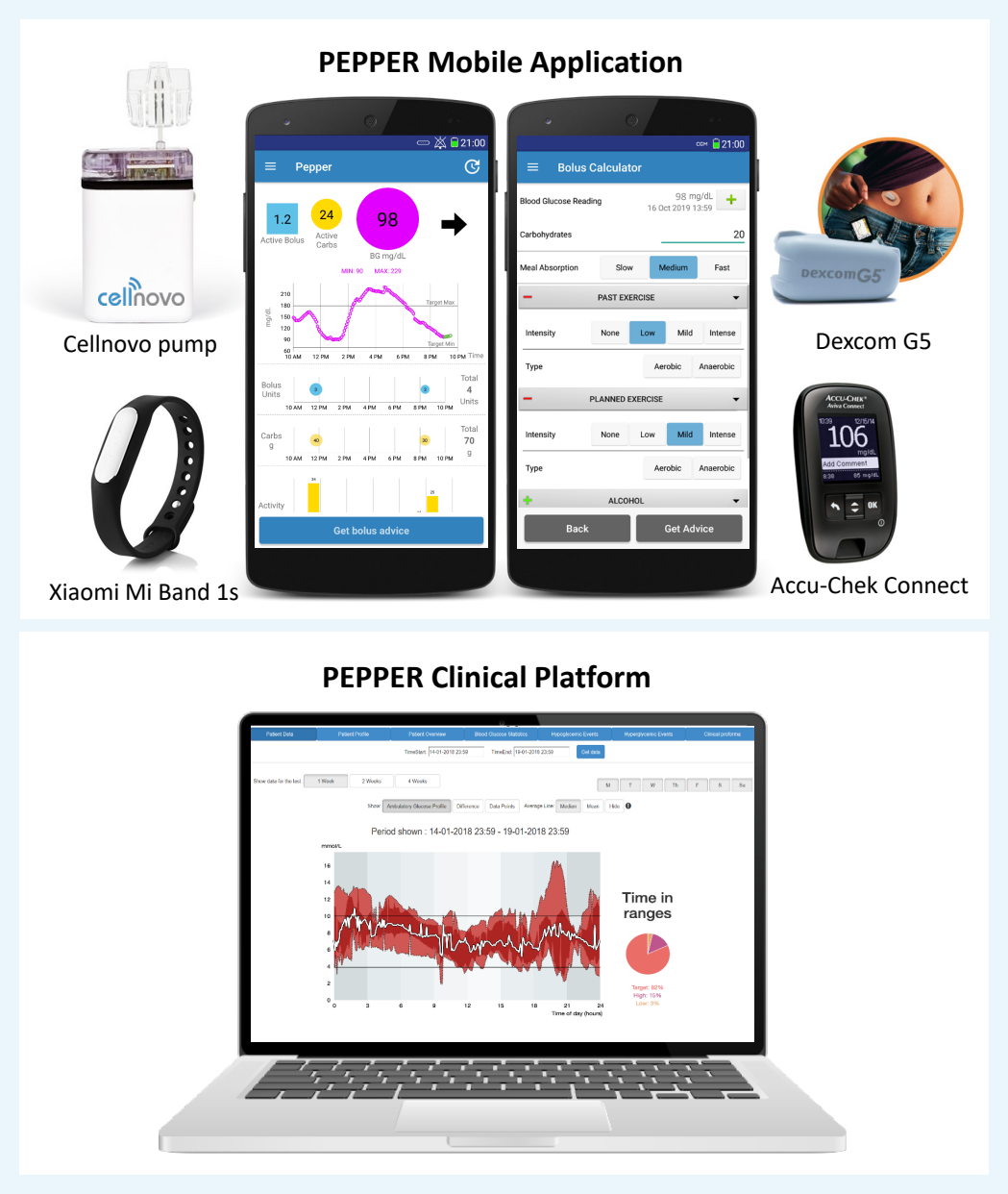

Figure 2.1: The PEPPER system architecture for use with MDI and CSII.

The user wears real-time CGM and an activity monitor which communicate with the PEPPER mobile application (app). Additional data such as food intake, alcohol consumption, stress, hormone cycles are inputted by the user. The hand-held unit remotely communicates to a secure web server where all collected data is uploaded and stored, and the clinical team can monitor the functioning of the system (i.e. PEPPER clinical platform).

The PEPPER app is integrated into the handheld device unit. For MDI users this is an Android smartphone (Google Nexus 5x) and for CSII users, this is via

Cellnovo's own handset running an Android OS. The PEPPER app enables input of carbohydrate intake for bolus recommendations, and additional data such as alcohol consumption, stress, hormonal cycles through the user interface (Figure 2.2). The handheld unit remotely communicates to a secure web server where all collected data, including insulin information, is automatically uploaded and stored via wireless internet connection or mobile data.

Insulin pen devices with half-unit increments are used with the PEPPER system (i.e. Echo pen [Novo Nordisk] for insulin aspart, Junior Star [Sanofi] for insulin glulisine, or HumaPen Luxura HD [Lilly] for insulin lispro) as insulin bolus advice was provided to the nearest 0.5 units. When the user accepts insulin recommendations, the data are automatically uploaded into the remote server. If the bolus advice is rejected by the user, the app requests the user to input the dose of insulin administered. The CBR uses the user insulin dose for revision of cases (see Section 2.4). The web-based interface enables the clinical team to monitor the functioning of the system (PEPPER clinical platform).

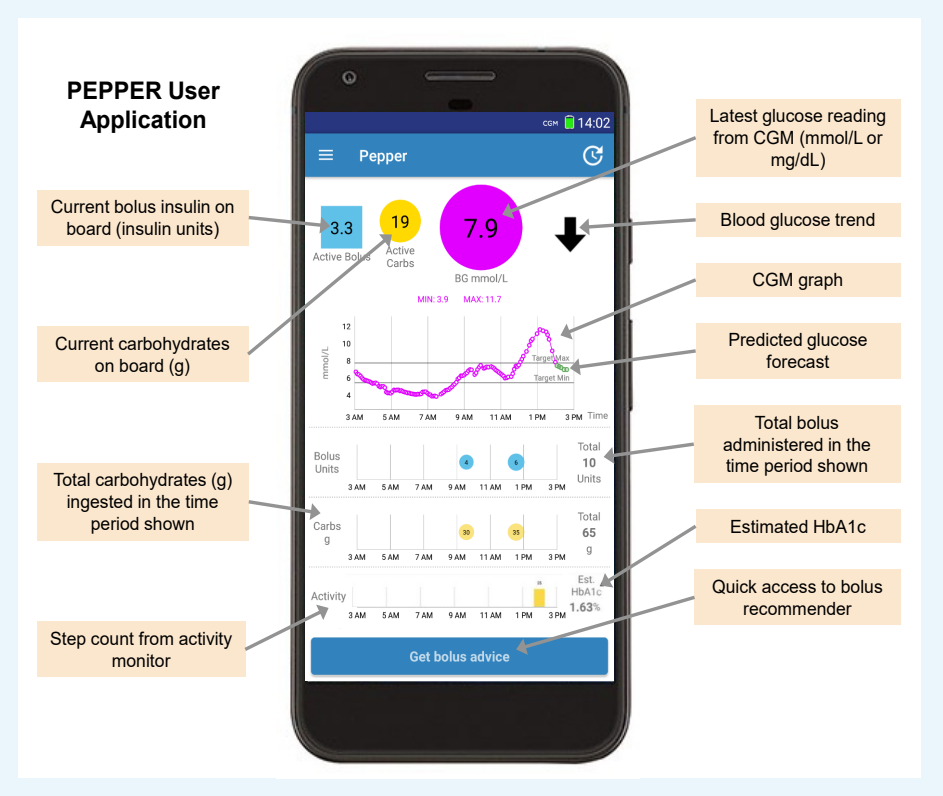

Figure 2.2: PEPPER interface on the smartphone version

The displays provides the user with an estimate of the active insulin bolus (blue square), an estimate of the remaining carbohydrates on-board (yellow circle), and the blood glucose level coming from the CGM (pink circle). The pink dotted line in the upper graph shows the CGM measurements, with the green dotted link displaying the 30-minute forecasted glucose. The "Get bolus advice" button triggers quick access to the insulin bolus recommender.

2.3 PEPPER Safety System

The novel PEPPER safety system encompasses four active modules (Figure 2.3): the first module consists of alerts crossing predictive glucose thresholds and standard glucose threshold crossing alarms. The second module is devised specifically for CSII users and automatically suspends basal insulin delivery when predicted glucose levels fall below threshold. A third module provides personalised carbohydrate recommendations (in grams) to improve glycaemia to safe levels.

Finally, the fourth module comprises of dynamic bolus insulin constraint, which eliminates extreme bolus advice, by safely restricting the amount of insulin that can be recommended to the user. Further details on the four modules are given in the following sections.

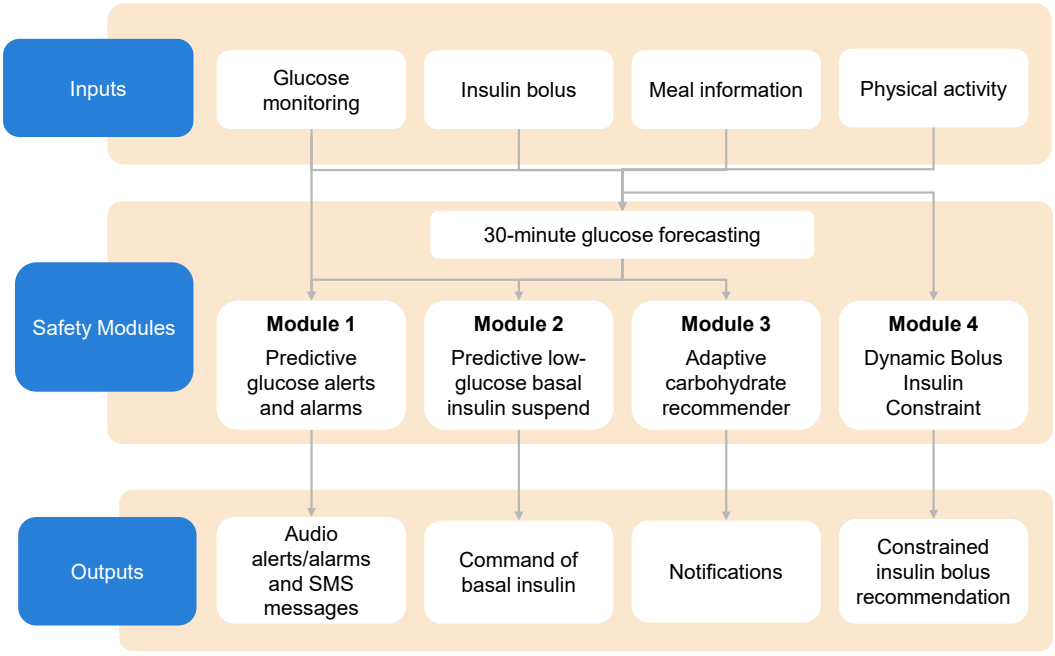

Figure 2.3: The modular PEPPER safety system

Block diagram of the novel PEPPER safety system and the four modules namely, predictive glucose alerts and alarms, predictive low-glucose basal insulin suspend, adaptive carbohydrate recommender and dynamic bolus inulin constraint. Corresponding inputs and outputs outlined.

2.3.1 Glucose alerts and alarms module

This module includes a novel 30-minute glucose forecasting algorithm (232) to provide two predictive alerts to notify the user before reaching predefined high and low glucose thresholds. Additionally, when thresholds measured by the rtCGM are exceeded, standard glucose alarms are used to notify the user. The user is able to select the thresholds for when alerts are triggered, meanwhile the alarm thresholds

cannot be modified and are hard-coded (3.9mmol/l for hypoglycaemia and 16.6mmol/l for hyperglycaemia).

In order to prevent alarm fatigue, once the user has snoozed an alert/ alarm, another alert/ alarm cannot be triggered until a predefined time interval of 30minutes has elapsed. Furthermore, for safety reasons, alarms cannot be muted, but alerts can. In addition, if a hypoglycaemia alarm is not addressed by the user within a predefined time interval of 30minutes, an SMS message containing the type of alarm (i.e. hypoglycaemia or hyperglycaemia) and the time it was triggered, is sent to a designated carer. Finally, the system continues to send messages every 30minutes until the alarm is snoozed on the handheld unit.

2.3.2 Predictive low glucose basal insulin suspend module

The predictive low glucose basal insulin suspension module allows suspension, or partial suspension, of basal insulin delivery in response to predicted low glucose levels. As a result, it aims at minimising the incidence and severity of hypoglycaemia. Basal insulin delivery is partially suspended by 50% if the 30-minute forecasted glucose value falls below a predefined threshold (Threshold 1). There is full suspension of insulin delivery when glucose falls below a second predefined threshold (Threshold 2), which is lower than Threshold 1. Whilst full insulin suspension is not possible due to a technical limitation of the pump, the rate is set at 0.01 U/h, which is virtually negligible for most people with T1D. This was the only way to make the pump resume without manual intervention by the user.

During basal insulin suspension, insulin delivery is resumed to 50% when forecasted glucose is above Threshold 2 and is fully resumed when forecasted above Threshold 1. To prevent excessive insulin deficiency and rebound hyperglycaemia, a total suspension time limit of 90 minutes is set. After this time limit, insulin is resumed to 50% for up to 30 minutes. Throughout, the user can resume basal insulin delivery at any time.

Further details of the PEPPER modular safety system and forecasting algorithm with predictive low-glucose basal insulin suspend have been published by Liu *et al* (273). Note, this feasibility study only includes MDI participants and the predictive low glucose basal insulin suspend module was not formally evaluated in the published study.

2.3.3 Adaptive carbohydrate recommender

In the event of hypoglycaemia, the adaptive carbohydrate recommender module recommends an oral dose of carbohydrates with the aim of reverting hypoglycaemia and minimising rebound hyperglycaemia. This is personalized and adaptive, based on the participant's weight and carbohydrate sensitivity factor (282).

The carbohydrate recommendation (CHO_{rescue}) is calculated using the following formula:

$$CHO_{rescue} = \frac{G_{setpoint} - G_{forecast}}{CSF} - COB$$

where $G_{setpoint}$ is the target glucose concentration after ingesting the rescue carbohydrates (6.7 mmol/l), $G_{forecast}$ is the 30-minute predicted glucose concentration, CSF is the carbohydrate sensitivity factor defined as the glucose concentration increase (mmol/l) per 1 gram of carbohydrates, and COB is the estimated rescue carbohydrates on board.

The carbohydrate sensitivity factor is initialised using body weight (150), however it is thereafter adapted using an R2R control algorithm to minimize both hypoglycaemia and rebound hyperglycaemia (282).

2.3.4 Dynamic bolus insulin constraint

The dynamic bolus insulin constraint (DBIC) module aims to eliminate potentially dangerous, extreme bolus advice that could be recommended to the user, resulting in severe hypo- or hyperglycaemia. As part of the PEPPER safety system by Liu *et al*, the DBIC is an additional safety layer to the CBR-based insulin recommender (252,282,285).

DBIC is based on a standard insulin bolus calculator (Section 1.3.2), and is expressed by:

$$Bolus = \frac{CHO}{ICR} + \frac{G_c - G_{sp}}{ISF} - IOB$$

where CHO (grams) is the amount of estimated carbohydrate, G_c (mmol/l) is the blood glucose measurement, G_{sp} (mmol/l) is the blood glucose target, *ICR* (g/U) and *ISF* (mmol/l/U). The *IOB* (units) is calculated using linear decay expressed as:

$$IOB = \sum_{i=1}^{N} Bp_i \left(1 - \frac{T_{int_i}}{T_{act}}\right),$$

where Bp_i is the previously administered insulin bolus, N is the total number of insulin boluses delivered within the time window [t - $T_{act,}$ t], T_{int_i} is the time elapsed since the last insulin bolus administered and T_{act} is the insulin action time, which is person dependent. Note, in order to estimate the IOB, only glucose centric insulin calculated from the correction dose is accounted for.

The recommended insulin dose is bounded by numerical intervals, accounting for the inherent uncertainty of the bolus calculator parameters and inputs. If the recommended insulin dose is outside the limits of ICR (±30%), ISF (±30%), T_{act} (±30min), G_c (±9%), and CHO (±15%), it is saturated to the corresponding upper or lower bound (282). For example, in the scenario where G_c=8.3mmol/l, G_{sp}=6.7mmol/l, CHO=70grams, ICR=10grams/unit, ISF=2.2mmol/l/unit and IOB=0 unit. Then, the resulting bolus insulin intervals are 4.8 units and 13.0 units for the lower and upper bound respectively. The resulting value is displayed to the user when the “request bolus advice” button is pressed on the handset.

To summarise, the standard formula above is used to calculate the DBIC bounds, whilst the CBR algorithm is used to calculate the adaptive bolus advice in real time (see Section 2.4).

2.4 PEPPER Adaptive Bolus Advisor

The PEPPER adaptive bolus advisory system implements an AI-derived insulin bolus calculator based on CBR, which provides personalised insulin recommendations and automatically adapts its parameters over time. The core of the adaptive case revision process in the PEPPER system has been created by University of Girona, and has been previously published by Torrent-Fontbona *et al* (285,286). Furthermore, the advisory system has been validated in-silico (285).

To understand the functioning of the system, an explanation of each process and its integration has been described below.

2.4.1 Cases

As part of the CBR-based adaptive bolus advisor, in each instance of insulin recommendation, a case is created and stored. Each case captures all the information pertaining to when the user administers a bolus dose through the PEPPER system. The following case parameters are captured: time of day, past and planned exercise, alcohol, meal absorption rate, stress, tiredness, menstrual cycle for women, fever and digestive illness.

Prior to a case being introduced in to the CBR cycle, an evaluation step occurs on the server and requires approval by an expert clinician before a new case is incorporated to the case base. The evaluation step has been described in Section 2.4.6.

2.4.2 Retrieve

The retrieve step selects similar cases to the new case, based on the input data. In this phase, two main steps occur: 1) feature identification, and 2) the match-and-selection of cases.

Feature identification: In the feature identification step, all variables used in the retrieve step are quantified.

Physical activity before a meal, is quantified in four levels according to the average exercise performed in the last 10 hours measured by the activity monitor (MiBand 1s, Xiaomi, China). Each activity level is personalised for each participant by determining their mean step count. The mean step count was determined by total step count/days. Levels were determined as follows: “None” is defined as <1000 steps, “low” is <(2000 + individual mean/2) steps, “mild” <(5500 + individual mean/2) steps and “intense” >(5500 + individual mean/2) steps.

For consideration of future physical activity, the user is asked to provide a subjective prediction of the physical activity that is likely to be carried out during the postprandial phase. Four quantification levels are used (none, low, mild and intense).

The carbohydrate content of the meal also impacts the ICR and ISF. Therefore, the quantity of carbohydrates is computed on three levels (low, medium, high)

depending on whether the meal has less than 30g, between 30g - 70g, or more than 70g of carbohydrates, respectively.

The time of day is a discrete variable with possible values ranging from 0 to 23 (i.e. as integer hours of the day). The timestamp is adjusted to the nearest hour.

Match and select: The retrieval of similar cases is based on a similarity measure. The method uses k-nearest means, and consists of an average Euclidean distance between all the attributes. The Euclidean distance is the most widely used distance function. Several other types of distance functions exist, such as cosine, Chi square, and Minkowsky similarity measure (287).

The PEPPER recommender is able to deal with missing values and ensures that selected cases are the most similar to the new query case (285). Other techniques such as replacing the unknown value with an average value may introduce bias in the selection of cases.

For case retrieval, all parameters are weighted differently. The system learns the weighting for each participant based on user input, and these weights change with each recommendations and case retrieval (286).

The final outcome of the retrieval stage is a number of the most similar cases.

2.4.3 Re-use

During the re-use process, retrieved and new "query" situations are not identical. Thus, the PEPPER recommender provides the ICR solution using a weighted mean of the ICR of the retrieved cases.

The formulae used have been previously published in the work by Torrent-Fontbona *et al* (285). The following equation is used where Q is the query case, K is the number of retrieved cases, ICR_Q is the ICR of the query case, C_k is the kth retrieved case, and ICR_{Ck} is its corresponding ICR.

$$ICR_Q = \frac{\sum_{i=1}^{K} S\,(Q, C_k) ICR_{C_k}}{\sum_{i=1}^{K} s\,(Q, C_k)}$$

The insulin sensitivity factor of the query case ISF_Q is calculated using the equation below, based on the hypothesis that ICR and ISF are correlated (288), where W is the weight of the user in kg.

$$ISF_Q = \frac{341.94 \cdot ICR_Q}{W}$$

Following the calculations of ICR_Q and ISF_Q, the recommended bolus (B) for the query case is calculated according using the same equation as that used in standard bolus calculators (202), with the same input data:

$$B = \frac{CHO}{ICR} + \frac{G_c - G_{sp}}{ISF} - IOB$$

2.4.4 Revise

The proposed ICR solution is evaluated by the postprandial glucose curve of the user. If the outcome is sub-optimal (i.e. above or below glucose target range), then the new ICR and ISF are revised accordingly (289). The minimum postprandial glucose value, G_{min}, is the main focus with the revise step.

G_{min} is calculated by the below equation for any given mealtime t_m, with the minimum glucose value of $G_{cgm}(t)$ measured by rtCGM between t_1 and t_2 time after t_m, with $t_1 < t_2$, e.g. t_1 = 1h and t_2 =5h (285).

$$G_{min} = \min_{t \in \{t_m + t_1, t_m + t_2\}} \{G_{cgm}(t)\}$$

Given G_{min}, the revised ICR_Q is recommended by the re-use process according to the following equation, where ICR_Q is the corrected ICR of the query case, and α ∈ [0,1] is the learning rate. The learning rate is incorporated to smooth changes, which could be influenced by noisy measurements of the continuous glucose monitor (285).

$$\hat{ICR}_Q = (1-\alpha)ICR_Q + \alpha \frac{CHO + \frac{G_C - G_{sp}}{341.94/W}}{B_Q + IOB + \frac{G_{min} - G_{low}}{ISF_Q}}$$

The target glucose values, G_{sp}, and G_{low}, may be agreed upon between the participant and the clinician. For the PEPPER clinical study, these were both standardised to 5.5mmol/l, but were later modified if required.

2.4.5 Retain

The retain step is responsible for updating the case base for further recommendations. Hence, the maintenance process decides whether the case should be stored in the case base, or whether they should be removed because they are redundant or old.

Over time, there may be changes in users' physiology, for example age or changes in body weight. PEPPER deals with this problem, called concept drift, by a maintenance strategy consisting of keeping the most recent cases (i.e. to the query case) over similar cases in the case base if they are sufficiently similar. This maintenance process relies on the assumption that similar cases should have the same (or very similar) ICR and, if not, the case should be removed due to a change in the individual's physiology. Thus, similar old cases are removed because they are either redundant (have the same ICR) or obsolete (285).

2.4.6 PEPPER clinical platform

The PEPPER clinical platform enables clinician supervision of bolus insulin adjustments proposed by the CBR algorithm. The platform is available for case revisions to be made online and is designed to run on a desktop computer (using Chrome). For the UK participants, the revision process by accepting cases into the case base was performed by myself, and for the participants in IDIBGI (Spain), this was conducted by Dr Marzena Wos, clinician at IDIBGI.

The clinician is able to accept/reject clinical cases that are presented for adaptation. If the minimum postprandial glucose is sub-optimal (i.e. above or below glucose target range), then the new ICR and ISF are revised accordingly. Figure 2.4 shows a screenshot of the clinical platform, which presents the proposed adaptation for revision of the ICR and ISF of a presented case.

Figure 2.4: The clinical platform for case revisions

Glucose data visualisations and the corresponding meal scenarios were available for review on the clinical platform. Clinicians would approve or reject clinical cases based on predefined criteria. Exclusion criteria include: if a meal or insulin bolus was taken within the 5-hour postprandial period, if quality of the CGM sensor data affected the postprandial curve, if insulin on board was > 4 units, and if carbohydrate content of a meal was <20g (i.e. a snack). Approved cases would be introduced into the case base for future use.

The following rejection criteria were used based on rules co-written by Dr. Pau Herrero and myself for revision of the cases. Cases were rejected under the following conditions:

1. If extra carbohydrates were ingested within the 0-5hours window frame of a bolus administered (unless this was to correct impending hypoglycaemia)
2. If an extra bolus was given within the 0-5hours window frame of a bolus administered (unless the extra bolus was to correct hyperglycaemia and duration was sufficiently long enough post initial bolus to confirm need for change in ICR)
3. If the postprandial glucose value was equal to 0 or −1
4. If the postprandial curve looked suspicious (e.g. sensor malfunctioning or pump occlusions)
5. If the IOB for the case was more than 4 units
6. If the carbohydrate content for the meal consisted of less than 20g
7. If values were greater than the constraints placed on the minimum and maximum values that the ICR/ISF can take.

2.5 PEPPER Aims, Objectives and Hypotheses

2.5.1 Aims and objectives

The study aims and objectives include:

1. ***Phase 1 (Chapter 3):*** To demonstrate safety, feasibility and proof of concept for the PEPPER safety system (without CBR-based adaptive bolus calculator) in the participant's own environment.

2. ***Phase 2 (Chapter 4):*** To demonstrate safety, feasibility and proof of concept for the complete PEPPER system (with CBR-based adaptive bolus calculator enabled) in the participant's own environment.

3. ***Phase 3 (Chapter 5):*** To demonstrate safety, feasibility and efficacy of the complete PEPPER system (i.e. safety system and CBR-based adaptive bolus calculator) compared to a standard bolus calculator.

2.5.2 Hypotheses

1) ***Phase 1 (Chapter 3):*** The PEPPER safety system is safe and feasible for use in people with TID using MDI or CSII.

2) ***Phase 2 (Chapter 4):*** The PEPPER adaptive bolus calculator with safety system is safe and feasible for use in people with TID using MDI or CSII.

3) ***Phase 3 (Chapter 5):*** The complete PEPPER system (safety system and adaptive bolus calculator) is safe and effective for use in people with TID using MDI or CSII.

2.5.3 Study design

The full project is designed to address the objectives through three clinical phases (Figure 2.5) as follows:

1) ***Phase 1 (Chapter 3):*** A non-randomised single-arm open-label study to evaluate the PEPPER safety system over 8 weeks.

2) ***Phase 2 (Chapter 4):*** A non-randomised single-arm open-label study to evaluate the PEPPER safety system and adaptive bolus advisor over 8 weeks.

3) ***Phase 3 (Chapter 5):*** A randomised controlled open-label study evaluating the complete PEPPER system compared to standard care over 8-months.

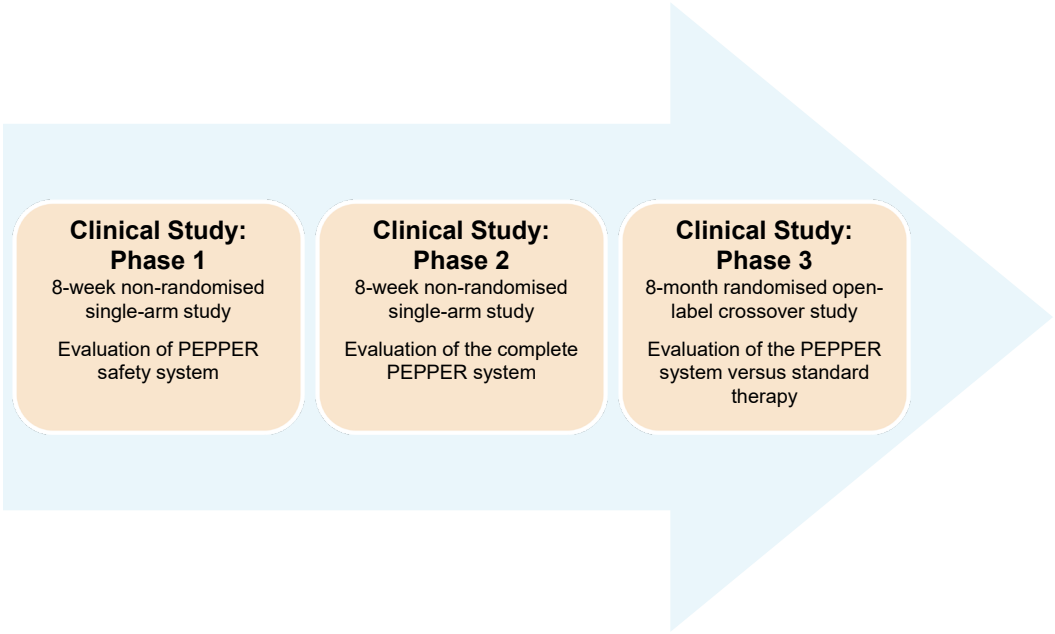

Figure 2.5: Overview of the PEPPER clinical studies

2.5.4 Regulatory approvals

The following approvals were obtained for study trials in the UK:

Research and Development at Imperial College Healthcare NHS Trust (Ref no 17HH3961)

Sponsor (Ref no 17HH3961)

NRES London Committee–Westminster (REC Ref no 17LO/0939)

MHRA (Ref no CI/2019/0030)

The study has been registered at ClinicalTrials.gov with identification number: NCT03738982

PEPPER complies with medical software standards (IEC 62304, IEC 62366, SnomedCT, and HL7).

3 Phase 1: Safety and Feasibility of the PEPPER Safety System

3.1 Introduction and Aims

Despite the benefits of intensive insulin management, many individuals with T1D find it challenging to follow and/or adjust their insulin regimens as needed. Key contributors to this include fear of hypoglycaemia, lack of self-efficacy and difficulties associated with insulin dose determination, such as carbohydrate counting or dose calculation. Automated bolus advisors can help individuals meet prandial insulin dosage requirements more accurately, improve postprandial glycaemic excursions and help achieve optimal glycaemia (290).

The Patient Empowerment through Predictive Personalised Decision Support (PEPPER) project is an adaptive bolus calculator derived from AI, coupled with a safety system unique to PEPPER. This safety system is designed to minimise any risk of insulin overdosing, whilst the insulin recommender system is designed to propose a safe insulin dose.

The PEPPER safety system has been comprehensively reviewed in Chapter 2. To summarise, it implements state-of-the-art techniques for hypoglycaemia detection and prevention, through rtCGM derived alarms, predictive glucose alerts and predictive automated suspension of basal insulin for CSII users. It further innovates with a novel carbohydrate recommendation system that advises the ingestion of a personalised carbohydrate dose in the case of impending hypoglycaemia. The safety system also includes a set of safety constraints that guarantee that the proposed insulin dose remains in a safe range. Finally, if an alarm is not addressed in a timely manner by the user, caregivers/relatives are informed by SMS through the use of 3G-connectivity employed within the handset device.

At the first stage of clinical evaluation, it was pertinent to ensure the safety system was evaluated on its own, prior to adding in the adaptive bolus calculator. Although insulin pump and rtCGM systems are relatively mature technologies, faults may still occur within the coded algorithms. It was initially planned that the predictive low glucose suspend system would run in the background, without being active, for safety reasons. It was, however, activated in a software update and thus the whole safety system (see Section 3.2.6)

Thus, the aim of the first stage of the clinical assessment of the PEPPER system was to demonstrate safety and feasibility of the safety system within PEPPER in adults with T1D. It is important to remark that, during this stage, the CBR-based adaptive bolus calculator was not active. Bolus recommendations were based on a standard bolus calculator, which was embedded within the PEPPER handset. Generic details of the system architecture have been discussed in Chapter 2.

The hypothesis of Phase 1 of the clinical study is that the PEPPER safety system is safe and feasible for use in people with TID using MDI and CSII therapy.

The results in this chapter on MDI participants have been published in the *Journal of Diabetes, Science and Technology*, on which I am joint-first author (282).

3.2 Methodology

3.2.1 Study design and recruitment

Phase 1 was a non-randomised, open-label study evaluating the PEPPER safety system over 8 weeks. Recruitment was undertaken at Imperial College London (UK) and the Institut d'Investigacio Biomedica de Girona (IDIBGI) in Spain. Potential participants were identified through diabetes clinics at each respective site, or from interested participants who contacted the research team through the NIHR Research Gateway.

Ethics and device approvals were obtained from the relevant regulatory bodies at each of the sites. All participants provided verbal and written informed consent.

3.2.2 Participants

Study participants fulfilled the following inclusion / exclusion criteria:

Inclusion criteria:

- Adults ≥ 18years of age
- Diagnosis of T1D for > 1 year
- On MDI using a basal-bolus insulin regime or CSII (insulin pump) for at least 6 months
- Structured education (either in a group or 1:1 sessions) and good ability to perform CHO counting
- HbA1c ≥ 48mmol/mol and ≤ 86mmol/mol
- Using ICR and ISF to calculate the mealtime bolus
- An understanding of and willingness to follow the protocol and sign the informed consent
- CBG measurements at least 2 times per day for calibration of the rtCGM

Exclusion criteria:

- Severe episode of hypoglycaemia (requiring 3rd party assistance) in the 6 months prior to enrolment
- Diabetic ketoacidosis in the last 6 months prior to enrolment

- Impaired awareness of hypoglycaemia (based on Gold score ≥4 for participants in UK or Clarke score ≥4 for participants in Spain)
- Pregnancy, breastfeeding or intention of becoming pregnant over time of study
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Suspected or diagnosed endocrinopathy e.g. adrenal insufficiency, unstable thyroidopathy, endocrine tumour
- Gastroparesis
- Autonomic neuropathy
- Macrovascular complications (acute coronary syndrome, transient ischaemic attack, cerebrovascular event within the last 12 months prior to enrolment in the study)
- Visual impairment including unstable proliferative retinopathy
- Reduced manual dexterity
- Inpatient psychiatric treatment
- Abnormal renal function test results (calculated estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73m^2)
- Liver cirrhosis
- Abuse of alcohol or recreational drugs
- Oral steroids
- Regular use of the acetaminophen, beta-blockers or any other medication that the investigator believes is a contraindication to the participant's participation.

Withdrawal criteria:

- Loss of capacity to give informed consent
- The subject has a serious event related to the study
- Cessation of MDI of insulin as usual care for T1D
- Severe hypoglycaemia
- Diabetic ketoacidosis
- Positive pregnancy test
- Terminal illness
- Investigators initiated discontinuation of study due to participant or equipment concerns.

For participants withdrawn due to investigator-initiated discontinuation, or if participants withdrew their consent, any identifiable data already collected with consent was retained and used in the study. No further data was collected, nor any other research procedures carried out in relation to the participant.

3.2.3 Procedures and visit schedule

The study comprised of four visits over 8 weeks as outlined below:

Visit 1: Screening and consent

At study enrolment, participants gave a full medical and medication history, and underwent a physical examination and electrocardiogram. Venous bloods assessing HbA1c, creatinine, lipids, liver function, full blood count and thyroid

function were taken and sent to Imperial College Healthcare NHS Trust (ICHNT) laboratory for analysis. A urine sample was taken to measure albumin:creatinine ratio and women of child-bearing age additionally had a urinary pregnancy test. Participants meeting the inclusion criteria had a brief T1D education refresher. Eligible participants were provided with the PEPPER study handset, real-time CGM (Dexcom G5 transmitter and sensor) and an activity monitor. The PEPPER user app was integrated into the hand-held device.

Instructions were provided for rtCGM sensor change for the Dexcom G5 every 7 days as per manufacturer's guidance (or sooner in event of sensor failure). In addition, participants were instructed to test capillary blood glucose every 12 hours for calibration, if symptoms of hypo- or hyperglycaemia were present, or if the sensor glucose was out of the desired range (3.9 mmol/l - 13.3 mmol/l). RtCGM alarm thresholds were set at 3.9 mmol/l and 16.6 mmol/l.

For the run-in period, the PEPPER safety system and adaptive bolus advisor were disabled. Standard rtCGM alarms were received through xDrip+, which ran in the background of the PEPPER app. Standard bolus calculator settings were used throughout this phase. Insulin pen devices with half-unit increments were provided to MDI users, as insulin bolus advice was provided to the nearest 0.5 units.

Participants on CSII were switched to the Cellnovo pump and trained on its use. Differences from their own home pump were discussed including important aspects such as calculation of IOB and correction boluses. Additional topics for discussion included: site initiation, cartridge/priming procedures, setting up the

pump, changing batteries, navigation through menus and bolus procedures including stopping a bolus. User manuals were provided for the PEPPER handset, Cellnovo insulin pump and continuous glucose monitor.

Participants were also asked to complete validated study questionnaires (Diabetes treatment satisfaction questionnaire (DTSQs), Gold Score, Problem Areas in Diabetes [PAID], and Diabetes Quality of Life (DQOL)) to assess psychosocial outcomes. Details on the questionnaire components can be found in Table 3.1.

Each screening visit lasted for approximately 4-6 hours and, for UK participants, was conducted at the Imperial Clinical Research Facility.

Participant accounts on the online PEPPER portal were created in advance of the study visit by myself, with corresponding serial code numbers of the handset and pump devices. Each anonymised participant account was paired with a handset and pump serial code, with details sent to Cellnovo for linkage on their server in advance of each visit. There were frequent technical issues during the set-up process of linking the equipment, particularly with the CSII participants (i.e. cartridge ejection issues – further details in Discussion Section 3.6). As a result, sessions lasted longer than anticipated. Where necessary, I requested support from the Imperial engineering team and our commercial collaborators. In some instances, participants were requested to attend again on another day.

Questionnaire Tool	Description	Scoring
Problem Area in Diabetes (PAID) (291)	Covers a range of emotional states frequently reported in diabetes. It is primarily a measure of diabetes-specific emotional distress	Each of 20 items scored from: 0='not a problem' to 4='serious problem'. Total scores scaled out of 100 with higher scores indicating distress PAID summary score: 0 to 39 – no distress, 40 to 59 – mild distress, 60 to 79 –moderate distress, 80 to 100 – severe distress
Diabetes Treatment Satisfaction Questionnaire (DTSQs) (292)	Measures patient satisfaction with diabetes treatment	DTSQs – Each item scores from 0='very bad' to 6='very good'. All scores, except those from DTSQ items 2 and 3, (which assess glycaemic control rather than satisfaction through perceived hypo-/ hyperglycaemia), are added up to produce a DTSQ total score (range 0–36). Higher scores reflect higher satisfaction DTSQs perceived frequency of hypo- and hyperglycaemia are scored from 0 (none of the time) to 6 (most of the time)
Diabetes Quality of Life (DQOL) (293)	Assesses the relative burden of diabetes	The DQOL measure consists of 46 items, forming 4 domains i.e. satisfaction, impact, worry: social/vocational; worry: diabetes related. Responses are ranked on a 5-point Likert scale with higher scores indicating dissatisfaction, frequent impact, or frequent worry
GOLD Scale (28)	Categorises awareness of having reduced awareness of hypoglycaemia in patients with diabetes	One item with score on a scale from 1='always aware' to 7='never aware' in response to the question: "Do you know when your hypos are commencing?" Impaired awareness if Gold score is ≥4

Table 3.1: Psychosocial questionnaires used in the PEPPER clinical study

Abbreviations: DTSQs, diabetes treatment satisfaction questionnaire; DQOL, diabetes quality of life; PAID, problem area in diabetes

Visit 2: Safety System switched on

Following the 2-week run-in period, the PEPPER safety system was switched on. The PEPPER CBR-based adaptive bolus calculator remained disabled throughout Phase 1 and the standard bolus calculator was used.

RtCGM data was reviewed by the researcher with the participant and changes were made to the basal insulin/ISF/ICR if required at each of the visits.

Visit 2 lasted for approximately 1 hour and took place at the clinical research facility. Where technical issues arose, often a whole system reset was required, resulting in longer session visits. Support from the engineering team was requested when required.

Visit 3: Review

At visit 3, participants attended the research unit and discussed any technical issues encountered between visits. Technical issues identified during the assessment were documented within a clinical and technical log of issues and fed-back to the relevant engineering teams, analysed and incorporated into system redevelopment. Any new software versions were made available to participants as required.

This visit lasted for approximately 1 hour, however occasionally required further time to address any software updates or technical issues arising.

Visit 4: End of Study at 8 weeks

The final visit lasted approximately 1 hour and was held at the clinical research facility. The PEPPER system was switched off and returned. Semi-structured interviews were conducted and participants completed the PAID, DQOL and DTSQs questionnaires.

At each visit, the rtCGM data was reviewed by the researcher with the participant and changes were made to the basal insulin/ISF/ICR as required. Verbal feedback from participants was obtained regarding any technical issues encountered. Technical issues identified in the assessment were dealt with system redevelopment.

The Phase 1 clinical study protocol is summarised in Figure 3.1.

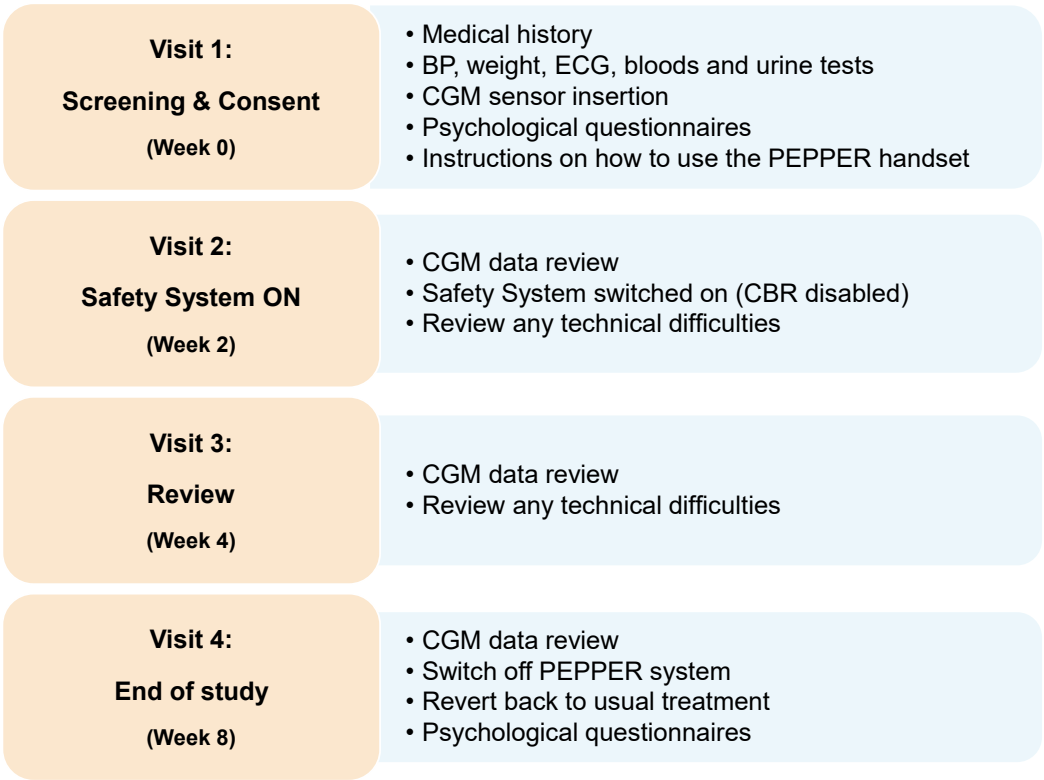

Figure 3.1: Summary of Phase 1 study visit attendances

3.2.4 Study outcomes

The primary outcome was % time in hypoglycaemia <3.9mmol/l from baseline to endpoint. Secondary outcomes regarding glycaemic control included percentage (%) time in range (TIR) 3.9-10mmol/l, % time in hyperglycaemia >10mmol/l and % time in lower thresholds of hypoglycaemia (<3.3mmol/l and <3.0mmol/l).

Secondary outcomes relating to the safety system included the incidence of predictive low and high glucose alarms and carbohydrate recommendations (number per week). The scores from the quality of life questionnaires (PAID, DQOL, DTSQ) at baseline and endpoint were compared to assess treatment satisfaction, social functioning, and factors important to quality of life.

3.2.5 Statistical analysis

All glycaemic outcomes from baseline (weeks 1 and 2) were compared with endpoint (weeks 7 and 8). Non-normally distributed data were analysed with the Wilcoxon matched-pairs signed-rank test. All outcomes are reported as median (interquartile range [IQR]), unless stated otherwise. P-values <0.05 were considered statistically significant.

The glycaemia and safety system data for each participant were stored on the PEPPER clinical platform, which were exported and run on Matlab to calculate the primary and secondary outcomes for each week of the study. A formal power calculation was not performed for the Phase 1 pilot study assessing feasibility and safety of new technology.

3.2.6 Analysis deviation from protocol

The study protocol was designed to analyse combined data from MDI and CSII participants recruited from UK and Spain for Phase 1 (total n=15; a sample size comparable to other technology pilot safety studies). This assumed that both clinical sites would be using the same hardware and software during the study.

For MDI participants, I was able to analyse the combined outcomes from the two clinical sites using the maximum available participant numbers.

However, there were several technical issues encountered with the Cellnovo pump, including frequent cartridge ejection and signal loss. The manufacturers attempted to resolve this with software and firmware updates.

During this time, ICL paused the clinical study, whilst IDIBGI completed the clinical trial to meet project deadlines. In addition, it was initially planned that the predictive low glucose suspend system would run in the background for this phase, without being active, in order to ensure both groups received the same safety interventions. However, as part of the software updates to improve usability, the pump manufacturers inadvertently activated the predictive low glucose suspend for CSII participants at ICL. As a result, the two clinical sites had different features with two very different software versions.

For CSII analysis, in view of the aforementioned issues encountered with the Cellnovo pump, I restricted the dataset to participants recruited at the ICL site only. At this site, optimal pump software was used with the complete safety system, including the predictive low glucose suspend feature, which was functional from week 5 onwards only. The MDI and CSII groups are, therefore, presented separately.

3.3 Results for Participants on MDI

Eight participants were recruited between November 2017 and January 2018 at IDIBGI (n=4) and ICL (n=4). Participants (3 men and 5 female) had a median (IQR) age of 37.5 (31.8-53.5) years, body mass index (BMI) 23.8 (23.2-27.5) kg/m^2, HbA1c 63.0 (57.4-66.1) mmol/mol and duration of diabetes 22.5 (18.0-26.5) years (Table 3.2). Intact awareness of hypoglycaemia was present in all participants at baseline.

Demographics	**Median (interquartile range)/ n (%) (n=8)**
Gender (female)	5 (62.5%)
Age (years)	37.5 (31.8-53.3)
BMI (kg/m^2) Height (cm) Weight (kg)	23.8 (23.2-27.5) 164.5 (162.3-173.8) 71.1 (61.3-74.7)
Duration of diabetes (years)	22.5 (18.0-26.5)
Hypoglycaemia awareness (i.e. Gold/Clarke score <4)	8 (100%)
HbA1c (mmol/mol)	63.0 (57.4-66.1)
Number of CBG measurements per day	3.5 (2.0-5.0)
Previous episode of DKA	3 (37.5%)
Previous episode of severe hypoglycaemia	0 (0.0%)
Participants with: Diabetic retinopathy (background/ stable treated) Diabetic nephropathy Diabetic neuropathy Diabetic arteriopathy	 3 (37.5%) 0 (0.0%) 2 (25.0%) 0 (0.0%)
Participants with: Hypertension Dyslipidaemia IHD CVA Hypothyroidism Hyperthyroidism Liver disease COPD GI disease Anxiety Depression	 2 (25.0%) 4 (50.0%) 0 (0.0%) 0 (0.0%) 1 (12.5%) 2 (25.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 2 (25.0%)
TSH (mU/L)	1.75 (1.67-2.07)
Total cholesterol (mmol/l)	4.4 (4.1-4.7)

Table 3.2: Baseline characteristics for Phase 1 participants on MDI

Results are expressed as median (IQR). Previous episodes of DKA/ severe hypoglycaemia refer to lifetime incidence, occurring any time prior to the 6 months before recruitment on the study. Abbreviations: BMI, body mass index; CBG, capillary blood glucose; DKA, diabetic ketoacidosis; IHD, ischaemic heart disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; TSH; thyroid stimulating hormone

The 8-week Phase 1 study was completed by six participants. The reasons for two participants not included in the final analysis, were due to one drop-out for personal commitments and one participant having handset issues.

3.3.1 Glycaemic outcomes

Glucose outcomes were derived from the run-in rtCGM data (baseline weeks 1 and 2) and compared with endpoint (weeks 7 and 8; Table 3.3). For the primary outcome comparison (% time in hypoglycaemia <3.9mmol/l), no significant differences were observed between the two groups. However, reduction in median % time in hypoglycaemia <3.0 mmol/l was observed, from 0.8 (0.1-4.8)% during run-in (weeks 1 and 2) to 0.3 (0.0-0.9)% at endpoint (weeks 7 and 8; p=0.02). Reduction in %time <3.0mmol/l was seen as early as consecutive fortnightly weeks 1 and 2, and weeks 3 and 4 (p=0.049).

Percentage %TIR 3.9-10.0 mmol/l significantly increased with use of the PEPPER safety system compared to standard system (61.3 (47.5-71.7)% vs 52.8 (38.3-61.5)% respectively; p=0.03). No significant difference for time in hyperglycaemia >10mmol/l was observed.

No adverse incidents of DKA or severe hypoglycaemia requiring third-party assistance occurred during the study period. One participant was admitted to hospital following hyperglycaemia secondary to chest infection. There were no significant changes to basal insulin dosing between run-in and endpoint.

	Run-in (n=6) Weeks 1 and 2	**Endpoint (n=6)** Weeks 7 and 8	**P-value**
% time in hypoglycaemia			
<3.9mmol/l (<70mg/dL)	3.7 (1.6-6.4)	2.7 (0.9-7.3)	0.15
<3.3mmol/l (<60mg/dL)	1.8 (0.7-5.6)	0.8 (0.0-1.5)	0.05 *
<3.0mmol/l (<54mg/dL)	0.8 (0.1-4.8)	0.3 (0.0-0.9)	0.02 *
% time in range			
3.9 – 10.0mmol/l (70 -180mg/dL)	52.8 (38.3-61.5)	61.3 (47.5-71.7)	0.03 *
% time in hyperglycaemia			
>10mmol/l (>180mg/dL)	44.3 (37.3-57.8)	33.8 (27.5-49.2)	0.09

Table 3.3: Glycaemic outcomes in MDI users with safety system on.

Median percentage time (and IQR) spent within various glucose ranges at baseline (weeks 1 and 2) and endpoint (weeks 7 and 8). Data presented as median (IQR). * $p<0.05$ indicates significance.

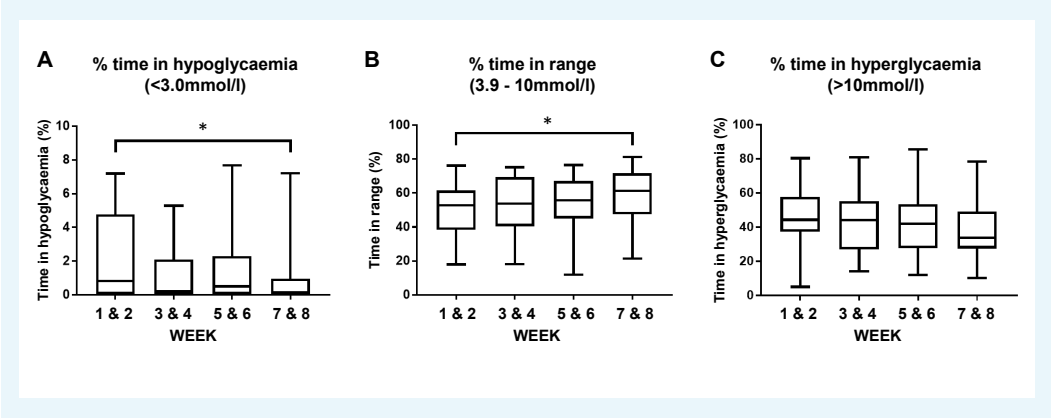

Figure 3.2: Change in glycaemic outcomes on a fortnightly basis

Box plots showing the change in glycaemia over the eight-week study. (A) Change in percentage time in hypoglycaemia (<3.0 mmol/l). (B) Change in percentage time in range (3.9-10.0 mmol/l). (C) change in percentage time in hyperglycaemia (>10 mmol/l). *ANOVA $p < 0.05$ indicates significance.

3.3.2 Safety system outcomes

Whilst the safety system was not enabled during the run-in period, the algorithm was running in the background to allow comparisons to be made. The total incidence of PEPPER safety system outcomes (i.e. glucose alerts, alarms and

carbohydrate recommendations) between run-in and endpoint are shown in Table 3.4. The total incidence of glucose alerts significantly reduced by approximately one-third at endpoint compared to run-in (31.5 (24.5-38.8) vs 20.0 (12.8-25.3); $p<0.05$). However, when categorised into type of alert (i.e. hypoglycaemia/ hyperglycaemia), no difference was observed. The incidence of glucose alarms did not change.

Carer alarms significantly decreased at endpoint from 14.5 (6.3-22.0) to 8.5 (3.3-10.8), $p=0.005$. This was specifically associated with a reduction in carer alarms triggered for hypoglycaemia ($p=0.004$).

	Run-in (n=6) Weeks 1 and 2	**Endpoint (n=6)** Weeks 7 and 8	**P-value**
Incidence of all glucose alerts	31.5 (24.5-38.8)	20.0 (12.8-25.3)	0.03 *
For hypoglycaemia	7.0 (3.8-12.0)	3.5 (2.00-14.0)	0.37
For hyperglycaemia	18.0 (10.0-26.0)	10.5 (6.75-14.0)	0.06
Incidence of all glucose alarms	15.0 (7.25-23.5)	12.0 (8.3-20.8)	0.19
For hypoglycaemia	5.5 (4.0-9.3)	5.5 (3.0-8.3)	0.42
For hyperglycaemia	4.0 (0.8-6.3)	3.5 (1.5-6.0)	0.33
Incidence of all carer alarms	14.5 (6.3-22.0)	8.5 (3.3-10.8)	0.01 *
For hypoglycaemia	5.5 (4.0-9.5)	2.5 (1.8-5.3)	0.004 *
For hyperglycaemia	4.0 (0.8-6.5)	2.0 (0.0-5.0)	0.07
Incidence of CHO recommendations	4.5 (1.0-88.3)	0.0 (0.0-25.3)	0.18
Percentage of missing rtCGM data (%)	49.6 (6.6-52.8)	19.1 (8.3-23.7)	0.17

Table 3.4: Safety system outcomes comparing run-in and endpoint

Incidence refers to all glucose alerts/ alarms over the analysed 14-day periods (run-in vs endpoint). CHO recommendations refer to personalized oral dose of carbohydrates to revert hypoglycaemia and minimize rebound hyperglycaemia. Data presented as median (IQR). * $p<0.05$ indicates significance. Abbreviations: CHO, carbohydrate.

Carbohydrate recommendations were considered irrespective of whether the advice provided by the PEPPER system was acted upon by the user. By the study endpoint, the number of carbohydrate recommendations reduced to zero.

3.3.3 CGM data loss

Data loss was observed for periods of time between the rtCGM device and handset. As part of ongoing development to the system, data loss was identified as a limitation and was addressed throughout the study period. During the initial run-in period, approximately 49.6% of missed signals were observed. This was reduced to 19.1% by endpoint (Figure 3.3).

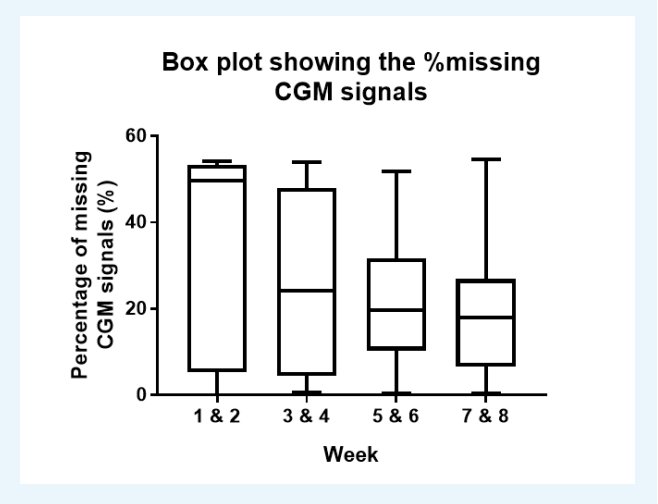

Figure 3.3: Percentage of missed rtCGM signal data, on fortnightly basis

Data presented as median (IQR).

3.4 Results for Participants Using CSII

Seven participants on CSII were recruited between December 2017 and January 2018 at IDIBGI (n=3) and ICL (n=4). Data from the IDIBGI cohort (n=3) were not included in this analysis because the predictive low glucose suspend safety feature was not enabled during the study intervention period.

The four participants recruited at ICL (2 men and 2 female) had a median (IQR) age of 45.5 (36.8-54.5) years, duration of diabetes 37.5 (30.3 – 43.5) years, BMI 25.5 (22.8-27.2) kg/m^2 and HbA1c 49.0 (48.5-51.3) mmol/mol (Table 3.5). All participants had intact awareness of hypoglycaemia with a Gold score of 2.0 (2.0-2.3).

Demographics	**Median (IQR)/ n (%) (n=4)**
Gender (female)	2 (50.0%)
Age (years)	45.5 (36.8-54.5)
BMI (kg/m^2) Height (cm) Weight (kg)	25.5 (22.8-27.2) 174.8 (155.8-193.6) 72.4 (64.8-82.7)
Duration of diabetes (years)	37.5 (30.3 – 43.5)
Hypoglycaemia awareness (i.e. Gold score <4)	4 (100%)
HbA1c (mmol/mol)	49.0 (48.5-51.3)
Previous episode of DKA	0 (0.0%)
Previous episode of severe hypoglycaemia	0 (0.0%)
Participants with: Diabetic retinopathy (background/ stable treated) Diabetic nephropathy Diabetic neuropathy Diabetic arteriopathy	 4 (100.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
Participants with: Hypertension Dyslipidaemia IHD CVA Hypothyroidism Hyperthyroidism Liver disease COPD GI disease Anxiety Depression	 0 (0.0%) 2 (50.0%) 2 (0.0%) 0 (0.0%) 1 (25.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
TSH (mU/L)	1.7 (1.4-1.9)
Total cholesterol (mmol/l)	4.0 (3.6-4.6)

Table 3.5: Baseline characteristics for Phase 1 participants on CSII

Results are expressed as median (IQR). Previous episodes of DKA/ severe hypoglycaemia refer to lifetime incidence, occurring any time prior to the 6 months before recruitment on the study (excluding diagnosis). Abbreviations: BMI, body mass index; CBG, capillary blood glucose; DKA, diabetic ketoacidosis; IHD, ischaemic heart disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; TSH; thyroid stimulating hormone.

3.4.1 Glycaemic outcomes

A comparison of glucose outcomes was derived from the run-in rtCGM data (baseline weeks 1 and 2) and compared with weeks 3 and 4 (with no predictive low glucose suspend) and weeks 7 and 8 (with predictive low glucose suspend).

Percentage time in hypoglycaemia <3.9 mmol/l significantly reduced from baseline at 3.8 (3.7–4.0)% to endpoint at 0.6 (0.6–1.9)% (p=0.04; Table 3.6; Figure 3.4). No significant differences were observed for reduction in clinically more significant hypoglycaemia i.e. % times in hypoglycaemia <3.3 mmol/l and <3.0 mmol/l. In addition, no significant differences were observed for %TIR and % time in hyperglycaemia.

There were no significant differences in basal insulin between run-in (weeks 1 and 2) and end-point (weeks 7 and 8); 17.4 (15.8-20.5) units vs 14.5 (10.3 – 20.9) units respectively (p=0.56).

	Run-in Weeks 1 and 2 (n=4)	**SS – PLGS** Weeks 3 and 4 (n=4)	**SS + PLGS** Weeks 7 and 8 (n=4)	**P-value**
% time in hypoglycaemia <3.9mmol/l (<70mg/dL) <3.3mmol/l (<60mg/dL) <3.0mmol/l (<54mg/dL)	 3.8 (3.7 – 4.0) 0.9 (0.8 – 1.2) 0.5 (0.4 – 0.9)	 1.4 (1.3 - 2.3) 0.5 (0.5 – 0.8) 0.4 (0.3 - 0.5)	 0.6 (0.6 – 1.9) 0.4 (0.2 – 0.7) 0.3 (0.2 - 0.5)	 0.04 * 0.08 0.15
% time in range 3.9 – 10.0mmol/l (70 -180mg/dL)	77.3 (75.6 – 85.4)	74.3 (65.2 – 84.3)	76.1 (66.1 - 84.7)	1.00
% time in hyperglycaemia >10mmol/l (>180mg/dL)	18.5 (11.0 – 20.0)	24.3 (14.4 – 32.5)	23.3 (14.7 - 32.0)	0.77

Table 3.6: Glycaemic outcomes in CSII users with safety system on.

Data presented as median (IQR) for baseline (weeks 1 and 2), with PEPPER safety system (no predictive low glucose suspend - weeks 3 and 4) and endpoint (with predictive low glucose suspend - weeks 7 and 8). * p<0.05 indicates significance.

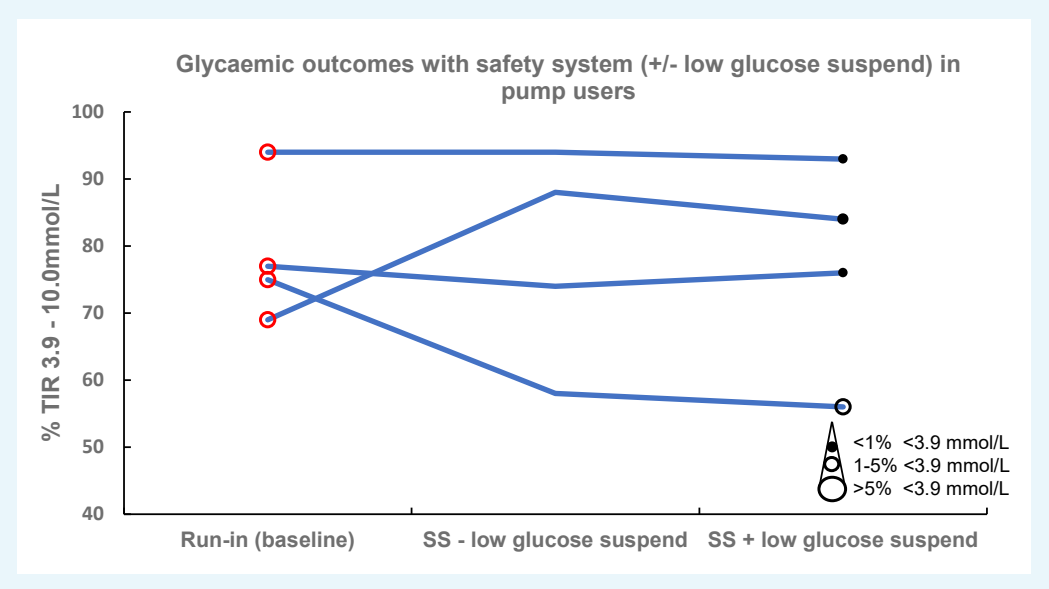

Figure 3.4: Times in range and hypoglycaemia amongst CSII users

Median glycaemia for each adult during baseline (weeks 1 and 2), with PEPPER safety system (no predictive low glucose suspend - weeks 3 and 4) and endpoint (with predictive low glucose suspend - weeks 7 and 8). The diameter of each circle is proportional to the percentage of time that the participant spent with a low glucose value (red circles for run-in; black circles for end-point).

No adverse incidents of DKA or severe hypoglycaemia requiring third-party assistance occurred during the study period. However, use of the PEPPER software was temporarily suspended within the first few days of the study commencing as a precaution for technical and safety reasons (no serious adverse events occurred; see Discussion Section 3.6). During this time, participants reverted to their standard therapy. Two participants withdrew just before the end of the study. Sufficient data were collected to calculate percentage times in glucose ranges and their data has been included in the analysis. Reasons for withdrawal include missing signals from rtCGM to pump, and inactivation of pump.

3.5 Quality of Life Outcomes

Quality of life outcomes in participants using the PEPPER safety system on MDI and CSII were combined for analysis. 4 out of the 15 participants recruited to Phase 1 withdrew during the study (IDIBGI (n=2) and ICL (n=2)). In addition, the 3 participants on CSII recruited at IDIBGI did not have the full safety system enabled, and have therefore not been included. Results from the remaining 8 participants (MDI (n=6) and CSII (n=2)) are presented here.

The baseline diabetes distress score for the PAID questionnaire was 21.9 (18.4-36.9). No statistical difference was observed in psychosocial measures for diabetes distress, quality or life and treatment satisfaction (Table 3.7).

Quality of Life questionnaire	Baseline score (n=8)	Endpoint score (n=8)	P-value
PAID	21.9 (18.4-36.9)	26.9 (12.8-41.9)	0.94
DQOL (total)	2.1 (1.8-2.4)	1.9 (1.7-2.5)	0.78
DTSQs global	28.0 (26.0-32.8)	33.0 (30.8-35.5)	0.11

Table 3.7: Psychosocial outcomes using the PEPPER safety system

Data combined for MDI and CSII users and presented as median (IQR). Abbreviations: PAID, problem areas in diabetes (scored out of 100 with higher scores indicating distress); DQOL, diabetes quality of life (based on Likert 5-point scale from 1 to 5 with high scores indicate dissatisfaction, frequent impact, or frequent worry). DTSQs, diabetes treatment satisfaction questionnaire (scored out of 36 indicating very satisfied).

3.6 Discussion

This feasibility study has demonstrated safety and feasibility of the PEPPER safety system for use in people with Type 1 diabetes. For MDI participants, the results suggest that intervention with the PEPPER safety system for 6 weeks has the benefit in improving glycaemia by reducing % time in clinically significant hypoglycaemia (<3.0 mmol/l) and increasing time in range (3.9-10mmol/l). Similarly, in the CSII participants, the results are promising to suggest an intervention with the PEPPER safety system has the potential to reduce % time in mild hypoglycaemia (<3.9 mmol/l).

The study was limited by a short follow-up period, small numbers, and was not designed to show superiority. However, study design and population are comparable with previous reports for a feasibility study. For the CSII participants, there was the additional limitation of fewer study participants, as data from IDIBGI (n=3) was not included in this analysis. This was due to the software version available at the time not having the predictive low glucose suspend feature enabled. As a result, similar comparisons between ICL and IDIBGI data could not be made. Furthermore, the full safety system was not functional over the complete intervention period at ICL, hence, the CSII participants have been analysed and presented separately to the MDI cohort.

Baseline data derived from weeks 1 and 2 (rtCGM without safety system), were compared to endpoint weeks 7 and 8 (with PEPPER safety system). For CSII participants, a reduction was observed in the primary endpoint (% time in

hypoglycaemia <3.9mmol/l). For MDI participants, no significance was observed in the primary endpoint, however the International Hypoglycaemia Study Group (IHSG) recommend using a cut-off of <3.0mmol/l to report 'clinically important' hypoglycaemia (294). This is of particular relevance to individuals with highest risk of hypoglycaemia, as those who are unaware at glucose levels <3.0mmol/l have a four-fold increased risk of severe hypoglycaemia (27). This study had originally defined the level of hypoglycaemia at <3.9mmol/l before this recommendation was published.

As a single arm study, without a control group, another limitation includes part of the effect observed may be resultant from prolonged rtCGM use. However, there are some key differences between the PEPPER safety system and standard alarms and alerts associated with rtCGM. These include predictive hypoglycaemia alerts, although it is important to note latest commercial rtCGM systems (Dexcom G6 and Medtronic Enlite Sensor with the Guardian 3 transmitter (295)) have introduced this feature. Other novel features include personalised carbohydrate recommendations, based on weight and blood glucose, to eliminate hypoglycaemia and avoid rebound hyperglycaemia. If potentially dangerous events are not properly addressed by the subject, automated alarms are sent via an SMS service to pre-selected family members/carers.

The reduction in number of alerts and carbohydrate recommendations observed in the MDI cohort as the study progressed is consistent with the improved glycaemia whilst using the PEPPER safety system. A limitation of this analysis includes that the incidence of alerts/alarms were based on the safety system algorithm running

in the background, and hence it is difficult to establish whether these had been acted upon by the participant or whether the handset had been switched off. Additionally, alert thresholds were altered by participants due to “alarm fatigue”. The high frequency of alerts/alarms carry significant burden and as a result of this, predictive high glucose alerts were switched off. A suggestion from several users was to include a vibration feature, which was subsequently incorporated into the system design.

Another consistent issue amongst most participants was signal loss between the rtCGM sensor and the PEPPER handset. The handset and rtCGM could only connect within a 5-metre range, and participants frequently reported this range was likely to be much lower than that. In order to address this problem, it was hoped that direct integration of rtCGM to the PEPPER handset may be available through contractual agreement with a rtCGM software provider (e.g. Dexcom G6). However, despite several negotiations, this was not possible. Data loss was addressed during the course of the study and remained a key focus for improvement within the system. One method of achieving this, was through ensuring the handset woke from “deep sleep” overnight.

Additional technical issues were particularly experienced by the CSII participants. At ICL, the trial was initially held for over 1 month, from 11th January 2018 and later restarted on 27th February 2018. It was later put on hold again due to a significant issue of frequent insulin cartridge ejection from the pump. Users experienced insulin cartridge ejection during the initial phase of inserting the cartridge into the pump, or spontaneously, up to several times a day. Early

manufacture at Flex (Flex Ltd, Althofen, Austria) had greater cartridge variation and issues, which was reflected in frequent ejection of "faulty" insulin cartridges and in the alarm frequency experienced. Following change in manufacturing, the latest generation of insulin cartridges were significantly more consistent.

No adverse events were reported due to the safety system. One participant on MDI was admitted to hospital following hyperglycaemia secondary to chest infection. Two CSII participants withdrew before the study ended, despite the change to more stable insulin cartridges. Reasons were due to missing signals from the rtCGM to pump, and inactivation of pump. Inactivation was of particular concern as this would prevent the user from administering a further bolus dose through the pump. During the study, clinical safety of the participants was of paramount importance and they were carefully monitored and supported during these occurrences. Where required, they were advised to return to their usual diabetes care.

All participants that completed Phase 1 with the PEPPER system expressed a wish to continue using the system in to Phase 2 of the study. The QOL questionnaires were used to identify whether using the PEPPER system had changed the participants' view of living with and managing their diabetes. The lack of improvement in diabetes distress scores, diabetes quality of life scores and diabetes treatment satisfaction were possibly due to several reasons. Firstly, this is likely to be due to the small cohort of participants and short intervention time period. Additionally, participants were more likely to be aware of their glycaemia and glucose fluctuations when using the system, compared to prior to using rtCGM. Participants experienced and reported alarm fatigue on a regular basis. For this

reason, alterations were made to new feature releases, which include a vibration feature (instead of sound) and to downgrade hyperglycaemia alarms to alerts.

Human factors play an important role in usability and acceptance of new technology (296). The major advantage of this study phase enabled the implementation of a more reliable and consistent system for users. Key issues outlined above were addressed through further software updates, which when required, were provided to the participants as soon as there were released.

Software Version	Issues/ Fixes addressed
V1.5.3 **V1.5.4** **V1.6.0**	• Issues over missed rtCGM readings fixed. (The software would convert missing values as zero, taking the calculated postprandial minimum glucose as zero. Bolus advise would return as 0) • Carbohydrate and glucose values on bolus items in the event log fixed for MDI version • Code implemented to check validity of user information before passing to the safety system • More Spanish translations introduced
V1.6.0 b	• User notification to appear when rtCGM data lost • When bolus advice requested during missed rtCGM signal, lack of recent rtCGM reading made clear to the user • Alarms not received when handset asleep (at night) fixed • Basal profiles (including temporary basal) display graphs optimised • Carbohydrates and glucose levels added to “Event Log” list • Minimum temporary basal applied when safety says fully suspend • The date/time format in CBR was wrong format • The postprandial minimum glucose value was set to -1 if the handset doesn’t have any rtCGM data for the entire postprandial phase
V1.7x (5 versions)	• The new safety system with predicted hyperglycaemia alerts disabled • Improved rtCGM connectivity for increasing glucose data inflow to the server • “Get Bolus advice” button enabled even if the database says a bolus is still running (previously could not obtain bolus advice whilst a bolus was running) • Postprandial phase minimum glucose reading fixed • Safety system alarms waking up the device (previous concerns the alarm would not be triggered overnight, but seen in the morning as notification)
V1.7.4	• New safety system to fix ICR and ISF issue • Splash screen freeze fix • Physical activity display and storage improved
V1.7.5	• Issues with timing of bolus recommendations recorded on server fixed. (System changed to use “system time”, rather than “user-time, in order to correct an inconsistency in the internal times used by the safety system)

V1.7.6	• Safety system alarms downgraded (in behaviour) to alerts except for hypoglycaemia alarm and pump suspension (both partially and fully) • Alerts muted with the 'Mute Alerts' setting. New vibrate setting for safety system alarms/alerts, which can be enabled/disabled in the Settings • Issues with safety system server sync fixed • Incorrect initial case base noted in system; removed • New improvements for rtCGM communication • Improvements to reduce chances of duplicate cases on the clinical platform • For CBR functioning, improved postprandial phase timer to ensure the case is closed at the correct time, even whilst device is asleep

Table 3.8: Changelog for the software during Phase 1 and prior to Phase 2

Abbreviations: CBR, case-based reasoning; ICR, insulin to carbohydrate ratio; ISF, insulin sensitivity factor; MDI, multiple daily injections; rtCGM, real-time continuous glucose monitoring

3.7 Conclusion

In conclusion, the PEPPER safety system is acceptable, safe and maintains improved glycaemia within an out-of-clinic environment. Despite the limitations of being a short study within a small pilot population, significant reduction in percentage time in hypoglycaemia was observed. These results are promising for the safe day-to-day use of PEPPER for managing diabetes in MDI and CSII users. The next chapter evaluates the safety system in combination with the adaptive bolus calculator.

4 Phase 2: Feasibility of an Adaptive Bolus Calculator and Safety System

4.1 Introduction and Aims

Standard automated insulin bolus calculators all lack the ability to automatically adapt over time to respond to an individual needs or changes in insulin sensitivity. It is hypothesised that a personalised and adaptive insulin advisory system will provide better glycaemic control than state-of-the-art standard bolus calculators.

In Phase 1, we determined the PEPPER safety system was safe and feasible, with the potential in improving glycaemia in a small pilot population of MDI and CSII users. Several developments and improvements were made to optimise the safety system and the overall PEPPER application. To summarise, these include the

predictive hyperglycaemia alerts being disabled to prevent alarm fatigue, as well as hyperglycaemia notifications to carers being disabled to reduce alarm burden for carers. A new generation of Cellnovo handset (CE marked in 2017) was introduced and more stable insulin cartridges were provided following a change in manufacturing. Due to concerns over significant missed rtCGM data, a change in coding algorithms enabled improved connectivity between the PEPPER handset and rtCGM.

In Phase 2 of the clinical assessment, the aim was to demonstrate safety and feasibility of the complete PEPPER system. This included the AI-derived adaptive bolus calculator with the optimised safety system in the participants' own environment.

The hypothesis of this stage was that the complete PEPPER system is safe and feasible for use in people with TID using MDI and CSII users.

4.2 Methodology

4.2.1 Study design and recruitment

Phase 2 was a non-randomised, open-label study evaluating the complete PEPPER system (safety system and adaptive bolus calculator) over 8 weeks. Similar to Phase 1, recruitment was undertaken at Imperial College London (UK) and IDIBGI (Spain). Potential participants were identified through diabetes clinics at each

respective site, or from interested participants who contacted the research team through the NIHR Research Gateway.

Ethics and device approvals were obtained from the relevant regulatory bodies at each of the sites. All participants provided verbal and written informed consent.

4.2.2 Participants

A full list of the inclusion and exclusion criteria can be found in Section 3.2.1. To summarise, participants aged >18 years with T1D for >1 year, on MDI or CSII (insulin pump) treatment for >6 months, and had HbA1c between 48mmol/mol and 86mmol/mol were included. In addition, individuals had to have completed structured education (either in a group or 1:1 sessions) and were competent at carbohydrate counting, using ICR and ISF to calculate mealtime insulin boluses.

Participants were excluded if, within the last six months, they had an episode of DKA or severe hypoglycaemia requiring third-party assistance. Participants were also excluded if pregnant, breastfeeding or intending to become pregnant during the trial, enrolled on other trials, under investigation for or have an active malignancy, have a suspected or diagnosed endocrinopathy, abnormal renal function or liver cirrhosis, or had a macrovascular complication in the past year.

4.2.3 Procedures and visit schedule

A detailed description of the study visits is outlined below and summarised in Figure 4.1.

Visit 1: Consent and training

At study enrolment, participants gave a full medical and medication history, and underwent a physical examination and electrocardiogram. Venous bloods assessing HbA1c, creatinine, lipids, liver function, full blood count and thyroid function were taken. A urine sample was taken to measure albumin/creatinine ratio and women of child-bearing age had a urinary pregnancy test.

Eligible participants were provided with the PEPPER study handset, rtCGM (Dexcom G5 transmitter and sensor), a standard bolus calculator (embedded within the study handset) and an activity monitor. For rtCGM, instructions were provided for sensor change for the Dexcom G5 every 7 days as per manufacturer's guidance (or sooner in event of sensor failure), and participants were instructed to test capillary blood glucose every 12 hours for calibration or if symptoms of hypo- or hyperglycaemia, in event of sensor failure or if the sensor glucose is out of the desired range (3.9 mmol/l - 13.3 mmol/l). RtCGM alarm thresholds were set at 3.9 mmol/l and 16.6 mmol/l.

Participants on insulin pump therapy were switched to the Cellnovo pump and trained on its use. Differences from their own home pump were discussed including important aspects such as calculation of IOB and correction boluses. Additional topics for discussion included: site initiation, cartridge/priming procedures, setting up the pump, changing batteries, navigation through menus and bolus procedures, including stopping a bolus. User manuals were provided for the PEPPER handset, Cellnovo insulin pump and continuous glucose monitor.

Participants were asked to complete validated study questionnaires including DTSQ, DQOL and PAID questionnaires.

In Phase 2, during the run-in period, the PEPPER safety system was activated, with the adaptive bolus calculator disabled. Insulin bolus recommendations were based on a standard bolus calculator embedded within the handset. Each session lasted approximately 4-6 hours, unless participants were already familiar with the system through their participation in Phase 1.

Participant accounts on the online PEPPER portal were created in advance of the study visit by myself. Each anonymised participant account was paired with a handset and pump serial code, with details sent to Cellnovo for linkage on their server in advance of each visit.

Visit 2: Adaptive bolus advisor (CBR) switched on

Following the 2-week run-in period, the PEPPER adaptive bolus calculator using CBR was switched on. RtCGM data was reviewed with the participant and changes were made to the basal insulin/ ISF/ ICR if required at each of the visits.

Target blood glucose on the PEPPER bolus calculator was standardized to 5.5 mmol/l, however this target could be individualised if required.

Visit 2 lasted for approximately 1 hour and took place at the clinical research facility.

Visit 3: Review

Visit 3 also required a visit to the clinical research facility, with each visit lasting approximately an hour. Participants discussed technical issues encountered between visits. Technical issues identified in the assessment were dealt with during system redevelopment.

A clinical and technical log of issues faced by participants was maintained and communicated with the engineering team. Regular teleconference meetings were held once weekly with the engineers to ensure any issues were addressed.

Software updates to the PEPPER application on the handset were required to be done manually, and in certain instances where there were technical issues, these required further time to address.

Visit 4: End of study

At visit 4, the PEPPER system was switched off and returned. Participants took part in a semi-structured interview and completed the PAID, DQOL and DTSQs questionnaires.

Verbal feedback from participants was obtained regarding any technical issues encountered. The final visit took approximately 1 hour.

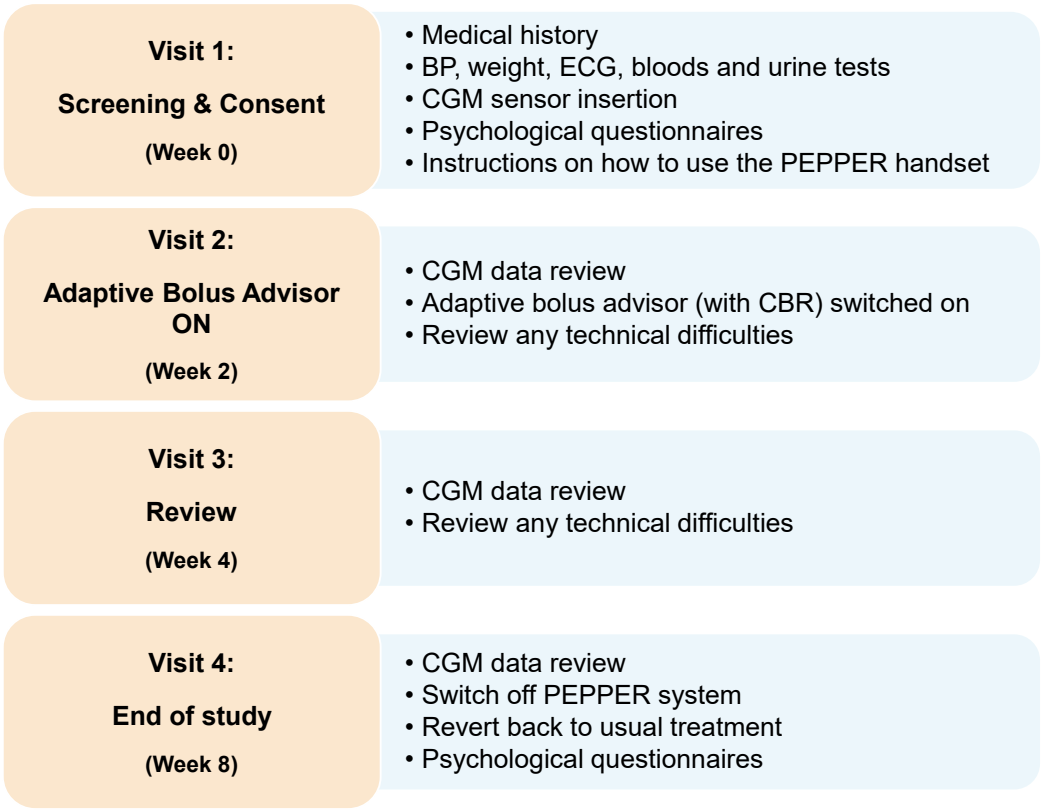

Figure 4.1: Summary of Phase 2 study visit attendances

4.2.4 Study outcomes

The study outcomes were similar to that of Phase 1 with the primary outcome being % time in hypoglycaemia <3.9mmol/l from baseline to endpoint. Secondary outcomes regarding glycaemic control include % TIR 3.9-10mmol/l, % time in hyperglycaemia >10mmol/l and % time in lower thresholds of hypoglycaemia (<3.3mmol/l and <3.0mmol/l). Secondary outcomes regarding the safety system were incidence of low and high glucose alarms, carbohydrate recommender and predictive low glucose suspend (CSII users only). The scores from the quality of life questionnaires (PAID, DQOL, DTSQ) at baseline and endpoint were compared.

4.2.5 Statistical analysis

All glycaemic outcomes from baseline (weeks 1 and 2) were compared with endpoint (weeks 7 and 8). Non-normally distributed data were analysed with the Wilcoxon matched-pairs signed-rank test. All outcomes are reported as median (interquartile range [IQR]), unless stated otherwise. P-values <0.05 were considered statistically significant.

The glycaemic and safety system data for each participant were stored on the PEPPER Server Application. Data were exported to calculate the primary and secondary outcomes for each week of the study. A formal power calculation was not performed for the Phase 2 pilot study assessing safety and feasibility.

4.2.6 Analysis deviation from protocol

Similar to Phase 1, the study protocol was designed to analyse combined data from MDI and CSII participants recruited from UK and Spain for Phase 2 (total n=15; a sample size comparable to other technology pilot studies).

During the early weeks of the clinical study with the MDI participants, I encountered several technical issues with the CBR; importantly, case revisions could not be made, so participants did not receive the intended adaptive bolus advisory function. This impacted the four participant cohorts (MDI vs CSII and ICL vs IDIBGI) differently. IDIBGI went ahead without the necessary fix and completed the clinical trial to meet project deadlines. Thus, for data analysis,

outcomes from participants at IDIBGI have not been included as the novel bolus calculator driven by the CBR was not active during the study period.

Within the ICL cohorts, there was also variation in the duration of the CBR algorithm being active, hence I have reported outcomes from CSII and MDI users separately. Though I identified the aforementioned CBR issues during the early MDI weeks, our protocol did not allow for an extension to be able to repeat those weeks. I was able to successfully pause the study, allowing time for the fixes to be developed and tested. When we restarted, MDI users, had two weeks of fully functioning CBR, and CSII participants had the CBR functioning for the full 6-week intervention period.

4.3 Results for MDI Participants

Four participants were recruited at ICL in March 2018. All participants were male and had a median (IQR) age of 43.5 (37.3-48.3) years, duration of diabetes 28 (26.3-28.0) years, BMI 26.8 (24.9-27.4) kg/m^2 and HbA1c 64.0 (63.0-64.5) mmol/mol (Table 4.1). All participants had intact awareness of hypoglycaemia at baseline.

At ICL, the study was held from week 5 due to technical issues with the CBR. The study was later restarted in September 2018, with only weeks 7 and 8 remaining. Data from participants at IDIBGI (n=4) were not included in this analysis, as the CBR was not active during the intervention period.

Demographics	**Median (interquartile range)/ n(%) (n=4)**
Gender (male)	4 (100%)
Age (years)	43.5 (37.3-48.3)
BMI (kg/m^2) Height (cm) Weight (kg)	26.8 (24.9-27.4) 182.0 (176.5-184.8) 83.3 (69.7-95.1)
Duration of diabetes (years)	15.5 (9.3 – 22.0)
Gold score	2.0 (1.8-2.0)
HbA1c (mmol/mol)	64.0 (63.0-64.5)
Previous episode of DKA	2 (50.0%)
Previous episode of severe hypoglycaemia	0 (0.0%)
Participants with: Diabetic retinopathy (background/ stable treated) Diabetic nephropathy Diabetic neuropathy Diabetic arteriopathy	 3 (75.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
Participants with: Hypertension Dyslipidaemia IHD CVA Hypothyroidism Hyperthyroidism Liver disease COPD GI disease Anxiety Depression	 2 (50.0%) 3 (75.0%) 0 (0.0%) 0(0.0%) 1 (25.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
TSH (mU/L)	1.7 (1.3-1.7)
Total cholesterol (mmol/l)	4.1 (3.4-4.4)

Table 4.1: Baseline characteristics for Phase 2 participants on MDI

Results are expressed as median (IQR). Previous episodes of DKA/ severe hypoglycaemia refer to lifetime incidence, occurring any time prior to the 6 months before recruitment on the study. Abbreviations: BMI, body mass index; CBG, capillary blood glucose; DKA, diabetic ketoacidosis; IHD, ischaemic heart disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; TSH; thyroid stimulating hormone

Four participants completed the 8-week Phase 2 study. However, data from one participant was not included in the final analysis as no adaptations were made due to low carbohydrate intake at mealtimes (<20g CHO).

4.3.1 Glycaemic outcomes

A comparison of glucose outcomes were derived from the run-in rtCGM data with safety system (baseline weeks 1 and 2) and compared with endpoint, including the CBR (weeks 7 and 8). No statistically significant difference was observed for the primary endpoint % time in hypoglycaemia <3.9 mmol/l, nor <3.3 mmol/l and <3.0 mmol/l (Table 4.2; Figure 4.2).

No significant differences for %TIR 3.9-10.0 mmol/l were observed between the complete PEPPER system compared to the standalone safety system (p=0.83).

No adverse incidents of DKA or severe hypoglycaemia requiring third-party assistance occurred during the eight weeks. However, use of the PEPPER software was temporarily suspended for several months at Visit 3, due to non-functioning of the CBR system (no serious adverse events occurred; see Discussion Section).

	Run-in (n=3) **Safety System On** Weeks 1 and 2	**Endpoint (n=3)** **Safety System and CBR On** Weeks 7 and 8
% time in hypoglycaemia		
<3.9mmol/l (<70mg/dL)	1.5 (1.2 – 3.0)	2.0 (1.6 – 4.6)
<3.3mmol/l (<60mg/dL)	0.9 (0.5 – 1.2)	0.7 (0.7 – 3.3)
<3.0mmol/l (<54mg/dL)	0.6 (0.3 – 0.9)	0.4 (0.2 – 2.7)
% time in range		
3.9 – 10.0mmol/l (70 -180mg/dL)	59.1 (50.9 - 66.4)	55.4 (52.8 – 57.8)
% time in hyperglycaemia		
>10mmol/l (>180mg/dL)	39.4 (32.4 - 46.1)	42.6 (37.6 – 45.6)

Table 4.2: Glycaemic outcomes in MDI users with safety system and CBR.

Median (IQR) percentage time for baseline (weeks 1 and 2; safety system on) and endpoint (weeks 7 and 8; safety system and CBR on). CBR functioning for 2 weeks only. Abbreviations: CBR, case-based reasoning

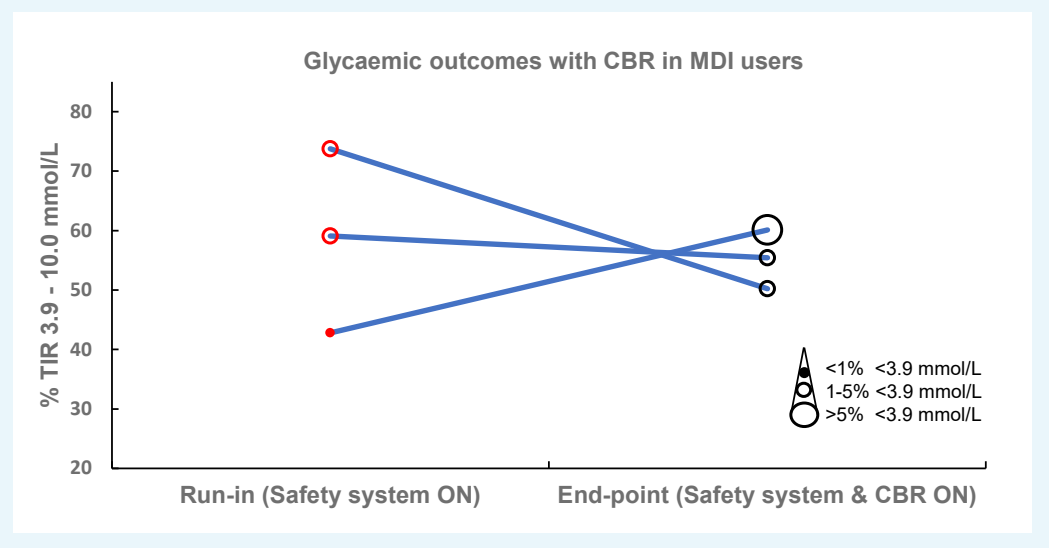

Figure 4.2: Times in range and hypoglycaemia with CBR amongst MDI users

Median glycaemia for each adult during run-in (safety system on) and endpoint (safety system and CBR on). The diameter of each circle is proportional to the percentage of time that the patient spent with a low glucose value (red circles for run-in; black circles for end-point). Abbreviations: CBR, case-based reasoning

4.3.2 Insulin recommender (CBR) outcomes

In view of the technical issues with the CBR, an assessment of the cases accepted by the user and by clinicians was made. One participant (P_001) had no cases accepted due to low carbohydrate intake (<20g CHO per meal). The median number of cases accepted by the user when bolus advice was presented on the handset was 90.0% (67.1% - 94.5%). The median number of cases accepted by the clinician to be reused as part of the learning algorithm was 14.1% (11.9% - 37.5%). Table 4.3 shows data from each participant whilst the CBR was active.

Participant	CBR Start Date	CBR End Date	Cases accepted by the user	Cases accepted by the clinician
P_001	24/07/2018	14/08/2018	94.3%	0.0%
P_002	17/09/2018	03/10/2018	44.2%	9.6%
P_003	12/09/2018	10/10/2018	99.0%	14.1%
P_004	05/09/2018	18/09/2018	90.0%	60.0%

Table 4.3: CBR case acceptance by users and clinicians

Cases of bolus advice accepted by the user and the cases accepted by the clinician for case re-use, for each participant. Abbreviations: CBR, case-based reasoning

4.4 Results for CSII Users

Four participants (75% male, median (IQR) age of 36.5 (34.5-43.0) years, duration of diabetes 22.0 (18.5 – 33.0) years, BMI 26.2 (24.3-27.7) kg/m^2 and HbA1c 54.5 (52.0-57.3) mmol/mol) on CSII were recruited at ICL in September 2018 (Table 4.4). Two participants withdrew due to technical issues related to the system.

Data from participants at IDIBGI (n=3) were not included in this analysis, as the CBR was not active during the intervention period.

Demographics	**Median (interquartile range) / n (%) (n=4)**
Gender (female)	1 (25.0%)
Age (years)	36.5 (34.5-43.0)
BMI (kg/m^2) Height (cm) Weight (kg)	26.2 (24.3-27.7) 172.0 (165.6-175.6) 72.3 (67.1-79.2)
Duration of diabetes (years)	22.0 (18.5 – 33)
Gold score	2.0 (2.0-2.0)
HbA1c (mmol/mol)	54.5 (52.0-57.3)
Previous episode of DKA	0 (0.0%)
Previous episode of severe hypoglycaemia	0 (0.0%)
Participants with: Diabetic retinopathy (background/ stable treated) Diabetic nephropathy Diabetic neuropathy Diabetic arteriopathy	 4 (100%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
Participants with: Hypertension Dyslipidaemia IHD CVA Hypothyroidism Hyperthyroidism Liver disease COPD GI disease Anxiety Depression	 2 (50.0%) 2 (50.0%) 0 (0.0%) 0 (0.0%) 1 (25.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
TSH (mU/L)	1.2 (0.6-1.8)
Total cholesterol (mmol/l)	4.7 (4.0-5.5)

Table 4.4: Baseline characteristics for Phase 2 participants on CSII

Previous episodes of DKA/ severe hypoglycaemia refer to lifetime incidence, occurring any time prior to the 6 months before recruitment on the study. Results are expressed as median (IQR). BMI, body mass index; CBG, capillary blood glucose; DKA, diabetic ketoacidosis, IHD, ischaemic heart disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; TSH; thyroid stimulating hormone

4.4.1 Glycaemic outcomes

Between the baseline run-in period (safety system on, without CBR) and endpoint (safety system with CBR on), no significant change in glycaemic outcomes were observed (Table 4.5; Figure 4.3).

	Run-in (n=2) **Safety System On** Weeks 1 and 2	**Endpoint (n=2)** **Safety System and CBR On** Weeks 7 and 8
% time in hypoglycaemia <3.9mmol/l (<70mg/dL) <3.3mmol/l (<60mg/dL) <3.0mmol/l (<54mg/dL)	 3.0 (2.7 – 3.3) 1.2 (1.1 – 1.3) 0.9 (0.9 – 0.9)	 5.2 (3.2 – 7.2) 1.5 (0.9 – 2.2) 0.7 (0.4 – 1.1)
% time in target 3.9 – 10.0mmol/l (70 -180mg/dL)	62.3 (60.1 – 64.5)	56.3 (55.3 – 57.2)
% time in hyperglycaemia >10mmol/l (>180mg/dL)	34.7 (32.2 - 37.2)	38.5 (35.6 – 41.5)

Table 4.5: Glycaemic outcomes in CSII users with safety system and CBR.

Data presented as median (IQR) for baseline (weeks 1 and 2; safety system on) and endpoint (weeks 7 and 8; safety system and CBR on).

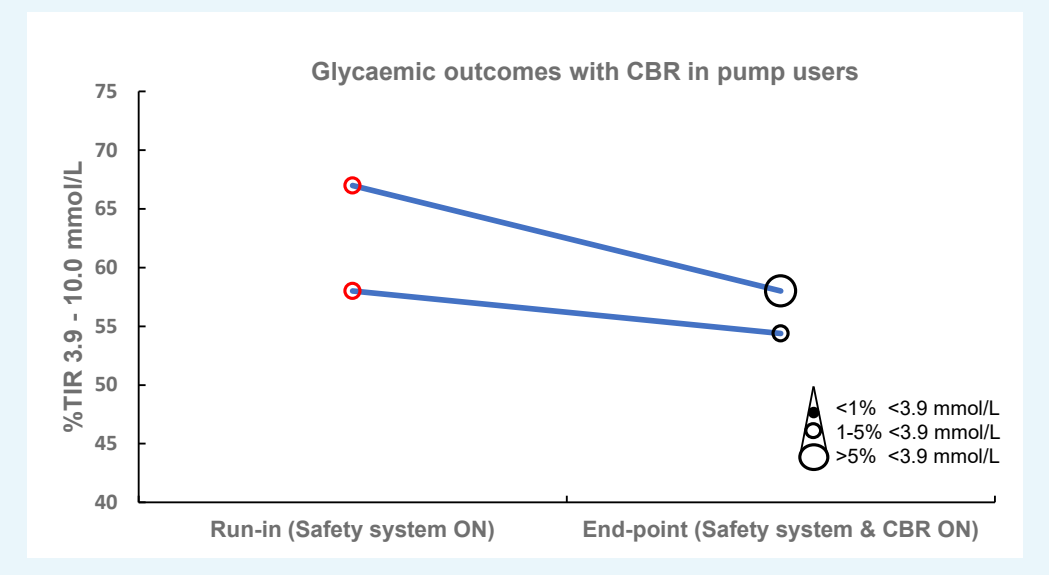

Figure 4.3: Times in range and hypoglycaemia with CBR amongst CSII users

Median (IQR) glycaemia for each adult during run-in (safety system on) and endpoint (safety system and CBR on). The diameter of each circle is proportional to the percentage of time that the patient spent with a low glucose value (red circles for run-in; black circles for end-point).

4.5 Quality of Life Outcomes

Quality of life outcomes for both MDI and CSII participants using the complete PEPPER system were analysed using the PAID, DQOL and DTSQ questionnaires (Table 4.6). No difference in psychosocial outcome measures were observed.

Quality of Life questionnaire	Baseline score (n=6)	Endpoint score (n=6)	P-value
PAID	32.5 (23.1-38.75)	26.3 (17.2-32.8)	0.47
DQOL – total	2.5 (2.3-2.5)	2.2 (2.0-2.3)	0.07
DTSQ	30.5 (28.0-31.5)	31.0 (29.8-32.8)	0.27

Table 4.6: Psychosocial outcomes using the complete PEPPER system

Data combined for MDI and CSII users and presented as median (IQR). Abbreviations: PAID, problem areas in diabetes (scored out of 100 with higher scores indicating distress); DQOL, diabetes quality of life (based on Likert 5-point scale from 1 to 5 with high scores indicate dissatisfaction, frequent impact, or frequent worry). DTSQ, diabetes treatment satisfaction questionnaire (scored out of 36 indicating very satisfied).

4.6 Discussion

This feasibility study optimised the adaptive bolus calculator (i.e. CBR algorithm) in participants with T1D using both MDI and CSII. Whilst no statistically significant differences in clinical outcomes were observed due to small participant numbers, no serious adverse events occurred during the study period, and was therefore deemed safe and feasible.

During this phase, there were multiple issues associated with the integration of the CBR within the online clinician platform to enable case revision. Several bugs and

errors were fixed within the CBR code. As a result of this, ICL participants on the study were held till these issues were addressed. The completion date for ICL was 18th December 2018, whilst participants in Spain were completed by 7th May 2018. As a result, none of the data collected from IDIBGI during this phase had a functioning adaptive insulin recommender, and therefore data from IDIBGI have not been included in the analysis (n=8).

The overall results were limited by small numbers and a short duration for running the CBR algorithm. For the MDI participants, this was only 2 weeks due to technical issues, meanwhile for CSII participants this was 6 weeks but in only 2 participants. This is likely to explain the lack of significance observed for glycaemic outcomes, as well as quality of life. Initial in-silico data showed that the time in glycaemic range increases over days with the CBR, and finally converges around a value after two weeks (285). However, in real world clinical studies, the duration of CBR required to facilitate glycaemic improvements is likely to be different due to the variability experienced by people, which cannot be mimicked by in-silico data. Furthermore, not all cases were clinically accepted for CBR revision, and due to the use of multiple parameters, this may result in a longer time required to populate the case base to achieve maximum time in range.

In the case of the one MDI participant where no cases were accepted, this was due to low carbohydrate intake at mealtimes. Consequently, the error margin in the revised adaptation is too large. Future recruitment aimed to exclude participants if carbohydrate intake was significantly low (<20g) at each meal.

Most users followed the bolus advice provided by the PEPPER system, however it was noted that 1 participant only accepted 44% of the bolus recommendations (P_002). Participants had been advised to reject the bolus advise if they felt the recommendation was too aggressive or little. Future goals were to support participants to trust the advice as much as possible.

During this phase, there were a number of design choices relating to the adaptive bolus calculator and its interplay within the PEPPER system. The further challenge with assessing the adaptive bolus calculator component within PEPPER, is that part of the effect in glycaemic outcomes may be resultant from the safety system component. In addition to the predictive alarms for hypoglycaemia and personalised carbohydrate recommendations, the dynamic bolus insulin constraint (DBIC) module, eliminates potentially dangerous insulin boluses that could be recommended to the user. Based on initial review of the constraints made on the insulin recommender, the engineering team believed it would be appropriate to relax these constraints to enable the CBR to adapt more effectively. The limits of ICR and ISF constraints were changed from ±25% to ±30%. This change was integrated into the next phase of the clinical trial.

Additional learning from Phase 2 was to change the learning rate within the algorithm (from α=0.1 to α=0.3) to enhance greater adaptation to insulin dose recommendations. This has been incorporated into the final study prototype for Phase 3. The convergence time to optimise the time in range achieved within a period of time (i.e. number of days) can be adjusted with the learning rate of the

revise step. However, there is a trade-off between the convergence time and the variability around the optimal after convergence (285).

Another issue that required addressing was that exercise did not appear to be correctly accounted for in the system, therefore activity levels corresponding to an individual's step count (low, mild and intense) were modified prior to Phase 3 of the study. Another software functional issue uncovered was that of changing time-zones between the mobile app and the servers. This was most notable when entering British Summer Time (BST) and/or Greenwich Mean Time (GMT) zones. This impacted the bolus advice, as an hour delay shifted the postprandial window. This issue was also addressed for the final study prototype.

Table 4.7 summarises key changes in development of the PEPPER software application during Phase 2 and in preparation for the next clinical phase.

Software version	**Issues**
V1.8.0	• CBR overhaul to fix values of 0.0 for "icrreuse" • 3 new CBR jars released • Various logic changes in the handset • Creation, update, storage and syncing of the PepperCase object • Correct CaseBase now obtained from the server • Reinitialised the postprandial phase object and the CaseBase correctly if the app is restarted • Changed "Nonaerobic" to "Anaerobic" for on-screen use • Low glucose suspend duration increased to 90 minutes • Fixed crash on the Safety System Settings screen when pressing "Save" button • Low glucose suspension fixed to handle an error communicating with the pump
V1.8.1	• Fixed issues with "NaN" returning from the CBR. (Occurred when a participant introduced cases with values of hormone cycle/fever/ digestive illness for the first time when there were no cases with these parameters in the case base yet) • New Safety System module with hyper alerts disabled
V1.8.2	• Device failure to wake up for alerts/alarms (both Nexus and Cellnovo handset) • RtCGM calibration does not overwrite previous readings anymore, so the minimum postprandial phase glucose reading should be correct

V2.0.0 **Prototype 2**	• Graphics and icons updated (Home screen page, settings, event logs, screen for pump). Screen colours optimised for PEPPER handset. Charts added with scroll view to Home Page. Consistency applied to basal, bolus, carbohydrates and activity charts to ensure same height • Clearer graphics for user basal profiles (most notably, the appearance when a temporary basal is running) • Extra notifications and pop-ups for users to provide clarity on pump functioning: (i.e. "Pump found" when connecting, "Bolus stopped" on completion of bolus screen) • Duplicate Mute Alerts and Flight Mode checkboxes removed; update on enabling/disabling flight mode • Statistics screen updated with improvements in graph (times were wrong and trace line made thinner). Minimum and maximum values coded • Estimated HbA1c and number of hypo/ hyperglycaemic episodes removed (not working accurately) • Blood glucose circle shows "Low" or "High" when the last reading is < 2.2mmol/l (40 mg/dL) or > 22.2mmol/l (400 mg/dL); i.e. outside the bounds of detected rtCGM glucose • Display of forecasted glucose values added as a green line on the home page screen • Pump button displays an icon with the temp basal percentage if the pump is partially/fully suspended or if the user has started a temp basal • Getting a glucose reading from the Bluetooth meter automatically calibrates the rtCGM readings • Ability to get a reading from the Bluetooth glucose meter on the Get Advice screen (click the + button next to the glucose reading and click the "Get From BGM" button on the popup). • New "Low Glucose Suspend" event log item
V2.0.1	• Fixed vibrate setting for alarms/alerts • Glucose reading timestamp on the recommendation screen corrected for all inputs • Menu button fixed on "Insulin" screen for CSII version • Home screen pump button now displays information for all temporary basal, not just low glucose suspension • Safety system rtCGM reading timestamps fixed (multiple readings with same timestamp occurring previously) • Separate "Add Bolus" page for recording additional insulin doses, - warning message playing saying that it does not go to the pump. (This is done on the "Get Bolus Advice" page) • Basal injections appear in the "Event Log" in the MDI version • Notes timestamps were displayed with system time, now it's user-time • "Reused cases" added to the PepperCase object so that the PEPPER clinical platform can display the correct information for each case • Updated the clinical platform with aborted bolus information • Updated the clinical platform with temporary basal information
V2.0.2	• New Safety System • Notes timestamp corrected • All notification pop-ups translated for Spanish • "Carbohydrate Event Log" item now displays the carbohydrate value in Spanish; previously missing • Safety System rtCGM readings given the correct timestamp; avoids multiple readings with the same timestamp
V2.0.3 **V2.0.4**	• PepperCase sent to the server after device, or app, is restarted and the postprandial phase end time elapsed whilst the device/app was not running. • Minor changes made to the activity monitor screen; but no noticeable differences to the user • Home screen basal insulin chart total would sometimes show 0 units even with a valid profile running on pump – fixed

V2.0.5	• Fixed multiple Safety System syncs for Spanish MDI participants • New Safety System, 12th December 2018 • Fixed CBR failure to provide a recommendation when it does not have a case base because the handset was not able to download it from the server due to no data connection. (i.e. 0 unit recommendations)
V2.0.6	• Fixed missing (ghost) bolus issue (i.e. boluses which were not being recorded on the handset/event log despite the participant getting the insulin). Occurred when participants requested bolus advise and turned off screen; rather than pressing "ok" to confirm. – Issue fixed. • Implemented a warning dialogue displayed if the patient rejects a recommendation and enters a bolus value greater than, or equal to, the Max Bolus Setting
V2.0.7 ***(Final version)***	• The following are the finalised version: For standard rtCGM – xDrip+ alerts to produce alerts/alarms based upon its own thresholds. - Hyperglycaemia = alert. The volume profile can be set in xDrip+ to High/Med/Low/Vibrate or Silent. - Hypoglycaemia = alarm. The alert is audible and cannot be adjusted (xDrip+ default behaviour and logically safest). • During run-in/Control, the PEPPER safety system is off – xDrip+ has hyper- and hypoglycaemia limits set within xDrip+, and the volume level set as required by the clinician/ user. Participants thereafter have minimal interaction with xDrip+ beyond this set up (other than calibrations and volume changes). Alerts can be snoozed and or silenced from the xDrip+ settings • During PEPPER use with the safety system on – xDrip+ should have the volume profile set to silent. Hence no alarms/alerts formally triggered from xDrip+ during the PEPPER phase, and all alarms/alerts come from within the PEPPER safety system.

Table 4.7: Changelog for the software during Phase 2 and prior to Phase 3

Abbreviations: BGM, blood glucose monitoring; CBR, case-based reasoning; CSII, continuous subcutaneous insulin infusion; ICR, insulin to carbohydrate ratio; ISF, insulin sensitivity factor; NaN, "not a number"; MDI, multiple daily injections; rtCGM, real-time continuous glucose monitoring

4.7 Conclusion

This feasibility study demonstrated proof of concept, safety and feasibility of the combine PEPPER safety system and adaptive bolus calculator in MDI and CSII participants with T1D. The advantage of the PEPPER insulin recommender is its ability to adapt its advisory function over time, making it dynamic and personalised. Despite the technological challenges, the system has been further optimised through iterative development. Further work in the form of evaluation is

required and a powered, randomised controlled trial over 8 months assessed whether the PEPPER system is superior to a nonadaptive bolus calculator.

5 Phase 3: Clinical Evaluation of the PEPPER System

5.1 Introduction and Aims

Safety and feasibility of the PEPPER system has been demonstrated for people with T1D using MDI and CSII (Chapters 3 and 4). In addition, the safety system demonstrated potential to reduce percentage time in hypoglycaemia for CSII and MDI users.

During the earlier feasibility studies, the system has been optimised and developed for use. Some of the integral changes include an increase in the learning rate of the algorithm (from α=0.1 to α=0.3) to enhance greater adaptation to insulin dose recommendations. Furthermore, the dynamic bolus insulin constraints were relaxed to enable the CBR component to greater adapt its insulin dose recommendations.

The aim of the work presented in this chapter was to assesses the efficacy and safety of the complete PEPPER system compared to standard therapy (standard bolus advisor and standard rtCGM).

The hypothesis of this phase was that the complete PEPPER system is effective and safe for use in people with TID using MDI and CSII therapy.

Results shared in this thesis chapter are currently under review with the journal *Diabetes Technology and Therapeutics*. I wrote the data analysis plan and analysed the data for both clinical sites, as well as wrote the first draft of the submitted manuscript (on which I am joint first author).

5.2 Methodology

5.2.1 Study design and recruitment

Phase 3 of the PEPPER project was an 8 month prospective, randomised, multi-centre, cross-over study designed to assess the safety and efficacy of the PEPPER system. This included the AI-derived adaptive bolus advisor (based on CBR) alongside the safety system. The trial was conducted at two clinical sites; Imperial College London (UK) and IDIBGI (Spain). The study protocol was approved by the NHS Research Ethics Committee, UK and the Spanish Agency for Medicines and Healthcare Products in Spain. All individuals who participated in the study provided written informed consent at time of recruitment.

Potential participants were identified and recruited from the investigator's established population in diabetes clinics at each respective site, or from interested participants who contacted the research team through the NIHR Research Gateway.

5.2.2 Participants

The study recruited adult participants with T1D using an intensified MDI regimen or CSII therapy. Key inclusion criteria included: aged ≥18 years of age; T1D using MDI or CSII therapy for >6 months; HbA1c between 48 - 86 mmol/mol; good hypoglycaemia awareness. In addition, all participants were required to be able to adjust meal insulin doses based on CHO content of the meal, and had to have completed a structured diabetes education programme (either in a group or 1:1 sessions).

Key exclusion criteria included having an episode of DKA or severe hypoglycaemia requiring third-party assistance within the last 6 months, use of regular paracetamol, were pregnant or intending pregnancy, breastfeeding, had active malignancy or endocrinopathy, liver cirrhosis or abnormal renal function, or had a macrovascular complication within the past year.

5.2.3 Procedures and visit schedule

A detailed description of the study visits is outlined below and summarised in Figure 5.1. All UK-based study visits took place face-to-face at the Imperial Clinical Research Facility. Participant accounts on the online clinical PEPPER

portal were created in advance of the study visit by myself. Each anonymised participant account was paired with a handset and pump serial code, with details sent to Cellnovo for linkage on their server in advance of study visits.

Visit 1: Consent, training and study enrolment

The first study visit entailed an enrolment session, where individuals confirmed their eligibility based on the above inclusion/ exclusion criteria. Written informed consent was recorded and demographic information collated alongside relevant medical and drug history. Participants were required to provide a urine sample for analysis and their height and weight measurements, alongside an ECG. The following laboratory tests were performed: full blood count, HbA1c and biochemistry panel with lipids. Pregnancy testing for women of child-bearing age was performed on the urine sample provided. Validated study questionnaires (DTSQs, PAID and DQOL) were also completed.

All participants were provided with the PEPPER study handset and completed an initial 4-week run-in period using rtCGM (Dexcom G5), an activity monitor (MiBand) and a standard bolus calculator to familiarise themselves with the equipment. The standard bolus calculator was integrated into the PEPPER handset. As per manufacturing instructions, the Dexcom G5 sensor change was performed every 7 days, or earlier in the case of sensor failure. Study participants were required to calibrate once every 12 hours, or check their capillary glucose in the event of sensor failure, symptoms of hypo- or hyperglycaemia, or if the sensor glucose was out of the desired range (3.9 mmol/l - 13.3 mmol/l).

Participants using CSII (insulin pump therapy) were required to use the Cellnovo pump for the duration of the study and were trained on how to use it. The differences between their home pump and the Cellnovo pump were outlined, including fundamental features such as calculation of IOB and correction boluses. Additional points of discussion included: site initiation, setting up the pump, cartridge/priming procedures, navigation through menus and bolus procedures including stopping a bolus. User manuals for the PEPPER handset and the Cellnovo insulin pump were supplied.

Participants were informed to obtain bolus advice (via the standard bolus calculator) using the PEPPER handset, as well as use it for any dose correction or additional carbohydrate intake.

Target blood glucose levels as part of the CBR algorithm settings were standardised to 5.5 mmol/l, however this target could subsequently be individualised if deemed required by the clinician. Alert thresholds were standardised at 4.4 mmol/l for hypoglycaemia and 14.0 mmol/l for hyperglycaemia. These could subsequently be altered by the individual if required. Hypoglycaemia alarms were hard-coded at 3.9 mmol/l due to safety reasons.

Each session lasted approximately 4-6 hours. For clinical and technical support, participants were able to contact the study team during visits. Where necessary, glucose data could be reviewed remotely by the PEPPER clinical team.

Visit 2: randomisation

At visit 2, a selection technique was applied to enrolled participants (utilising the online randomisation tool; www.sealedenvelope.com) to randomise participants in a 1:1 ratio to PEPPER/Control or Control/PEPPER. The groups were stratified by insulin delivery modality i.e. CSII or MDI. Randomisation was done independently at each site.

Participants in the intervention PEPPER group had algorithms activated on the PEPPER clinical server remotely. For participants in the control group, the standard bolus calculator was integrated into the PEPPER handset, which had the CBR algorithm disabled. The PEPPER safety system was also switched off, but standard rtCGM alarms remained active through xDrip+ (283,284).

Visit 3: Review

Technical issues reported by participants were reviewed at the visit, and adjustments to basal rates were made if necessary.

Visit 4: end of first intervention period

Once 3 months in the intervention phase were completed, each group went through 3-4 weeks of wash-out period. During this time, participants reverted to their standard therapy. For participants completing the PEPPER group first, they were not aware of their ICR and ISF values from the adaptive PEPPER algorithm, and therefore reverted back to their initial parameters from the run-in period.

Venous bloods were obtained (non-fasting) for HbA1c levels, weight and basal insulin requirements were documented, and study questionnaires completed.

Visit 5-7: start of second intervention period

The same protocol structure applied for Visits 5-7, as they did for Visits 2-4. Participants were crossed over from Control/PEPPER to PEPPER/Control, or *vice-versa*. For participants starting in the PEPPER intervention arm second, the CBR system was initialised at Visit 5. Thus, for each participant, the case-base was built up over the intervention period of 12 weeks only.

At the end of the study (i.e. visit 7 at the end of 8 months), repeat venous blood tests were undertaken to obtain participants' most recent HbA1c. Weight and basal insulin requirements were recorded, and psychological questionnaires similar to that at baseline and visit 4 were completed. Study equipment was returned, and individuals resumed back to their standard care.

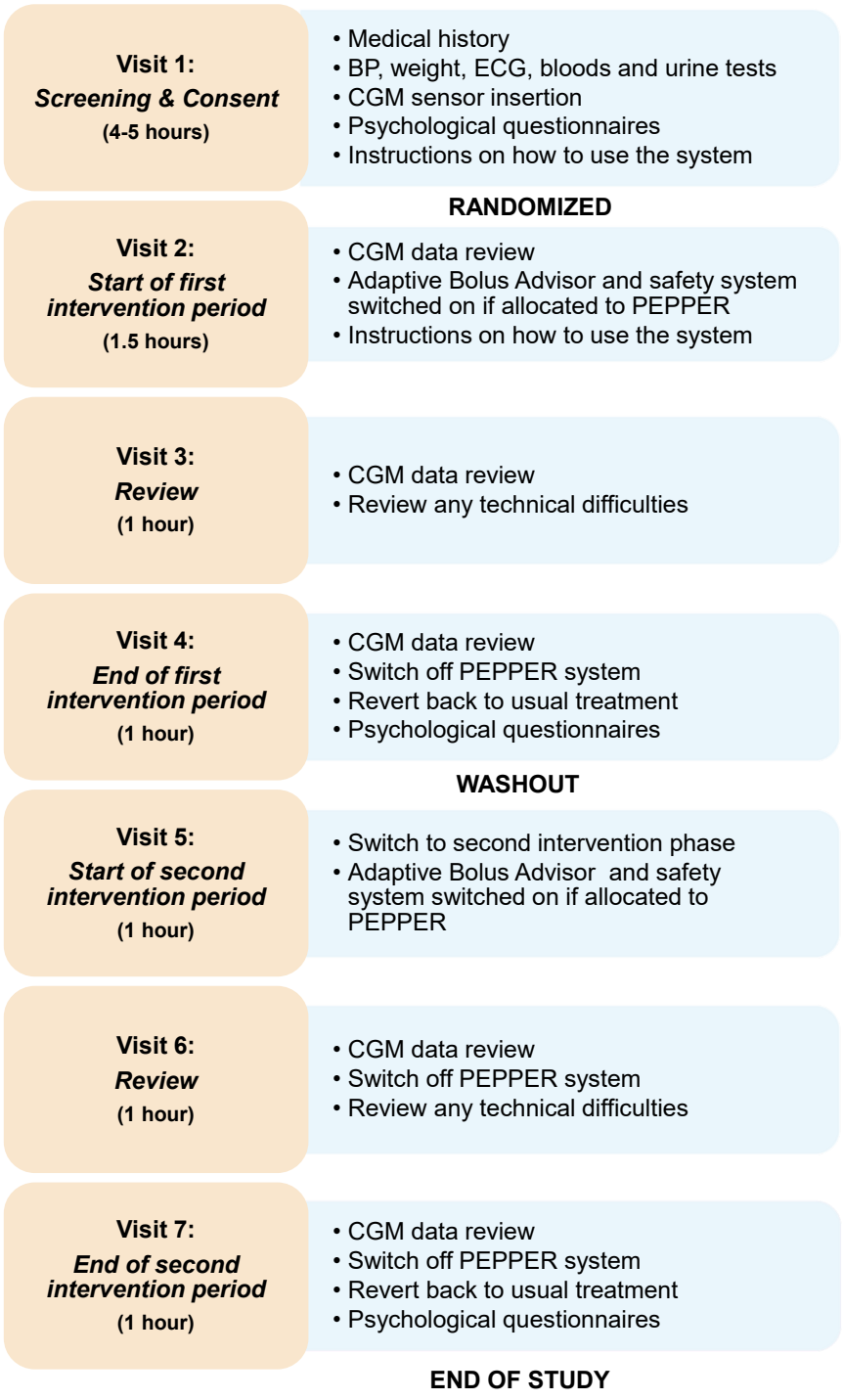

Figure 5.1: Summary of Phase 3 study visit attendances

Abbreviations: BP, blood pressure; ECG, electrocardiogram; CGM, continuous glucose monitoring

5.2.4 PEPPER cased-base revision

Whilst the algorithm was running, the study participants were provided with real-time adaptive insulin dosing at mealtimes. All glucose data was automatically uploaded from the PEPPER handset to the secure PEPPER webserver. The case base was reviewed through a semi-automated process completed remotely by clinicians twice weekly during the intervention period (PEPPER with CBR). The criteria used by clinicians for revision of the CBR cases are outlined in Section 2.4.6.

5.2.5 Study outcomes

A comprehensive data analysis plan was written by me for the PEPPER study group and has been included in Appendix 2.

For Phase 3, the primary outcome was percentage time in range (3.9 – 10.0mmol/l) between the PEPPER intervention arm (safety system with adaptive bolus advise), and the control arm. Endpoint assessment was not blind to the study intervention arm allocated.

Secondary outcomes include assessments of the variables listed below:

- Percentage time in hypoglycaemia (< 3.9 mmol/l and <3.3 mmol/l)
- Percentage time spent in hyperglycaemia (> 10.0 mmol/l)
- Number of episodes of serious hypoglycaemia (defined as a sensor glucose < 3.0 mmol/L (55 mg/dl) for > 20 min)
- Episodes of hypoglycaemia within 5-hours post-prandially

- Postprandial mean area under the curve (AUC) at 5 hours
- Glycaemic risk and variability measures
- HbA1c
- Change in weight (kg)
- Basal insulin dose requirements
- Psychosocial outcomes (PAID, DQOL and DTSQs Questionnaires)
- Safety system outcomes: number of low and high glucose alarms, alerts, carbohydrate recommendations, and predictive low glucose suspend
- CBR outcomes: number of CBR revision cases, number of bolus recommendations accepted by user, and usage of the case parameters

5.2.6 Statistical analysis

Glycaemic outcome measures were analysed at baseline and from each intervention period, using data from the last 28 days. Changes from baseline between groups were assessed. The primary analysis was conducted using the intention-to-treat (ITT) principle, with further analysis completed with the per-protocol population. The per-protocol population consisted of participants who completed the study without any significant deviation from the planned protocol procedures. Additional sub-analyses were conducted to evaluate differences in glycaemia between day (07.00 – 23.00hrs) vs night (23.00 – 07.00hrs), as well as pump and MDI users, and by site of recruitment (UK vs Spain).

Glycaemic variability

Measures of GV were computed using EasyGV (v10.0) software (297). Evaluated GV measures included SD, CV, MAGE, CONGA, MODD, LI, MAG, GVP, PGS, M-Value, IGC, RI, GRADE, M-value, ADRR, J-Index, HBGI and LBGI. GRADE score is also reported as %GRADEhypoglycaemia, %GRADEeuglycaemia, and %GRADEhyperglycaemia representing percentages of GRADE scores attributable to glucose values <3.9 mmol/l (<70 mg/dL), and between 3.9–7.8 mmol/l (70-140 mg/dL) and >7.8 mmol/l (>140 mg/dL) respectively.

Safety system

Safety system measures were reported for the PEPPER and control groups. Whilst the safety system was not enabled in the control group, the algorithm was running in the background to allow comparisons to be made. Data from the run-in period for the safety system was not used in the analysis because the safety system was optimised using the run-in data itself.

Statistical considerations

The data were tested for normal distribution using normal distribution quantile plots and the Shapiro-Wilk test of normality. The result of the Shapiro-Wilk test for %TIR 3.9-10.0mmol/l was $p < 0.05$, indicating that the data were not normally distributed. The Wilcoxon Rank Sum test was used to test differences between groups in the ITT analysis. For the per-protocol analysis, the Wilcoxon matched-pairs signed-rank was used for analysis for differences between each of the arms. Where appropriate the nonparametric Spearman rank tests (r_s) was performed for correlation.

Data have been presented as medians (IQR), unless otherwise stated. Statistical tests were performed using Stata version 15 (StataCorp, College Station, Texas) and the results considered statistically significant if $p < 0.05$ (two-tailed).

The secondary outcomes of the study were not powered to detect statistical differences between groups.

5.3 Results

5.3.1 Baseline demographics

Of the 60 participants screened for the study, 58 participants were enrolled between November 2018 and March 2019. In total, 54 participants completed the run-in period (3 declined to participate and 1 did not meet inclusion criteria due to high HbA1c), thus making up the ITT study population (Figure 5.2; UK = 28 participants; Spain = 26 participants). Participants were median (IQR) aged 41.5 (32.3-49.8) years, with HbA1c of 61.0 (58.0-66.1) mmol/mol, and had a diabetes duration of 21.0 (11.5–26.3) years. Median BMI was 26.0 (23.8-29.2) kg/m^2. Twenty-eight participants (51.8%) used an insulin pump and twenty-six participants (48.1%) were male. All participants had intact awareness of hypoglycaemia. Table 5.1 summarises the baseline characteristics of the participants. No differences were observed between the intervention groups at baseline.

Following the run-in period, an additional 4 participants declined to participate during the first intervention phase. Fifty participants were randomised to PEPPER (n=24) or Control (n=26). Four participants then withdrew (PEPPER (n=2) and Control (n=2)) and 1 was withdrawn due to a serious adverse event. Thus, the first crossover phase was completed by 45 participants (22 PEPPER, 23 Control).

Subsequently, 10 participants were withdrawn after the first intervention phase due to loss of Cellnovo device support (PEPPER (n=5) and Control (n=5)). A further participant was withdrawn due to a serious adverse event. In total, 17 participants crossed-over to the PEPPER and Control arms each. All (n=34) completed the second intervention phase. In total, for the ITT, 39 participants allocated to PEPPER and 40 allocated to Control completed the intervention.

For the per-protocol analysis, 1 participant was excluded for not using the PEPPER adaptive bolus advisor (n=1). Both intervention phases were fully completed, with the PEPPER adaptive insulin recommender system used, by 33 participants, making up the pre-protocol analysis. The flow diagram (Figure 5.2) summarises recruitment and withdrawals.

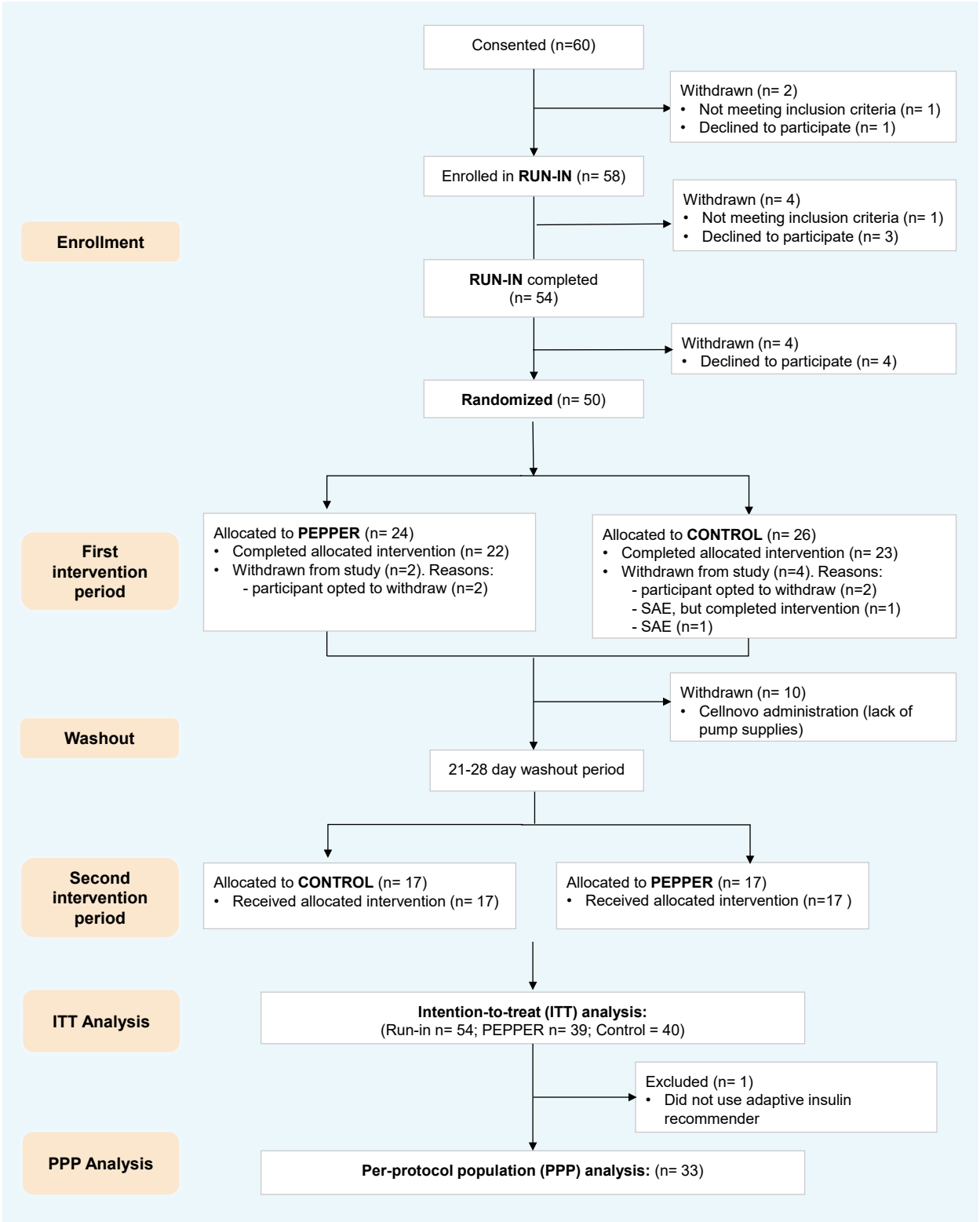

Figure 5.2: Consort flow diagram

The ITT study population included 54 participants completing the run-in period. For the PPP analysis, 33 participants were included. Reasons for exclusion from the PPP analysis include participants declining to participate (n=8), Cellnovo withdrawal from market resulting in early study termination (n=10), SAE (n=2), study completion without use of PEPPER adaptive bolus advisor (n=1). Abbreviations: ITT, intention-to-treat; PPP, per protocol population; SAE; serious adverse event

Demographics	ITT cohort (n=54)	PEPPER/Control (n=24)	Control/PEPPER (n=26)
Gender (female)	28 (51.8%)	13 (54%)	13 (50.0%)
Age (years)	41.5 (32.3-49.8)	42.0 (37.8-48.0)	41.0 (32.8-49.8)
BMI (kg/m^2) Height (cm) Weight (kg)	26.0 (23.8-29.2) 169.0 (162.4-177.4) 72.9 (65.1-86.2)	26.3 (23.9-28.0) 169.3 (161.5-174.0) 71.6 (64.9-83.0)	25.8 (23.2-29.9) 170.0 (163.1-178.3) 74.2 (66.0-86.2)
Duration of diabetes (years)	21.0 (11.5-26.0)	22.0 (13.0-27.5)	17.5 (11.0-24.0)
Hypoglycaemia awareness (i.e. Gold/Clarke score <4)	54 (100%)	24 (100%)	26 (100%)
CSII: MDI users	28:26	11:13	13:13
Baseline use of rtCGM CSII user MDI user	 3 (5.6%) 1 (1.9%)	 1 (4.2%) 0 (0.0%)	 2 (7.7%) 1 (3.8%)
Baseline use of Freestyle Libre	4 (7.4%)	2 (8.3%)	2 (7.7%)
HbA1c (mmol/mol) HbA1c (%)	61.0 (58.0-66.1) 7.7 (7.5-8.2)	61.0 (58.8-67.1) 7.7 (7.5-8.3)	59.3 (56.0-66.0) 7.6 (7.3-8.2)
Participants with previous DKA	10 (18.5%)	6 (25.0%)	4 (15.4%)
Participants with previous severe hypoglycaemia episode	11 (18.5%)	5 (20.8%)	4 (15.4%)
TSH (mU/L)	1.7 (1.1-2.3)	1.8 (1.2-2.3)	1.7 (1.2-2.3)
Total cholesterol (mg/dl) Total cholesterol (mmol/l)	172 (158-194) 4.4 (4.1-5.0)	174 (159-200) 4.7 (4.4-5.4)	171 (151-190) 4.5 (4.2-5.0)

Table 5.1: Baseline demographics for ITT population

The PEPPER/Control group started with the PEPPER intervention and Control/PEPPER started with Control. Results are expressed as median (IQR)/ n (%). BMI, body mass index; DKA, diabetic ketoacidosis; TSH, thyroid stimulating hormone.

5.3.2 Glycaemic outcomes

For the primary outcome, no significant differences were observed in glycaemia %TIR 3.9-10.0 mmol/l between the PEPPER system compared to Control ((62.5 (52.1-67.8)% vs 58.4 (49.6-64.3)% respectively; p=0.27; Table 5.2). For % time in hyperglycaemia for thresholds >10.0 mmol/l (PEPPER 35.2 (29.8-43.9)% vs Control 38.6 (30.6-48.0)%; p=0.40) and >15 mmol/l (PEPPER 4.5 (2.2-7.5)% vs

Control 4.9 (2.7-9.4)%; p=0.50) no significance was observed. Similarly, for all ranges of % time in hypoglycaemia, there were no significant differences.

The per-protocol analysis findings were similar to that of the ITT cohort (Table 5.3). No significant difference in %TIR was observed with the PEPPER system +4.2 (-4.9 to 10.4) compared to Control +1.2 (-7.2 to 7.3), p=0.10. Similarly, % times in hypoglycaemia and hyperglycaemia did not reach statistical significance.

Within the sub-analysis stratified by insulin delivery modality, participants using CSII therapy with the PEPPER system achieved a greater increase in %TIR compared to those on MDI, albeit significance between groups was not achieved (p=0.46). For analysis by day and night (Table 5.5) and when stratified by country of recruitment (UK vs Spain) no significant differences were observed (Table 5.6). Furthermore, the predictive low glucose suspend with PEPPER was not associated with improved nocturnal hypoglycaemia for CSII users. Nocturnal %TIR 3.9-10.0 mmol/l with the PEPPER intervention was 60.8% (49.8 – 65.4) % vs Control 55.6% (45.3 – 67.6) % (p=0.66).

	RUN-IN (n=54)	CONTROL (n=40)	PEPPER (n=39)	P-value (PEPPER vs CONTROL)
PRIMARY ENDPOINT				
% time in range 3.9-10mmol/l (70 -180mg/dL)	55.0 (46.4-65.6)	58.4 (49.6-64.3)	62.5 (52.1-67.8)	0.27
SECONDARY ENDPOINTS				
% time in euglycaemia 3.9-7.8mmol/l (70 -140mg/dL)	30.5 (23.9-39.9)	34.0 (24.0-40.1)	34.7 (28.7-38.9)	0.70
% time in hypoglycaemia				
<3.9mmol/l (<70mg/dL)	2.7 (1.6-5.5)	2.3 (1.1-6.4)	2.2 (1.5-3.3)	0.64
<3.3mmol/l (<60mg/dL)	1.4 (0.7-3.0)	0.8 (0.4-3.3)	0.8 (0.5-1.8)	0.69
<3.0mmol/l (<54mg/dL)	1.0 (0.4-1.9)	0.4 (0.1-2.0)	0.4 (0.2-1.1)	0.84
% time in hyperglycaemia				
>10mmol/l (>180mg/dL)	42.8 (30.1-49.3)	38.6 (30.6-48.0)	35.2 (29.8-43.9)	0.40
>15mmol/l (>270mg/dL)	6.8 (3.0-12.6)	4.9 (2.7-9.4)	4.5 (2.2-7.5)	0.50
Glycaemic variability measures				
Mean	9.6 (8.6-10.3)	9.2 (8.8-10.1)	9.0 (8.7-9.7)	0.56
Standard deviation	3.4 (3.0-3.9)	3.3 (2.9-3.9)	3.1 (2.8-3.6)	0.40
CV (%)	35.9 (33.9-39.6)	35.6 (31.8-40.7)	34.6 (31.6-38.0)	0.43
CONGA	3.8 (3.2-4.3)	3.4 (2.9-4.0)	3.5 (3.0-4.0)	0.91
LI	9.2 (6.7-12.0)	7.9 (5.7-10.8)	8.1 (5.8-10.3)	0.91
JINDEX	55.1 (44.3-65.0)	50.9 (43.9-60.0)	48.6 (43.7-56.5)	0.42
LBGI	0.7 (0.5-1.4)	0.6 (0.4-1.5)	0.6 (0.4-1.0)	0.71
HBGI	9.0 (6.4-11.6)	8.0 (6.3-10.5)	7.6 (6.2-9.8)	0.40
GRADE	9.9 (8.1-11.7)	9.3 (7.9-11.0)	8.7 (7.7-10.4)	0.32
GRADE - % Hypo	3.8 (1.5-8.2)	2.1 (1.1-8.5)	2.3 (1.4-4.8)	1.00
GRADE - % Eugly	5.7 (3.9-7.9)	6.3 (4.0-8.6)	7.5 (5.0-9.3)	0.25
GRADE - % Hyper	89.9 (85.2-93.6)	88.5 (84.0-93.5)	89.8 (85.2-92.1)	0.98
MODD	3.9 (3.4-4.5)	3.7 (3.2-4.2)	3.5 (3.3-4.0)	0.58
MAGE	7.7 (7.0-9.0)	7.3 (6.5-9.1)	7.3 (6.5-8.3)	0.56
ADDR	49.3 (43.3-57.3)	44.3 (41.0-53.9)	42.0 (38.6-51.6)	0.38
M-VALUE	13.3 (10.7-18.5)	11.8 (9.1-17.0)	10.0 (8.1-13.6)	0.22
MAG	3.5 (3.1-4.5)	3.5 (2.8-3.8)	3.3 (2.8-4.0)	0.87
PGS	19.7 (16.7-23.7)	18.6 (15.3-21.7)	16.2 (14.3-21.1)	0.18
IGC	3.1 (2.5-4.0)	2.8 (2.2-3.8)	2.4 (1.9-3.0)	0.21
GVP	61.1 (48.5-86.5)	59.9 (43.1-70.1)	55.4 (44.4-74.2)	0.95
Secondary Glycaemic Outcomes				
Mean Glucose 1hr (mmol/l)	10.3 (9.4-11.3)	9.9 (9.2-11.6)	10.0 (9.0-10.6)	0.79
Mean Glucose 2hr (mmol/l)	10.4 (9.2-11.3)	9.8 (9.1-11.4)	9.9 (9.9-10.7)	0.84
Mean AUC (min x mmol/l)	2215.9 (2024.8-2395.9)	2081.1 (2035.5-2413.5)	2160.8 (1970.2-2243.5)	0.92
Mean minimum glucose (mmol/l)	6.8 (6.1-7.5)	6.8 (6.1-7.5)	6.7 (6.0-7.3)	0.75
Number of hypo episodes	4.5 (2.0-7.0)	2.0 (1.0-7.0)	2.0 (1.0-4.0)	0.62
Postprandial hypo episodes (5hr)	1.0 (0.0-2.0)	1.0 (0.0-1.0)	0.0 (0.0 -1.0)	0.75
HbA1c (mmol/mol)	61.0 (57.5-66.1)	58.5 (53.0-63.4)	58.5 (54.0-61.9)	0.82
HbA1c (%)	7.7 (7.5-8.2)	7.5 (7.0-7.9)	7.5 (7.1-7.7)	-
Weight (kg)	72.9 (65.1-86.2)	73.9 (64.8-84.9)	75.0 (66.7-85.0)	0.81
Basal insulin (units)	21.6 (18.0-27.7)	25.9 (18.0-29.2)	25.0 (18.5-29.2)	0.76

Table 5.2: Intention-to-treat pooled analysis of glycaemic outcomes

Glycaemic outcome measures were analysed at baseline using data from the 28-day run-in period and data from the last 28 days of each intervention period. Results are expressed as median (IQR). Abbreviations: CV, coefficient of variation; CONGA, continuous overlapping net glycaemic action; LI, lability index; LBGI, low blood glucose index; HBGI, high blood glucose index; GRADE, glycaemic risk assessment in diabetes equation; MODD, mean of daily differences; MAGE, mean amplitude of glycaemic excursions; MAG, mean absolute glucose change; PGS, personal glycaemic status; IGC, index of glycaemic control; GVP, glycaemic variability percentage; AUC, area under the curve.

	Run-in (Baseline)	Control	PEPPER	Median change from baseline to endpoint		
				Δ Control	Δ PEPPER	P-value
PRIMARY OUTCOME						
% time in range 3.9-10mmol/l (70 -180mg/dL)	55.1 (49.0-66.9)	58.9 (50.9-64.3)	62.5 (52.3-68.7)	+1.2 (-7.2 to 7.3)	+4.2 (-4.9 to 10.4)	0.10
SECONDARY OUTCOMES						
% time in euglycaemia 3.9-7.8mmol/l (70 -140mg/dL)	31.7 (26.0-43.8)	33.9 (24.1-39.3)	35.0 (29.1-38.7)	-0.4 (-7.1 to 4.4)	+2.1 (-4.7 to 6.9)	0.27
% time in hypoglycaemia						
<3.9mmol/l (<70mg/dL)	3.5 (1.7-5.9)	2.4 (1.1-6.5)	2.2 (1.5-3.3)	-0.5 (-1.9 to 0.9)	-0.9 (-2.4 to 0.2)	0.30
<3.0mmol/l (<54mg/dL)	1.1 (0.4-2.1)	0.4 (0.1-1.9)	0.4 (0.2-1.0)	-0.1 (-0.9 to 0.2)	-0.2 (-1.0 to 0.1)	0.92
% time in hyperglycaemia						
>10mmol/l (>180mg/dL)	42.3 (27.9-47.5)	39.1 (30.6-47.1)	42.3 (27.9-47.5)	-1.0 (-7.1 to 8.9)	-3.9 (-10.5 to 5.2)	0.33
>15mmol/l (>270mg/dL)	4.9 (2.8-10.3)	4.3 (2.6-8.9)	4.3 (2.2-7.3)	-0.7 (-2.7 to 1.6)	-0.8 (-2.8 to 0.3)	0.54
Glycaemic variability measures						
Mean	9.6 (8.5-10.0)	9.3 (8.7-10.0)	9.0 (8.7-9.6)	-0.1 (-0.7 to 0.7)	-0.2 (-0.8 to 0.4)	0.61
Standard deviation	3.3 (3.0-3.9)	3.2 (2.9-3.6)	3.0 (2.8-3.4)	-0.2 (-0.4 to 0.1)	-0.3 (-0.4 to 0.0)	0.21
CV (%)	35.6 (33.8-40.3)	34.9 (31.2-40.2)	34.5 (31.8-38.0)	-0.5 (-3.6 to 2.1)	-1.1 (-4.6 to 1.1)	0.48
CONGA	3.8 (3.4-4.3)	3.3 (2.9-4.0)	3.5 (3.0-3.9)	-0.3 (-0.9 to 0.0)	-0.2 (-0.7 to 0.1)	0.06
LI	9.5 (7.5-12.0)	7.0 (5.6-10.1)	8.2 (5.9-10.1)	-1.2 (-4.4 to 0.2)	-1.2 (-3.5 to 0.1)	0.06
JINDEX	52.7 (42.7-60.5)	50.0 (43.8-58.6)	48.6 (44.1-55.7)	-1.5 (-9.6 to 6.2)	-3.5 (-8.5 to 3.2)	0.40
LBGI	0.9 (0.5-1.6)	0.6 (0.3-1.4)	0.6 (0.4-0.9)	0.0 (-0.4 to 0.3)	-0.2 (-0.4 to 0.1)	0.33
HBGI	8.7 (6.0-10.8)	8.0 (6.2-10.0)	7.6 (6.2-9.4)	-0.4 (-2.7 to 1.9)	-1.1 (-2.2 to 1.1)	0.40
GRADE	9.5 (7.7-11.4)	9.2 (8.0-10.6)	8.7 (7.7-10.2)	0.0 (-1.6 to 1.1)	-0.3 (-1.7 to 0.8)	0.08
GRADE - %Hypo	4.9 (1.9-9.1)	2.1 (1.0-8.1)	2.6 (1.4-4.7)	-0.6 (-3.8 to 1.9)	-1.1 (-3.8 to 0.6)	0.84
GRADE - %Eugly	6.1 (4.2-8.8)	6.5 (4.4-8.5)	7.5 (5.1-9.4)	+0.1 (-0.9 to 1.2)	+0.9 (-0.6 to 2.1)	0.06
GRADE - %Hyper	89.3 (84.4-92.1)	88.6 (84.4-93.4)	89.6 (84.0-92.2)	-0.2 (-3.3 to 3.9)	+0.1 (-2.7 to 2.5)	0.81
MODD	3.7 (3.3-4.2)	3.5 (3.2-3.9)	3.4 (3.3-4.0)	-0.1 (-0.4 to 0.1)	-0.1 (-0.5 to 0.2)	0.88
ADDR	49.6 (43.1-57.0)	43.7 (40.7-49.7)	42.0 (39.1-50.8)	-4.5 (-10.0 to -1.2)	-6.0 (-8.7 to 0.6)	0.82
M-VALUE	11.8 (10.2-16.0)	11.1 (8.5-15.3)	10.0 (8.1-13.1)	-0.5 (-3.5 to 2.7)	-2.5 (-4.4 to 1.4)	0.07
MAG	3.6 (3.3-4.7)	3.2 (2.8-3.8)	3.3 (2.9-4.0)	-0.4 (-1.1 to 0.2)	-0.3 (-0.8 to 0.2)	0.47
PGS	19.3 (17.2-24.0)	18.2 (15.3-20.8)	16.2 (14.7-20.4)	-0.9 (-4.6 to 0.8)	-3.0 (-5.0 to -0.4)	0.06
IGC	2.9 (2.5-3.9)	2.6 (2.2-3.6)	2.4 (2.0-2.9)	-0.3 (-0.8 to 0.3)	-0.6 (-1.1 to 0.2)	0.07
GVP	63.3 (55.6-88.3)	52.1 (42.9-69.0)	55.4 (45.7-73.9)	-9.8 (-25.1 to 5.7)	-7.3 (-19.2 to 4.8)	0.56
Secondary Glycaemic Outcomes						
Postprandial mean glucose 1hr (mmol/l)	10.2 (9.1-11.2)	9.8 (8.8-11.4)	9.9 (8.8-10.6)	-0.2 (-0.8 to 0.8)	-0.1 (-0.7 to 0.5)	0.74
Postprandial mean glucose 2hr (mmol/l)	10.3 (9.0-11.3)	10.3 (9.0-11.3)	9.9 (8.6-10.6)	-0.3 (-0.7 to 0.7)	-0.1 (-0.8 to 0.3)	0.80
Mean AUC (min x mmol/l)	2117.7 (1977.6 -2330.3)	2081.1 (2004.7-2400.1)	2137.6 (1923.0 -2222.3)	-35.7 (-142.2 to 119.2)	-58.4 (-165.3 to 72.2)	0.62

Mean minimum glucose (mmol/l)	6.7 (6.1-7.4)	6.8 (6.2-7.6)	6.7 (5.9-7.2)	+0.2 (-0.6 to 0.6)	-0.2 (-0.6 to 0.6)	0.66
Number of hypo episodes	5.0 (2.0-9.0)	2.0 (1.0-7.0)	2.0 (1.0-4.0)	-1.0 (-4.0 to 0.0)	-0.1 (-0.3 to 0.0)	0.77
Postprandial hypo episodes (5hr)	1.0 (1.0-4.0)	1.0 (0.0-1.0)	0.0 (0.0-1.0)	-1.0 (-2.0 to 0.0)	0.0 (-0.1 to 0.1)	0.57

Table 5.3: Per-protocol analysis of glycaemic outcomes (n=33)

Participants completing both intervention phases (Control and PEPPER) were included in the per-protocol analysis. One participant was excluded for not using the PEPPER bolus advisor. Results are expressed as median (IQR). Abbreviations: CV, coefficient of variation; CONGA, continuous overlapping net glycaemic action; LI, lability index; LBGI, low blood glucose index; HBGI, high blood glucose index; GRADE, glycaemic risk assessment in diabetes equation; MODD, mean of daily differences; MAGE, mean amplitude of glycaemic excursions; MAG, mean absolute glucose change; PGS, personal glycaemic status; IGC, index of glycaemic control; GVP, glycaemic variability percentage; AUC, area under the curve.

	CSII				MDI			
	RUN-IN (n=28)	**Control (n=15)**	**PEPPER (n=14)**	**P-value (PEPPER vs Control)**	**RUN-IN (n=26)**	**Control (n=25)**	**PEPPER (n=25)**	**P-value (PEPPER vs Control)**
PRIMARY OUTCOME								
% time in range								
3.9-10mmol/l (70 -180mg/dL)	55.0 (48.5-61.6)	54.7 (47.4-65.6)	64.1 (53.3-66.5)	0.46	52.0 (44.8-66.8)	60.2 (50.5-64.3)	61.4 (51.7-69.6)	0.46
SECONDARY OUTCOMES								
% time in euglycaemia								
3.9-7.8mmol/l (70 -140mg/dL)	31.8 (24.8-39.3)	33.9 (25.7-40.3)	34.8 (30.4-38.1)	0.83	28.9 (23.6-42.1)	34.6 (23.8-39.3)	34.4 (28.3-41.8)	0.72
% time in hypoglycaemia								
<3.9mmol/l (<70mg/dL)	2.6 (1.3-3.8)	2.2 (1.6-4.7)	1.9 (1.1-2.5)	0.22	3.4 (1.7-6.0)	2.8 (1.1-6.5)	2.7 (1.6-4.5)	0.84
<3.3mmol/l (<60mg/dL)	1.3 (0.5-2.0)	0.7 (0.5-2.3)	0.7 (0.3-1.0)	0.38	1.5 (1.1-3.6)	0.9 (0.4-3.4)	1.0 (0.5-2.4)	0.85
<3.0mmol/l (<54mg/dL)	0.7 (0.2-1.4)	0.3 (0.2-1.5)	0.3 (0.2-0.5)	0.54	1.1 (0.7-2.4)	0.5 (0.1-2.0)	0.7 (0.3-1.8)	0.82
% time in hyperglycaemia								
>10mmol/l (>180mg/dL)	42.3 (31.7-49.3)	39.2 (32.8-46.6)	34.0 (31.3-43.0)	0.51	44.4 (28.9-49.2)	38.0 (30.6-48.3)	35.2 (29.0-43.9)	0.54
>15mmol/l (>270mg/dL)	7.6 (3.7-11.0)	6.4 (2.5-13.7)	4.8 (3.0-7.5)	0.54	6.3 (2.8-15.4)	4.9 (2.7-8.9)	4.5 (2.2-7.3)	0.57
Glycaemic variability								
Mean	9.6 (8.7-10.3)	9.3 (8.8-10.0)	9.0 (8.9-9.8)	0.76	9.8 (8.6-10.6)	9.0 (8.7-10.1)	9.0 (8.4-9.6)	0.66
Standard deviation	3.5 (3.1-3.9)	3.3 (2.8-4.1)	3.1 (2.8-3.4)	0.41	3.3 (3.0-4.0)	3.2 (2.9-3.6)	3.1 (2.9-3.6)	0.71
CV (%)	35.8 (34.7-38.8)	35.7 (31.6-40.9)	33.9 (30.4-36.7)	0.19	36.2 (33.5-40.2)	35.5 (32.1-40.5)	35.2 (32.5-38.5)	0.93
CONGA	3.5 (2.9-3.8)	3.4 (2.8-3.7)	3.1 (2.8-3.5)	0.63	4.1 (3.6-4.6)	3.4 (3.1-4.1)	3.6 (3.3-4.3)	0.76
LI	8.1 (5.7-9.7)	7.7 (5.1-9.2)	6.4 (5.3-7.8)	0.60	11.2 (8.8-13.8)	8.2 (6.3-11.7)	8.4 (7.2-12.4)	0.79
JINDEX	55.1 (49.1-63.9)	51.9 (46.7-65.1)	48.3 (44.3-57.3)	0.46	55.8 (43.1-70.4)	50.7 (43.8-59.7)	49.7 (43.2-56.3)	0.69
LBGI	0.7 (0.4-1.1)	0.6 (0.4-1.1)	0.5 (0.4-0.7)	0.32	0.9 (0.5-1.6)	0.8 (0.3-1.5)	0.8 (0.5-1.2)	0.82
HBGI	9.0 (7.2-11.2)	8.3 (6.8-10.9)	7.2 (6.4-9.9)	0.57	9.5 (6.1-11.9)	7.7 (6.2-10.4)	7.7 (6.2-9.4)	0.66
GRADE	9.8 (8.5-11.3)	9.7 (7.9-11.6)	8.3 (7.9-10.4)	0.54	10.5 (7.8-12.1)	9.1 (8.0-10.6)	8.8 (7.6-10.2)	0.55
GRADE - %Hypo	3.3 (1.1-5.3)	2.1 (1.2-4.2)	1.7 (1.0-2.8)	0.51	5.2 (2.3-9.8)	2.9 (0.8-9.8)	3.6 (1.7-7.8)	0.76
GRADE - %Eugly	6.0 (4.1-7.8)	5.4 (3.9-9.1)	8.2 (5.3-8.9)	0.46	5.4 (3.7-8.6)	7.0 (4.0-8.1)	7.4 (4.9-9.6)	0.44
GRADE - %Hyper	91.7 (85.3-93.8)	91.0 (86.9-92.9)	89.8 (88.6-91.6)	0.73	88.7 (84.6-92.4)	88.4 (80.1-94.6)	89.6 (80.7-92.2)	0.84
MODD	3.9 (3.4-4.3)	3.7 (3.1-4.5)	3.4 (3.1-3.8)	0.46	3.9 (3.4-4.6)	3.7 (3.3-4.1)	3.5 (3.3-4.1)	0.95
MAGE	8.1 (6.9-8.6)	7.8 (6.4-9.2)	6.8 (6.3-7.7)	0.31	7.5 (7.0-9.4)	7.3 (6.7-9.0)	7.3 (6.8-9.0)	0.83
ADDR	48.1 (42.1-55.1)	46.7 (36.0-54.1)	41.1 (36.9-42.8)	0.46	52.8 (44.4-60.4)	44.0 (41.9-53.9)	44.7 (40.6-53.5)	0.81
M-VALUE	13.3 (11.2-17.1)	11.1 (9.0-21.3)	9.8 (7.9-13.5)	0.34	13.3 (10.3-21.7)	12.0 (9.3-14.6)	10.6 (8.7-13.4)	0.34
MAG	3.2 (2.7-3.7)	3.0 (2.5-3.6)	2.8 (2.5-3.2)	0.46	4.1 (3.5-5.0)	3.7 (2.8-4.1)	3.4 (3.2-4.2)	0.98
PGS	19.1 (16.4-21.5)	18.7 (13.5-23.1)	15.5 (14.1-19.0)	0.49	20.5 (17.2-24.2)	18.4 (16.5-20.8)	16.6 (14.7-21.4)	0.29
IGC	2.9 (2.4-3.7)	2.3 (1.9-4.0)	2.1 (1.8-2.7)	0.38	3.3 (2.7-4.1)	2.8 (2.3-3.3)	2.4 (2.0-3.7)	0.40
GVP	54.0 (42.4-65.6)	50.8 (37.0-64.2)	45.5 (37.7-53.)	0.57	75.8 (60.9-97.6)	66.1 (45.8-76.4)	58.9 (53.0-79.3)	0.92
HbA1c (mmol/mol)	61.0 (58.2-66.1)	57.4 (54.6-61.2)	58.5 (57.4-61.9)	0.29	59.8 (56.5-66.1)	58.5 (51.0-64.2)	57.5 (52.0-64.2)	0.76
HbA1c (%)	7.7 (7.5-8.2)	7.4 (7.2-7.7)	7.5 (7.4-7.8)	-	7.6 (7.4-8.2)	7.5 (6.8-8.0)	7.4 (6.9-8.0)	-

Weight (kg)	69.2 (63.2-88.2)	70.1 (62.9-84.3)	70.5 (64.9-88.8)	0.53	75.3 (67.3-84.7)	75.0 (67.5-85.9)	76.5 (67.5-84.1)	0.99
Basal insulin (units)	20.8 (18.3-26.3)	23.0 (19.8-27.8)	23.8 (19.9-28.9)	0.59	25.0 (18.0-32.5)	26.0 (17.8-38.5)	26.0 (18.0-40.0)	0.98

Table 5.4: Glycaemic outcomes stratified by MDI and CSII users in intention-to-treat cohort

Results are expressed as median (IQR). Abbreviations: CV, coefficient of variation; CONGA, continuous overlapping net glycaemic action; LI, lability index; LBGI, low blood glucose index; HBGI, high blood glucose index; GRADE, glycaemic risk assessment in diabetes equation; MODD, mean of daily differences; MAGE, mean amplitude of glycaemic excursions; MAG, mean absolute glucose change; PGS, personal glycaemic status; IGC, index of glycaemic control; GVP, glycaemic variability percentage; AUC, area under the curve.

	DAY (07.00hrs – 23.00hrs)				NIGHT (23.00hrs – 07.00hrs)			
	RUN-IN (n=54)	**Control (n=40)**	**PEPPER (n=39)**	**P-value (PEPPER vs Control)**	**RUN-IN (n=54)**	**Control (n=40)**	**PEPPER (n=39)**	**P-value (PEPPER vs Control)**
PRIMARY OUTCOMES								
% time in range 3.9-10mmol/l (70 -180mg/dL)	57.4 (45.6-66.8)	58.0 (48.0-67.6)	63.1 (53.4-67.8)	0.32	51.8 (44.9-60.9)	58.4 (45.5-65.3)	61.0 (50.4-67.2)	0.34
SECONDARY OUTCOMES								
% time in euglycaemia 3.9-7.8mmol/l (70 -140mg/dL)	33.6 (23.2-39.1)	33.7 (26.1-40.4)	34.8 (27.7-39.2)	0.71	26.1 (20.6-37.7)	31.4 (22.0-41.0)	33.5 (27.5-39.8)	0.38
% time in hypoglycaemia								
<3.9mmol/l (<70mg/dL)	3.0 (1.6-5.4)	2.7 (1.3-6.4)	2.5 (1.5-3.9)	0.54	1.8 (0.9-5.0)	1.6 (0.8-4.9)	1.5 (0.6-4.0)	0.67
<3.3mmol/l (<60mg/dL)	1.5 (0.8-2.6)	0.9 (0.4-2.9)	0.9 (0.5-2.1)	0.84	0.7 (0.2-3.1)	0.6 (0.2-2.8)	0.5 (0.1-1.0)	0.60
<3.0mmol/l (<54mg/dL)	0.9 (0.4-1.8)	0.5 (0.1-1.7)	0.5 (0.2-1.3)	0.92	0.4 (0.1-2.2)	0.3 (0.0-2.4)	0.3 (0.0-0.7)	0.51
% time in hyperglycaemia								
>10mmol/l (>180mg/dL)	40.1 (30.3-49.5)	37.1 (28.4-47.6)	34.6 (28.6-44.3)	0.46	45.3 (29.7-53.8)	39.1 (31.6-50.5)	36.9 (30.5-46.7)	0.32
>15mmol/l (>270mg/dL)	5.8 (2.9-10.4)	5.1 (2.3-10.5)	3.6 (2.5-8.0)	0.59	7.0 (2.5-15.2)	5.4 (2.8-9.0)	5.5 (2.1-7.5)	0.52
Glycaemic variability								
Mean	9.5 (8.5-10.3)	9.3 (8.5-10.1)	9.0 (8.5-9.8)	0.58	9.8 (8.5-10.9)	9.4 (8.6-10.2)	9.1 (8.6-9.9)	0.40
Standard deviation	3.3 (3.0-3.8)	3.2 (2.9-3.8)	3.1 (2.9-3.5)	0.43	3.5 (3.1-3.9)	3.2 (2.9-3.8)	3.1 (2.7-3.7)	0.49
CV (%)	36.5 (33.2-39.0)	36.4 (32.2-40.1)	34.4 (32.7-37.8)	0.29	35.0 (33.1-40.3)	34.3 (31.8-38.8)	34.3 (30.9-38.1)	0.73
CONGA	4.4 (3.8-5.0)	4.1 (3.5-4.6)	4.1 (3.5-4.8)	0.96	3.4 (2.8-4.1)	3.2 (2.8-4.1)	3.1 (2.6-4.1)	0.37
LI	12.6 (9.4-15.9)	10.7 (8.0-14.4)	10.8 (7.7-14.6)	0.93	7.8 (5.3-11.8)	7.2 (5.3-11.5)	6.8 (4.5-11.3)	0.33
JINDEX	53.0 (43.4-61.8)	51.2 (43.0-62.0)	47.0 (43.7-56.1)	0.45	55.2 (46.2-69.5)	51.0 (43.8-62.0)	50.8 (42.1-56.6)	0.45
LBGI	0.8 (0.5-1.3)	0.6 (0.4-1.5)	0.7 (0.5-1.1)	0.67	0.6 (0.3-1.4)	0.5 (0.3-1.2)	0.5 (0.2-1.1)	0.52
HBGI	8.7 (6.0-10.9)	7.9 (6.0-11.1)	7.0 (6.2-9.6)	0.46	9.3 (6.6-13.1)	8.2 (6.5-10.8)	7.6 (5.9-9.9)	0.37
GRADE	9.6 (7.9-11.4)	9.2 (7.8-11.3)	8.6 (7.6-10.0)	0.34	10.1 (9.1-12.4)	9.2 (8.1-11.6)	8.9 (7.8-10.5)	0.31
GRADE - %Hypo	4.2 (2.1-7.9)	2.5 (1.3-8.8)	2.7 (1.2-5.3)	0.95	1.9 (0.4-7.5)	1.3 (0.4-7.9)	1.5 (0.4-4.1)	0.83
GRADE - %Eugly	6.3 (3.8-8.9)	5.7 (4.1-9.0)	7.6 (5.3-9.5)	0.28	5.0 (3.1-7.5)	6.5 (3.7-8.6)	6.2 (4.5-9.1)	0.34
GRADE - %Hyper	90.2 (85.7-92.3)	88.1 (82.8-93.6)	89.6 (84.9-92.9)	0.88	92.8 (83.7-95.2)	91.3 (85.0-94.6)	89.6 (87.2-94.0)	0.63
MODD	3.7 (3.3-4.3)	3.7 (3.3-4.2)	3.5 (3.3-4.0)	0.58	3.8 (3.6-4.3)	3.8 (3.3-4.5)	3.6 (3.0-4.1)	0.42
MAGE	7.6 (6.9-9.0)	7.2 (6.7-8.8)	7.4 (6.6-8.2)	0.82	8.0 (7.0-9.3)	7.3 (5.9-9.0)	7.5 (6.3-8.5)	0.85
ADDR	52.6 (44.3-59.6)	48.9 (40.6-55.4)	45.6 (40.7-55.1)	0.34	45.8 (36.8-54.6)	42.7 (37.0-55.3)	40.4 (33.7-49.8)	0.31
M-VALUE	12.8 (9.5-17.0)	11.9 (8.9-17.3)	9.5 (8.2-14.0)	0.23	14.6 (10.4-19.9)	12.3 (8.7-18.2)	11.3 (7.9-15.2)	0.36
MAG	4.5 (3.7-5.5)	4.1 (3.4-4.9)	4.1 (3.5-5.0)	0.91	3.1 (2.7-3.7)	2.8 (2.5-3.9)	2.8 (2.3-3.6)	0.39
PGS	19.0 (16.4-22.7)	19.5 (14.7-21.1)	16.6 (14.4-20.8)	0.25	19.3 (16.7-21.9)	17.8 (14.0-21.0)	16.0 (14.0-19.7)	0.31
IGC	2.9 (2.4-3.7)	2.8 (2.2-3.6)	2.2 (2.0-3.1)	0.20	3.3 (2.5-4.2)	2.7 (2.1-4.2)	2.2 (1.9-3.6)	0.28
GVP	86.6 (65.8-111.9)	75.5 (59.3-97.5)	77.1 (60.4-97.9)	0.91	55.3 (44.4-71.1)	49.3 (41.2-72.8)	47.7 (37.9-67.4)	0.34

Table 5.5: Intention-to-treat analysis of glycaemic outcomes stratified by day and night

Data presented as medians (IQR). Abbreviations: CV, coefficient of variation; CONGA, continuous overlapping net glycaemic action; LI, lability index; LBGI, low blood glucose index; HBGI, high blood glucose index; GRADE, glycaemic risk assessment in diabetes equation; MODD, mean of daily differences; MAGE, mean amplitude of glycaemic excursions; MAG, mean absolute glucose change; PGS, personal glycaemic status; IGC, index of glycaemic control; GVP, glycaemic variability percentage; AUC, area under the curve.

	UK				SPAIN			
	RUN-IN (n=28)	**Control (n=16)**	**PEPPER (n=16)**	**P-value (PEPPER vs Control)**	**RUN-IN (n=26)**	**Control (n=24)**	**PEPPER (n=23)**	**P-value (PEPPER vs Control)**
PRIMARY OUTCOME								
% time in range 3.9-10mmol/l (70 -180mg/dL)	52.0 (44.7-67.2)	62.5 (44.6-68.9)	63.3 (47.9-69.7)	0.97	55.2 (49.1-62.7)	54.8 (50.8-61.2)	61.4 (52.6-65.6)	0.14
SECONDARY OUTCOMES								
% time in euglycaemia 3.9-7.8mmol/l (70 -140mg/dL)	28.2 (22.1-39.3)	38.9 (26.6-41.2)	35.0 (28.8-42.0)	0.71	31.8 (25.9-39.7)	30.3 (23.9-38.9)	34.6 (28.7-38.0)	0.39
% time in hypoglycaemia								
<3.9mmol/l (<70mg/dL)	1.8 (1.0-3.7)	2.5 (1.4-6.0)	2.7 (1.7-4.6)	0.91	3.6 (2.4-5.9)	2.1 (1.1-6.6)	2.1 (1.3-3.1)	0.69
<3.3mmol/l (<60mg/dL)	1.2 (0.4-1.8)	0.8 (0.6-3.3)	1.0 (0.5-2.9)	0.85	1.8 (1.2-3.1)	0.7 (0.4-3.1)	0.6 (0.5-1.5)	0.83
<3.0mmol/l (<54mg/dL)	0.8 (0.2-1.3)	0.5 (0.3-2.0)	0.4 (0.1-2.4)	0.79	1.2 (0.6-2.0)	0.4 (0.1-1.9)	0.4 (0.2-0.9)	0.86
% time in hyperglycaemia								
>10mmol/l (>180mg/dL)	44.3 (30.8-52.2)	32.3 (29.3-47.9)	34.4 (28.2-41.3)	0.76	42.6 (30.6-47.5)	39.4 (35.3-48.0)	36.2 (30.5-44.8)	0.23
>15mmol/l (>270mg/dL)	8.0 (3.0-16.3)	4.0 (2.6-16.2)	4.3 (1.9-13.4)	0.77	6.3 (3.0-10.4)	5.5 (2.8-9.1)	4.5 (2.8-7.2)	0.42
Glycaemic variability								
Mean	9.9 (8.7-10.7)	8.8 (8.7-10.0)	8.9 (8.7-9.6)	0.50	9.6 (8.5-10.1)	9.3 (8.9-10.1)	9.2 (8.7-9.7)	0.34
Standard deviation	3.5 (2.9-4.0)	3.3 (2.9-4.1)	3.2 (2.8-4.2)	0.85	3.3 (3.1-3.9)	3.3 (2.9-3.6)	3.1 (2.9-3.4)	0.33
CV (%)	35.6 (32.6-38.8)	36.7 (33.2-41.8)	36.0 (33.2-38.8)	0.60	36.6 (35.0-40.6)	34.8 (31.1-38.8)	34.3 (31.4-36.9)	0.55
CONGA	3.8 (3.2-4.4)	3.6 (3.1-4.2)	3.5 (2.8-4.4)	0.71	3.6 (3.2-3.9)	3.3 (2.9-4.0)	3.5 (3.0-3.9)	0.83
LI	9.4 (6.8-13.0)	8.6 (6.2-11.9)	8.1 (5.3-7.8)	0.76	8.6 (6.9-9.8)	7.0 (5.5-10.2)	7.8 (5.9-9.8)	0.83
JINDEX	57.1 (44.3-72.0)	48.2 (43.1-72.9)	47.2 (42.9-63.6)	0.85	53.5 (45.0-60.3)	51.4 (47.5-59.7)	49.7 (44.2-54.9)	0.22
LBGI	0.6 (0.4-1.0)	0.7 (0.5-1.5)	0.7 (0.5-1.3)	0.88	0.9 (0.6-1.5)	0.6 (0.3-1.4)	0.6 (0.4-0.8)	0.77
HBGI	9.7 (6.4-12.7)	7.2 (6.1-12.7)	7.0 (6.0-10.3)	1.00	8.8 (6.5-10.7)	8.3 (7.2-10.1)	7.9 (6.3-9.3)	0.23
GRADE	10.5 (8.2-12.8)	8.4 (7.6-12.2)	8.2 (7.5-11.6)	0.94	9.7 (8.1-11.3)	9.6 (8.6-10.7)	9.0 (7.8-10.1)	0.15
GRADE - %Hypo	3.4 (1.1-6.1)	3.0 (1.2-9.7)	2.2 (1.7-8.9)	0.91	4.2 (2.3-9.0)	2.1 (0.9-7.8)	2.6 (1.4-3.8)	0.88
GRADE - %Eugly	5.4 (3.4-9.0)	7.7 (3.4-10.1)	7.8 (4.5-9.7)	0.97	6.0 (4.2-7.7)	5.6 (4.3-7.5)	7.5 (5.2-8.6)	0.07
GRADE - %Hyper	89.8 (85.2-94.0)	88.1 (82.2-90.4)	89.1 (84.7-90.8)	0.62	89.9 (84.6-92.1)	91.6 (86.2-94.0)	91.0 (86.8-92.4)	0.67
MODD	3.9 (3.3-4.7)	3.6 (3.3-4.7)	3.5 (3.2-4.6)	0.88	3.9 (3.5-4.2)	3.7 (3.2-3.9)	3.5 (3.3-4.0)	0.59
MAGE	8.1 (6.7-9.6)	7.7 (6.8-9.4)	7.5 (6.5-9.0)	0.73	7.5 (7.1-8.4)	7.3 (6.4-8.5)	7.2 (6.5-7.9)	0.59
ADDR	50.0 (42.4-58.6)	48.2 (42.0-56.1)	44.2 (40.7-55.0)	0.50	48.9 (44.4-57.0)	43.8 (38.2-50.3)	41.9 (37.6-48.4)	0.62
M-VALUE	13.9 (10.0-23.1)	10.2 (8.0-22.2)	9.8 (8.0-20.5)	0.85	12.8 (11.1-16.6)	12.6 (9.9-15.5)	10.7 (8.3-12.9)	0.11
MAG	3.8 (3.2-5.0)	3.8 (3.0-4.1)	3.4 (2.9-4.2)	0.82	3.4 (2.9-4.0)	3.1 (2.7-3.7)	3.2 (2.8-3.7)	0.88
PGS	19.6 (15.8-22.1)	17.4 (15.0-21.9)	15.2 (14.1-21.9)	0.60	19.7 (17.4-23.7)	19.2 (16.6-21.5)	17.0 (14.7-19.8)	0.13
IGC	3.0 (2.4-4.2)	2.9 (2.0-4.1)	2.3 (1.9-4.1)	0.97	3.1 (2.6-3.8)	2.8 (2.2-3.6)	2.4 (1.9-2.7)	0.09
GVP	71.5 (54.8-97.1)	66.8 (47.5-76.5)	59.3 (45.3-78.8)	0.73	58.8 (45.6-71.5)	51.4 (41.7-66.4)	55.0 (44.4-65.8)	0.80

HbA1c (mmol/mol)	61.0 (56.0-66.3)	53.0 (51.0-63.0)	57.0 (53.8-59.0)	0.49	60.8 (58.5-66.1)	58.5 (56.0-63.1)	59.6 (57.4-63.9)	0.89
HbA1c (%)	7.7 (7.3-8.2)	7.0 (6.8-7.9)	7.4 (7.1-7.6)	-	7.7 (7.5-8.2)	7.5 (7.3-7.9)	7.6 (8.9-8.0)	-
Weight (kg)	75.0 (67.6-88.2)	74.8 (69.3-84.4)	79.6 (72.0-88.5)	0.37	71.0 (62.6-83.9)	71.6 (62.9-84.9)	68.8 (64.0-84.0)	0.83
Basal insulin (units)	24.2 (18.3-27.0)	24.0 (19.4-31.4)	25.5 (19.7-29.6)	0.72	20.7 (18.0-28.0)	26.0 (17.0-28.5)	23.4 (17.0-29.3)	0.98

Table 5.6: Intention-to-treat analysis of glycaemic outcomes for UK and Spain cohorts

Data presented as medians (IQR). Abbreviations: CV, coefficient of variation; CONGA, continuous overlapping net glycaemic action; LI, lability index; LBGI, low blood glucose index; HBGI, high blood glucose index; GRADE, glycaemic risk assessment in diabetes equation; MODD, mean of daily differences; MAGE, mean amplitude of glycaemic excursions; MAG, mean absolute glucose change; PGS, personal glycaemic status; IGC, index of glycaemic control; GVP, glycaemic variability percentage; AUC, area under the curve.

5.3.3 Glycaemic variability and other secondary outcomes

For all measures of GV, no significant differences were observed between the PEPPER and Control groups in either the ITT analysis (Table 5.2) or the per-protocol analysis (Table 5.3).

A decline from baseline in the number of hypoglycaemic episodes was observed in both the PEPPER and Control groups, however no significant differences were observed between groups.

For HbA1c, both groups showed a reduction from baseline, but no between group differences were observed. AUC and postprandial glucose also showed no difference between PEPPER and Control.

Basal insulin and body weight remained constant throughout, with no differences between the intervention groups.

5.3.4 Quality of life

Overall, participants demonstrated a good quality of life without significant diabetes distress at baseline. At baseline, the median PAID score was 18.8 (11.3-31.3) and a global DQOL score of 1.9 (1.5-2.4).

With the PEPPER system, no significant differences were observed for diabetes distress, overall diabetes treatment satisfaction, the global quality of life, nor its subsections. However, there was an apparent increase in the frequency of

hypoglycaemia in the DTSQ questionnaire with PEPPER, in comparison to the Control group (p=0.03; Table 5.7). This signal persisted in the per-protocol analysis (p<0.01; Table 5.8)

	RUN-IN (n=54)	CONTROL (n=40)	PEPPER (n=39)	P-value (PEPPER vs CONTROL)
PAID Questionnaire[+]	18.8 (11.3-31.3)	15.6 (9.7-24.4)	17.5 (10.0-28.8)	0.44
DTSQs				
Global Score	26 (24-30)	32 (28-33)	31 (28-34)	0.83
Perceived hypoglycaemia	2 (1-3)	2 (1-2)	2 (2-4)	0.03*
Perceived hyperglycaemia	2 (1-3)	2 (1-2)	2 (2-4)	0.32
DQOL[++]				
Global Score	1.9 (1.5-2.4)	1.7 (1.3-2.1)	1.7 (1.4-2.0)	0.80
Satisfaction	2.1 (1.9-2.5)	1.9 (1.6-2.3)	1.8 (1.4-2.2)	0.29
Impact	2.5 (1.6-3.3)	2.0 (1.5-2.7)	2.1 (1.6-2.9)	0.49
Worry: Social/Vocational	1.3 (1.1-1.9)	1.4 (1.1-1.9)	1.4 (1.2-1.6)	0.84
Worry: Diabetes Related	2.0 (1.5-2.5)	1.8 (1.5-2.3)	2.0 (1.5-2.4)	0.29

Table 5.7: Quality of life analysis in intention-to-treat cohort.

Data presented as medians (IQR). Abbreviations: PAID, problem areas in diabetes (scored out of 100 with higher scores indicating distress); DTSQs, diabetes treatment satisfaction questionnaire (scored out of 36 indicating very satisfied); DTSQs perceived frequency of hypo- and hyperglycaemia are scored from 0 (none of the time) to 6 (most of the time); DQOL, diabetes quality of life (based on Likert 5-point scale from 1 to 5 with high scores indicate dissatisfaction, frequent impact, or frequent worry). [+]PAID questionnaire: run-in n=53, control n=40; PEPPER =39. [++]DQOL questionnaire: run-in n=53, control n = 39; PEPPER n=39. * p<0.05 indicates significance.

	Run-in (Baseline)	Control	PEPPER	Median change from baseline to endpoint		
				Δ Control	Δ PEPPER	P-value
PAID Questionnaire	18.8 (10.0-26.3)	15.0 (8.8-23.8)	17.5 (10.0-26.3)	-2.5 (-6.3 to 2.5)	-1.3 (-7.5 to 5)	0.13
DTSQs						
Global score	26 (24-29)	31 (28-33)	31 (28-34)	+4 (0 to 9)	+5 (2 to 8)	0.72
Perceived hypoglycaemia	2 (1-3)	2 (1-3)	2 (2-4)	0 (-1 to 1)	+1 (0 to 1)	**<0.01***
Perceived hyperglycaemia	2 (1-3)	4 (2-4)	3 (2-4)	+1 (0 to 2)	0 (0 to 1)	0.08
DQOL						
Global Score	1.7 (1.4-2.1)	1.6 (1.4-2.1)	1.7 (1.3-1.9)	-0.1 (-0.1 to 0.0)	0.0 (-0.2 to 0.0)	0.26
Satisfaction	2.1 (1.7-2.3)	1.9 (1.6-2.2)	1.7 (1.4-2.1)	-0.1 (-0.4 to -0.1)	-0.2 (-0.5 to 0.0)	0.17
Impact	1.9 (1.5-2.7)	2.0 (1.6-2.8)	2.0 (1.6-2.8)	0.0 (-0.1 to 0.3)	0.0 (-0.2 to 0.1)	0.66
Worry: Social/Vocational	1.3 (1.1-1.5)	1.3 (1.1-1.6)	1.3 (1.2-1.6)	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.3)	0.47
Worry: Diabetes Related	1.8 (1.5-2.3)	1.8 (1.5-2.3)	1.8 (1.5-2.3)	0.0 (-0.3 to 0.3)	0.0 (-0.3 to 0.3)	0.54

Table 5.8: Per-protocol analysis of quality of life questionnaires (n=33).

Data presented as medians (IQR). Abbreviations: PAID, problem areas in diabetes (scored out of 100 with higher scores indicating distress); DTSQs, diabetes treatment satisfaction questionnaire (scored out of 36 indicating very satisfied); DTSQs perceived frequency of hypo- and hyperglycaemia are scored from 0 (none of the time) to 6 (most of the time); DQOL, diabetes quality of life (based on Likert 5-point scale from 1 to 5 with high scores indicate dissatisfaction, frequent impact, or frequent worry). * $p<0.05$ indicates significance.

5.3.5 Safety system outcomes

No safety data was obtained from the handset of one participant. In order to evaluate the system, the Control group had the safety system disabled, however the algorithm was running in the background without effect.

For the number of alerts, alarms, and carbohydrate recommendations, no significant differences were observed between groups. Similarly, there were no differences observed in the numbers of automated pump suspensions (total and partial) between the two groups for CSII users. The total bolus insulin per participant per day also remained similar in the two groups: 32.8 (23.9-53.5) units/day in the Control group vs 32.6 (22.1-51.0) units/day in the PEPPER group (p=0.96; Table 5.9).

	CONTROL (n=39)	**PEPPER (n=38)**	**P-value (PEPPER vs Control)**
Safety System			
Total bolus insulin (units/day)	32.8 (23.9-53.5)	32.6 (22.1-51.0)	0.96
No. of alarms/day	1.5 (0.9-2.4)	1.3 (1.0-2.0)	0.44
No. of hypo alarms/day	0.9 (0.5-1.3)	0.9 (0.6-1.1)	0.53
No. of hypo alerts/day	1.5 (1.0-1.9)	1.5 (1.1-2.0)	0.78
No. of CHO recommendations/day	3.2 (0.8-6.8)	2.6 (1.1-4.6)	0.74
Mean CHO recommendation (g)	13.8 (10.4-17.0)	12.1 (9.9-14.5)	0.16
For PUMP users	**(n=15)**	**(n=14)**	
Number of suspensions/day	1.1 (0.9-1.4)	1.2 (1.0-1.5)	0.54
% of total time in partial suspension	2.7 (2.3-3.4)	2.5 (2.0-3.4)	0.41
% of total time in total suspension	2.3 (1.9-3.7)	2.9 (2.2-3.5)	0.63

Table 5.9: Intention-to-treat pooled analysis of safety system outcomes.

Data analysed as last 28 days of each intervention phase. Total and partial percentage (%) suspension time in pump participants reported as proportions of the total timeframe (the remaining time was not in suspension). CHO recommendations refer to personalized oral dose of carbohydrates to revert hypoglycaemia and minimize rebound hyperglycaemia. Data presented as medians (IQR). Abbreviations: CHO, carbohydrate.

The overall MARD between the forecasting algorithm and the actual sensor glucose was 14.4 (12.6-15.9)%. The root mean square error (RMSE) of the 30min predictive forecasting PEPPER algorithm was 1.6 (1.4-1.9) mmol/l (Table 5.10).

	PEPPER (n=53)
Forecasting Algorithm	
Coefficient of determination (R^2)	0.74 (0.70-0.74)
Root Mean Square Error (mmol/l)	1.6 (1.4-1.9)
MARD (%)	14.4 (12.6-15.9)

Table 5.10: Performance of the PEPPER forecasting algorithm

Data presented as medians (IQR). Abbreviations: MARD, mean absolute relative difference

A total of 303 revisions were constrained and saturated by the safety system, i.e. 5 (2 – 14)% of all proposed bolus recommendations. Of these, 85% were for hyperglycaemia.

5.3.6 CBR outcomes

During the PEPPER intervention period, a total of 14,723 cases of insulin bolus recommendations were imported to the revision platform, with an average of 4.0 (3.3-5.5) cases per participant/day. No decay was observed in the number of bolus recommendations requested over the study period.

Greater than two-thirds (87 (65 – 96) %) of bolus advice cases were accepted by the user. Only 4 (1 – 10) % of all proposed recommendations were constrained and saturated by the safety system.

For all cases uploaded to the online platform, 46 (26-58)% of cases were approved by the physician to be integrated in to the learnt case base. 47 (36 – 62)% of cases were manually rejected with 6 (4 – 8)% automatically rejected by the system (Table 5.11). Reasons for the clinician rejecting the case include missing glucose sensor data or because of exclusion criteria relating to the adaptation metric (e.g. user had given additional insulin or consumed a snack shortly after the advice received).

There was no correlation between the number of cases per participant and the %TIR spent by participants ($r = 0.371$, $p=0.15$).

Variable	Median (IQR) (n=39)
Total number of cases/ participant	334 (276 – 465)
Weekday	72 (70 – 73) %
Weekend	28 (27 – 30) %
Average number of cases per day/participant	4.0 (3.3-5.5)
Proportion of boluses saturated by safety system/ participant	4 (1 – 10) %
For hyperglycaemia	3 (0 – 8) %
For hypoglycaemia	0 (0 – 1) %
Bolus doses accepted by participant	87 (65 – 96) %
Bolus doses changed by participant	13 (4 – 35) %
Cases revised by clinician/ participant	
Accepted cases	46 (26 – 58) %
Manually rejected	47 (36 – 62) %
Non-Eligible cases (automatic rejection by system)	6 (4 – 8) %
Case parameters/participant	
Past physical activity	
- None	48 (17 – 60) %
- Low	48 (39 – 80) %
- Mild	1 (0 – 3) %
- Intense	0 (0 – 1) %
Future physical activity	
- None	94 (71 – 99) %
- Low	4 (0 – 23) %
- Mild	1 (0 – 5) %
- Intense	0 (0 – 2)%
- Aerobic	100 (99 – 100) %
Meal Absorption Rate	
- Slow	3 (1 – 10) %
- Medium	88 (54 – 97) %
- Fast	3 (0 – 9) %
Alcohol	
- Moderate	5 (1 – 10) %
- High	0 (0 – 0) %
Psychological Stress	0 (0 – 0) %
Tiredness	1 (0 – 5) %
Hormone cycle (females only)	
- Pre-menstruation	0 (0 – 3) %
- Menstruation	3 (0 – 9) %

Table 5.11: CBR outcomes in the intention-to-treat population

Case usage and parameters recorded by participants using the PEPPER bolus calculator over the full intervention period (i.e. 12 weeks). Data presented as medians (IQR).

5.3.7 Adverse events

Within the Control group, two serious adverse events occurred. One participant experienced an episode of severe nocturnal hypoglycaemia, whilst another participant experienced mild diabetic ketoacidosis precipitated by denatured insulin +/- urinary tract infection. Both resolved without adverse sequelae.

Two other adverse events reported include appendicitis which required an appendicectomy and a fall resulting in a fractured fifth metatarsal, however these were not deemed to be linked to trial intervention with PEPPER safety system or AI algorithm.

5.4 Discussion

The PEPPER system with an AI-derived adaptive bolus calculator and safety system has overall been shown to be safe and feasible for people with T1D. Whilst all times in ranges in the intervention group moved towards improvement, none of the differences between the PEPPER and Control arms reached statistical significance.

To date, this is the largest randomised controlled study reporting clinical outcomes of a personalised adaptive bolus calculator for use with both MDI and CSII therapy. Unfortunately, the main limitation of this clinical study has been the administration of Cellnovo and its withdrawal from market. Despite extensive discussions by the PEPPER Consortium, the administrators were not forthcoming to seek additional

sales of the pump supplies, rendering no availability of further supplies to complete the study. As a result, 10 CSII participants in the UK were prematurely withdrawn, limiting the power and study outcomes. Although no final conclusions about the impact of adaptive intervention can be drawn from the outcomes of this study, the move towards improvement in all outcome measures for glycaemia and glycaemic variability are encouraging.

The initial drop-out rate, particularly in the UK participants, was noted to be high. One of the predominant reasons reported was the complexity of the system and the requirement for multiple components. For example, participants were required to carry an extra handset (in addition to their own mobile handset), rtCGM, an activity monitor (which may be in addition to their own wearable device, for example an Apple watch recording step count) and a glucometer. Furthermore, CSII participants were also required to carry additional Cellnovo pump supplies. That said, the PEPPER app is a system that would ultimately be available for download on to one's own mobile handset with easy and accessible integration with other wearable sensors.

There was additionally a high early drop-out rate in participants using CSII due to challenges with the Cellnovo hardware, including frequent cartridge ejection or signal loss. For those participants continuing on the study, they did not appear to experience the high frequency of issues as those who chose to drop-out at the earlier stage. The 10% drop-out rate chosen for this study sample size was relatively conservative for technology studies.

In our usability study analysed by colleagues at Oxford Brookes University, the average time taken for participants to request bolus advice for a particular situation (45gram of carbohydrates, medium meal absorption, low intensity non-aerobic past exercise, no planned exercise, no hormone cycle info, low alcohol consumption. not stressed and good mood) was 62.0 (49.5 – 86.0) seconds. Although these times are likely to have improved with use of the app, as these were assessed on first use and intuitiveness of the system, long-term sustainability in app usage is an important factor to consider.

For quality of life measures, there were no overall differences observed between the two arms. Differences emerging between the two groups may have been limited due to participants overall having a good quality of life without diabetes distress at baseline. Intriguingly, despite no objective difference in time spent in hypoglycaemia, participants reported higher perceived hypoglycaemia with the PEPPER system. Overall, this did not affect diabetes treatment satisfaction, however, may have been resultant from the additional forecasted alerts received when using the PEPPER system.

To minimise the burden of carbohydrate counting and the physical entry of meals into the system, innovative strategies could be incorporated into the PEPPER app. These include smart technologies with machine learning capabilities, such as GoCARB (298), which enables estimation of carbohydrate content from plated meals for individuals with T1D. Integration of a food library app, such as MyFitnessPal (299), or the ability to select meal-size estimation (rather than actual carbohydrate amount) may aid sustained long-term use. For pump participants, this

is particularly advantageous as the control algorithm in clinically approved and experimental hybrid CL systems, may compensate to some extent for the bolus delivered.

In terms of limitations associated with the PEPPER system, the CBR algorithm is likely to be most helpful to individuals maintaining a regular work pattern, rather than day/night shift workers. Also, the CBR algorithm only adapts for bolus insulin, and assumes that the basal insulin has been optimised. Furthermore, the system is dependent on meal scenarios where the user has not ingested a significant snack or taken an insulin bolus correction within 5 hours of a meal for revision. This may particularly be an issue for individuals tending to snack or eat their meal in phases. For CSII users, the bolus advisor is unable to make use of extended phase or dual wave bolusing, a feature incorporated into insulin pumps.

Despite the limitations and constraints of this study, the data are promising and suggest that, in a powered study over a sufficient period of time, an adaptive bolus advisor may facilitate an improvement in glycaemia. There is significantly broad scope for integrating PEPPER into routine diabetes management for CSII and MDI users. The adaptation feature of the PEPPER algorithm also has potential for future implementation in artificial pancreas systems.

5.5 Conclusion

In conclusion, the PEPPER system is acceptable, safe and maintains glycaemia in a diverse population. To confirm overall effectiveness, a larger powered randomised controlled trial is required.

6 Conclusions and Future Work

6.1 Summary of the PEPPER Project

Previous innovations in the management and treatment of people with T1D have significantly improved outcomes in long-term morbidity and mortality. However, disease burden remains considerable, with treatment targets often not met. Attaining adequate glycaemia requires significant effort by the individual. Furthermore, fear of hypoglycaemia and long-term complications often negatively impact quality of life. An adaptive bolus advisor is a system that provides personalised insulin decision support and holds promise to improve glycaemia by assisting people with calculating meal insulin doses and improving post-meal glucose excursions. Although not a cure, it may provide a practical solution for people with T1D, by standalone use with MDI or may be incorporated into insulin pump therapy or an artificial pancreas.

The main objective of the clinical project outlined in this thesis was to evaluate proof of concept, safety, feasibility and efficacy of the PEPPER personalised decision support tool integrated with a novel adaptive bolus calculator and safety

system for adults with T1D. The novelty lies in the adaptive AI-derived algorithm, which is able to provide automated personalised bolus advise to the individual and is coupled with a safety system to reduce the incidence of hypoglycaemia. It extends existing research and is currently the most comprehensive clinical trial to date assessing standalone adaptive bolus calculators.

In this thesis, the system has been assessed in three clinical phases. The initial pilot Phase 1 feasibility study evaluated the PEPPER safety system only. During this phase, there were several challenges faced particularly for the CSII participants, and thus the study was required to be put on hold till these issues were addressed. Early manufacturing at Flex (Flex Ltd, Althofen, Austria) resulted in significant insulin cartridge variation, causing frequent ejection of "faulty" insulin cartridges and increasing the alarm frequency experienced by users. As a result, the study had to be paused for the CSII participants to allow changes in manufacturing to enable the latest generation of insulin cartridges to be significantly more consistent.

Another significant issue during this phase was the amount of data loss experienced between the rtCGM and xDrip+ software. This was particularly problematic for the CSII participants, as users occasionally found they would be unable to request bolus advice nor administer a bolus dose during this period of time. Whilst this did not affect safety system outcomes of Phase 1 (as participants continued receiving their basal insulin dose through the pump), it was of significant inconvenience to the user to be unable to administer a bolus dose at mealtimes. To address this, negotiations by the PEPPER Consortium were pursued to seek contractual agreement with Dexcom for rtCGM data to be directly integrated into the PEPPER

handset (bypassing xDrip+). Unfortunately, this was unsuccessful, as were attempts to upgrade software to Dexcom G6. As a solution, whilst the study was paused, the source code was refined by the PEPPER Consortium to minimise data loss.

Glycaemic data from participants using CSII and MDI were analysed separately in view of the delays and changes made during iterative software development for the pump prototype. In addition, only CSII data from ICL site were used for analysis, as the system used by IDIBGI did not have the predictive low glucose suspend activated.

Despite the challenges outlined above, the overall results for MDI and CSII participants were encouraging. For MDI users, the results showed a significant reduction in percentage time in clinically significant hypoglycaemia (<3.0mmol/l) and increased percentage time in range (3.9-10 mmol/l). This was corroborated by a similar reduction in hypoglycaemia (<3.9mmol/l) observed in CSII users. One of the key limitations of this early stage feasibility study was that it was not designed to show superiority. This was a single arm study, without a control group, and therefore it was difficult to determine how much of the improvement was due to the safety system and how much to prolonged rtCGM use. Overall, the PEPPER system was deemed safe for use, including in CSII participants, following app refinements made in response to the issues outlined above.

After confirming feasibility of the PEPPER safety system, an assessment of the adaptive bolus calculator was performed in Phase 2. The main challenges faced at

this stage related to the data flow for the CBR system. The study was paused at ICL whilst I and Dr Pau Herrero (ICL engineer) led the investigation to ensure the CBR component worked and actively adapted decision support in line with the algorithm. During this time colleagues at IDIBGI completed Phase 2 without a functioning CBR. As a result, only data from ICL were included in the analysis. No significant differences between baseline and endpoint were observed. We learnt that there was scope to enhance the learning rate of the algorithm, and this was subsequently incorporated into the final study prototype. This phase also enabled the algorithm and clinical interface for CBR revisions to be optimised prior to starting the randomised controlled crossover study.

Many software design changes were integrated into the final design study prototype to improve the user experience, including enhancements to functionality and usability. As with many projects following agile development cycles, one of the key challenges experienced was a trade-off between introducing software changes and the risk of introducing bugs or errors.

Finally, the 8-month crossover clinical study was completed to assess efficacy between the intervention cohort that received the PEPPER safety system with adaptive bolus advise, and the control cohort. Whilst all times in ranges moved towards improvement in the intervention group, none of the differences observed between the PEPPER and Control arms reached statistical significance.

Participants did report higher perceived hypoglycaemia with the PEPPER system, however no objective difference in time spent in hypoglycaemic ranges were

observed. This is likely to be a result of the additional forecasted hypoglycaemia alerts (i.e. predictive low glucose suspend and carbohydrate recommendations) received whilst using the PEPPER system. More importantly, in our analysis of the psychosocial outcomes affecting participants, there was no equivalent rise in the worry subsections of diabetes quality of life. Overall diabetes treatment satisfaction was not affected.

For the final validation phase, the main limitation to show a statistically significant improvement, was that the study population was smaller than intended and therefore was not sufficiently powered. Despite an adequate number of participants recruited, there were a high volume of drop-outs due to technical issues related to the Cellnovo pump hardware. This was later exacerbated by the requirement for early study termination in 10 CSII participants due to the withdrawal of Cellnovo from market and lack of pump supplies. Interestingly, our sub-analysis stratified by mode of insulin delivery showed CSII participants demonstrated greater benefit with the PEPPER system with increased time in range. It is possible that had the study been completed in the intended population size, a significant result may have been observed.

The loss of a major commercial collaborative partner, Cellnovo, during the study had significant impact on securing sufficient quantities of pump supplies, but also in providing technical support for the CSII participants on a 24/7 basis. This resulted in full technical as well as clinical support for the UK participants being provided by the author. Additional challenges included that Cellnovo hosted the PEPPER source code and made the integration of the PEPPER system to the

specifics of their pumps. Thus, any modifications to the app required their support to integrate these.

It is important to note however, that it is not uncommon for diabetes technology studies to experience challenges within software development. Many such publications have alluded to various challenges faced. For example, in the International Diabetes Closed Loop (iDCL) trial using the hybrid closed-loop system (Control-IQ), the study was paused for a safety-critical software rewrite (98). Another example is the recent DREAM-5 Study using the MD-Logic closed-loop system (DreaMed GlucoSitter) for adaptive basal and bolus, a high rate of communication errors between the tablet computer running the algorithm and the insulin pump were noted (257). This was because the algorithm was not embedded within the pump itself, but rather used a communication device i.e. USB ComLink. In comparison, the PEPPER system algorithms have been successfully embedded within both a mobile handset for MDI users and an insulin pump.

Another key strength of the PEPPER Study Group was that software engineering was under continuous integration and continuous deployment, with short release cycles. This allowed for improvements, feature upgrades and usability optimisation based on user and clinician feedback to be implemented.

6.2 PEPPER System Limitations

Overall, no significant differences were observed between the intervention and control groups. Besides the study being underpowered, potential limitations have been discussed below in relation to the two key aspects of the PEPPER system: 1) the adaptive bolus calculator and 2) the safety system.

6.2.1 Adaptive bolus calculator

A key limitation with the adaptive algorithm included the level of user intervention and the time required for users to input their bolus information and the need for daily engagement with the app. This is required in a continuous cyclical manner to enable the case base to grow. As observed with one participant in the Phase 3 clinical study, only a total of 11 cases were revised, compared to the median number of 334 (276-465) cases per participant. It was therefore deemed unlikely to be sufficient to provide robust adaptive insulin advice. Thus, their data was excluded from the per-protocol analysis.

In two other cases, shift workers were included in the clinical study (a nurse in Spain and a paramedic in the UK). Although the algorithm takes into account the degree of exercise performed, insulin sensitivity is likely to vary at different times of the day in relation to working shift patterns and their day-night routine. At present, adaptation of the PEPPER system cannot manage shift work as it stands. To overcome this challenge, an additional parameter could be incorporated for individuals to record the type of working shift pattern (i.e. day vs night), which can be taken into consideration within the CBR algorithm. Other wearable technology

may be employed to determine physiological data, such as heart rate, accelerometery, sleep trackers and skin galvanometry.

Analysis of the CBR system suggested that stratification by level of exercise based on the step count generated from the MiBand was too high. The majority of cases had past exercise classified as low 73 (44 – 89) %, with only very few cases labelled as mild or intense levels of exercise. This was despite the activity thresholds being reduced before the start of Phase 3. Overall within the literature, there is a lack of a "best" or uniform approach on the way activity signals are classified and employed in detection algorithms (300). There are various wearables and sensors that can record an individual's physical activity load and duration. Some methods consider levels of activity as low, moderate, and high and other methods consider activity as a continuous variable with descriptive features by summarising the quantity, duration and intensity. The lack of consistency in recording activity also impacts consumer devices including Apple Watch, Samsung Gear S3 and Fitbit. In an evaluation comparing mainstream wearable devices, step count and distance were the only consistent measure, whilst activity duration, sleep quality, energy expenditure significantly varied between the wearable devices (301). Metabolic expenditure may be an another alternative method, calculated using heart rate and accelerometery (123). Hajizadeh *et al* (2018) employed an algorithm developed at the Illinois Institute of Technology, to calculate the "metabolic equivalent task" to express the energy cost of physical activity (i.e. the ratio of metabolic rate/ energy consumption to a reference metabolic rate during any specific physical activity) (302).

Additional algorithm limitations include that PEPPER assumes basal insulin is optimised and only adapts bolus insulin. It relies on meal scenarios where the user has not ingested a significant snack or taken an insulin bolus correction within 5 hours of a meal for revision. Future developments would be useful to incorporate the use of basal adaptation. CBR has been proposed as a method to support basal rate adaptation and has been tested in-silico (303). Dassau *et al* (2017) clinically evaluated an adaptive artificial pancreas with adaptations made to basal insulin delivery settings, but only on a weekly basis, and every 4 weeks to carbohydrate ratios (268). Compared to sensor augmented pump therapy during run-in, a reduction in time spent in hypoglycaemia was observed during the day from 5.0% to 1.9% (-3.1, 95% CI -4.1 to -2.1, $p< 0.001$) and overnight from 4.1% to 1.1% (-3.1, 95% CI -4.2 to -1.9, $p< 0.001$; (268)). Other methods for basal adaptation have been discussed in further detail in Section 1.5.5.

There is also an inability for the CBR to provide adaptive learning with extended phase or dual wave bolusing. Standard therapy suggests the use of extended or dual wave boluses to cover meals with high fat and/or protein content, due to potential delayed gastric emptying and changes in insulin sensitivity (54,304). Thus, we would expect to see improvements in glycaemia with dual wave bolusing. An adaptive system with the ability to respond to differences in meals and incorporate the effect of macronutrients (fat and protein), would be particularly advantageous if the intended system were able to adapt its bolusing pattern with learning from previous cases.

Finally, the algorithm uses CBR to adapt the bolus advice. CBR is commonly referred to as a "lazy learning method" (305), as it can be time-consuming to build up a large set of cases. Consequently, this may reflect the degree of time taken to observe noticeable changes in the adaptive bolus advice, with certain participants potentially needing to remain on the CBR algorithm for longer than others. An advantage of such a method, however, was that the retrieved cases could be used to provide understandable explanations as to why the given solution is produced and thus does not suffer from the "black-box" label many machine learning solutions suffer from. This is particularly useful and important when assessing whether the system is working as intended (for example during Phase 2), and for building clinician and user confidence in the system.

Besides using CBR, alternative methods have been proposed for an adaptive algorithm, such as fuzzy-logic (261), deep learning and neural networks (306). A key advantage of machine learning techniques is the ability to mine large databases of glucose and wearable sensor data to define domains in insulin bolus advice that are currently less well established. The challenge, common with all AI in T1D, will be to deploy the most appropriate algorithm for each given problem (i.e. to address meal detection, predictive glucose forecasting, as well as the environmental and physiological factors that affect insulin requirements at mealtimes). It is likely a combination of various AI algorithms may be required to address these multiple issues. For example, a system could use machine learning for the prediction and identification of meals and exercise through wearables (see Section 6.3) and subsequently integrate with CBR or fuzzy logic to determine the insulin dose required. Standard AI techniques have enabled short to medium-term glucose

forecasting for up to 15mins-2hours (231,232), however algorithms with extended prediction (233) could be integrated to support earlier detection of minimum postprandial glucose values. In addition to this, use of longer-term risk metrics over days or weeks may support algorithm learning.

6.2.2 Safety system

In terms of the PEPPER safety system, the predictive glucose forecasting algorithm had a RMSE of 1.6 (1.4-1.9) mmol/L and the overall MARD between the forecasting algorithm and the actual sensor glucose was 14.4 (12.6-15.9) %. Our engineering team at Imperial have since identified alternative AI-derived methods to enhance the accuracy of 30minutes predictive glucose forecasting using personalised deep learning forecasting algorithms, a system known as GluNet (307). GluNet reportedly has a forecasting performance in-silico of RMSE 19.2 ± 2.7 mg/dL and a MARD 10.4 ± 1.5%, which is superior to other forecasting methods including the neural network for predicting glucose (NNPG), the support vector regression (SVR), the latent variable with exogenous input (LVX), and the auto regression with exogenous input (ARX) algorithm (307). Inclusion of such highly accurate forecasting algorithms would help enable better predictions of hypo and hyperglycaemia. Although the RMSE and MARD of the techniques within GluNet are better than the PEPPER algorithm, these may not have overall changed the final study outcomes. At the moment, these comparisons have only been in simulations, rather than within a real-world clinical context.

6.2.3 Other limitations

Finally, as with many technology studies, due to the nature of the intervention, it can be difficult to blind the study participants or researchers. There is a possibility that the knowledge of being in a particular group may have affected certain lifestyle decisions. There can also be an unconscious bias by researchers when informing study participants. In this study, the PEPPER cohort were easily able to identify the group they were randomised to, due to the additional predictive glucose trace, predictive alarms and alerts, as well as the carbohydrate recommendations and varying bolus advise.

Other challenges observed with adaptive decision support systems are similar to those faced in AP systems. These include the lag time of glucose monitoring sensors (up to 10 minutes) when measuring interstitial fluid, as well as the pharmacokinetics of rapid acting insulin analogues (relatively slow with onset of 10–15 min) (101). Novel ultra-rapid insulins (including Fiasp and Liumjev) may support faster onset of action.

6.3 Technology Integration and the Next Generation

Currently the PEPPER software runs on Android handsets, either as a standalone application for MDI users or integrated within Cellnovo's own handset, based on an Android OS build. Whilst the employed PEPPER algorithm is only coded to support use with a Cellnovo pump, the application can be easily integrated in the microcontroller of any insulin pump. Additionally, carrying four devices (handheld

handset, rtCGM, activity monitor, and pump/insulin pens) and their supplies is not an optimal user experience. The plan for future generations of the system would be to enable direct communication of PEPPER with commercially available devices (i.e. insulin pumps by different manufacturers, as well as for app integration into Android or iOS mobile handsets). This would enhance system usability and practicality for daily use, as well as reduce device burden, such as integrating the user's own smartphone through a downloadable app with automated software updates available.

Integration with smartwatches (e.g. Apple Watch), where the menu on the watch is controlled either via swipe or touch gestures, would enable users to easily view glucose values, or receive notifications and reminders. In-built sensors within these wearables (e.g. accelerometer, heart rate data, sleep tracking) can add to the range of input datapoints used for prediction and modelling, such as physical activity, stress and sleep patterns. Furthermore, geographical data may be automatically updated from location settings which can further provide a broader set of impacting factors (e.g. ambient temperature, humidity and atmospheric pressure).

At present, besides the key parameters affecting insulin requirements, it is unclear which additional factors are most likely to be beneficial when adapting bolus advice. Further analyses may be extracted from the PEPPER CBR data to assess the effect of alcohol and exercise on postprandial minimum glucose and its correlation with the number of cases per participant. Hormone cycle in women can be reviewed more specifically within the women who recorded this on the app.

Next generations of the PEPPER system could be linked up with existing meal libraries, which contain detailed information about the composition of the meals. Examples include MyFitnessPal (299), MyNetDiary (308) and Fooducate (309). Alternatively, PEPPER users could create their own personalised meal library. The library can potentially be co-created personally or remotely with the help of a dietician in the set-up phase of the software. The integration of a meal library would allow consideration of parameters such as meal absorption, fat and protein content.

Other systems that could ease physical entry of meals into the system include smart technologies with machine learning capabilities, such as GoCARB (228). The vision-based smartphone system enables the estimation of carbohydrate content from plated meals for individuals with T1D (229,298). Besides rapid entry of meal content, using technologies such as these may offer individuals easy, accurate, and real-time estimation of carbohydrate content in their meals, without the need for accurate carbohydrate counting (228,298). Other food image recognition and deep learning algorithms include NutriNet (310), GoFood (311), Calpal (312) and Calorie Mama (313). Whilst photographing food for management is burdensome and may be difficult when eating out or eating at other peoples' homes, there is a long-trodden path for individuals to upload food photographs to social media, including Instagram and Facebook.

Additional modifications and features that may promote and sustain long-term user engagement include gamification, personal goal setting, social and peer support. Gamification uses elements of game design, such as points, leader boards, levels, competitions, rewards, achievements and goals of experience. Such methods in a

health behaviour change programme may be a way to intrinsically motivate users to continually engage with such applications (314,315).

Understanding individuals and their environments is critical to diabetes care. Both of these are seeing an explosion in potential data gathering. There are many areas which are being sensor enriched, from the individual to the home, which may further support diabetes management. Further accelerating this innovation, is the network effect brought about by an ecosystem of these solutions, where greater benefits are found through the interplay of multiple solutions; for example through analysing pillow sensors, bedroom lights, screen usage along with mealtimes and food, to build a better picture, not just of sleep patterns, but also on the influencers on sleep. Currently each of these solutions are sold separately, to solve their own niche, often from a separate company. However, these ecosystems are benefiting from a move towards common technology standards and an API driven business model making these interconnections easier.

The long-term challenges of such integration, however, will be data governance, potential impact on medical insurance and interoperability between systems to exchange and use information. Furthermore, at present, these ecosystems are largely, albeit informally, controlled by the large tech companies, such as Google and Amazon, who through their size, often dictate the standards and technology that they will support (316).

6.4 Ongoing Future Studies

In 2018, the DreaMed Advisor Pro (DreaMed Diabetes Ltd, Petah Tikva, Israel) artificial intelligence-based decision support system (AI-DSS) was approved by the FDA to provide insulin therapy adjustment recommendations to physicians for people with T1D using an insulin pump (not including hybrid closed loop). The system has been evaluated by healthcare professionals, which found the algorithm provided similar directional agreement to that of clinicians, with the magnitude of dosing change equal or less than that recommended by clinicians (165). In a six-month, parallel, randomised controlled trial, 108 participants aged 10-21 years were randomized 1:1 to receive remote insulin dose adjustment every three weeks guided by either an AI-DSS (n = 54) or by clinicians (n = 54). Percentage time within range (3.9–10.0 mmol/L) in the AI-DSS arm was statistically non-inferior to the clinician arm (50.2 ± 11.1% versus 51.6 ± 11.3% respectively, $p<1\times10^{-7}$). Percentage time <3.0 mmol/L was also statistically non-inferior to the clinician arm ($p < 0.0001$). It is important to note that insulin therapy adjustments (basal and bolus) were provided to clinicians on a three-weekly basis, with clinicians further able to make dose alterations in the AI-DSS arm. In contrast, the PEPPER system is designed to provide real-time advice directly to users, with optimised settings for different meals in different ambient scenarios. The potential implication of the DreaMed Advisor Pro is the ability to provide frequent adjustments to insulin therapy with similar levels of glucose control achieved by clinicians with diabetes expertise.

Two key clinical trials are underway by our group at Imperial College London, namely Phase 5 of the Advanced Bolus Calculator for Diabetes (ABC4D; NCT03963219) and the Adaptive, Real-time, Intelligent System to Enhance Self-care of chronic disease (ARISES; NCT03643692) study.

ABC4D is a decision support algorithm also based on CBR and has been implemented in a smartphone application for MDI users. An initial 6-week prospective non-randomised single arm pilot study with 10 adult participants showed more than a two-fold reduction in the number of postprandial hypoglycaemic episodes (167). Currently, an 8 month randomised non-inferiority clinical trial is underway (317). Whilst ABC4D lacks the integration of a combined safety system, it includes a more automated revision process. As safety was a priority in the PEPPER study, the research team approved ICR algorithmic changes on a weekly basis. However, frequent (e.g. weekly) manual revisions may not be practical for clinical adoption, and thus a more automated revision process to achieve similar performance would be beneficial.

The ARISES study includes the use of multiple wearable sensors to capture a range of biological, environmental and behavioural data to provide real-time therapeutic and lifestyle decision support. The decision support is based on deep machine learning algorithms and will be evaluated in 12 participants over 8 weeks (306). The Dexcom G6 will be used for continuous glucose monitoring and physiological signals will be collected using the wearable Empatica E4 (Empatica Inc, Cambridge, MA). The ARISES interface also enables dynamic data visualisations.

One of the key features of ARISES is that it runs wholly on the smartphone without any requirements for a server or backend processing. At a commercial level, this has the potential benefits of better data privacy, less internet or data bandwidth usage, and improved reliability (not affected by internet connectivity required for the PEPPER cases to upload and sync with the server). In this thesis, the mobile application PEPPER required a central server for backend processing and currently this was optimised for use in the Android (Nexus) handset only. The benefits of a central server include potentially quicker diagnostic processes for users, ability to process updates within the server to support all users, as well the opportunity to train machine learning algorithms in real-time (318).

6.5 Conclusion and Future Outlook

Digital health technology, particularly digital and health applications with AI, have rapidly developed to help people manage their diabetes. However, few are licenced for use with an evidence base for safety and effectiveness. Currently there is no decision support system available to individuals for insulin dosing on the market that adapts itself based on real-time activity and glucose data for users on pump and MDI.

The work outlined in this thesis showed that PEPPER is safe, acceptable, and maintains glycaemia in a diverse population. To our knowledge, this is the largest and first randomised controlled trial reporting clinical outcomes of a personalised, adaptive bolus calculator for use with both MDI and CSII therapy. Despite the

limitations and study being underpowered, all times in ranges moved towards improvement in the intervention group. Increased time in range was most notable in the pump cohort.

A larger powered randomised controlled trial is required to confirm overall effectiveness and would be particularly prudent to include CSII participants using a different pump provider. Since safety has been evaluated in this setting, other interesting cohorts would include children and people with poorer baseline glycaemia (HbA1c > 64mmol/mol), as well as individuals at highest risk of hypoglycaemia. One of the key challenges in engaging children and young adults in this group is missed boluses. Novel methods for user-directed support and motivation include gamification, rewards and peer or social support (Section 6.3).

In terms of exploitation of the PEPPER system, the PEPPER integration source code belonged to Cellnovo and therefore it was not possible to exploit the system as a single integrated solution. As a result, the PEPPER Consortium collaborators have developed multiple individual components in an independent way with application programme interfaces (API) to allow these components to be used by other future projects or commercial applications. The collection of these individual APIs comprise of the constituent parts of PEPPER i.e. (i) safety system (ii) insulin recommender and adaptive bolus calculator (iii) the web-based interface (iv) the graphic mobile interface implemented within the mobile application. The PEPPER APIs are currently available under different licencing agreements and its documentation are freely accessible online (www.pepper.eu.com/API). This provides a convenient way to integrate the variety of clinically validated software

modules outlined within this thesis, into an insulin decision support system or artificial pancreas.

7 References

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8 Appendix 1

Outputs

8.1 Peer-reviewed publications: Original articles

1) **Avari P***, Leal Y*, Herrero P, Wos M, Jugnee N, Arnoriaga-Rodríguez M, Thomas M, Liu C, Massana J, Lopez B, Nita L, Martin C, Fernández-Real JM, Oliver N, Fernández-Balsells M, Reddy R. *Safety and feasibility of the PEPPER adaptive bolus advisor and safety system; a randomized control study*. Diabetes Technol Ther. 2020 Mar;22(3):222-227. [Online DOI: 10.1089/dia.2020.0301]
2) Duce D, Martin C, Russell A, Brown D, Aldea A, Alshaigy B, Harrison R, Waite M, Leal Y, Wos M, Fernández-Balsells M, Fernández-Real JM, Nita L, Lopez B, Massana J, **Avari P**, Herrero P, Jugnee N, Oliver N, Reddy M. *Visualizing Usage Data from a Diabetes Management System*. EG UK Computer Graphics & Visual Computing. 2020. [Accepted]
3) **Avari P,** Uduku C, George D, Reddy M, Oliver N. *Differences for Times in Glycaemic Range Between Continuous Glucose Monitoring and Capillary Blood Glucose Monitoring in Adults with Type 1 Diabetes:*

Analysis of the REPLACE-BG dataset. Diabetes Technol Ther. 2020 Mar;22(3):222-227. [Online DOI: 10.1089/dia.2019.0276.]

4) **Avari P,** Moscardo V, Jugnee N, Oliver N, Reddy M. *Glycemic Variability and Hypoglycemic Excursions With Continuous Glucose Monitoring Compared to Intermittently Scanned Continuous Glucose Monitoring in Adults With Highest Risk Type 1 Diabetes.* J Diabetes Sci Technol. 2020 May;14(3):567-574. [Online DOI: 10.1177/1932296819867688]
5) **Avari P**, Reddy M, Oliver N. *Is it possible to constantly and accurately monitor blood sugar levels, in people with Type 1 diabetes, with a discrete device (non-invasive or invasive)?* Diabet Med. 2020 Apr;37(4):532-544 [Online DOI: 10.1111/dme.13942.]
6) Liu C*. **Avari P*,** Leal Y, Wos M, Sivasithamparam K, Georgiou P, Reddy M, Fernández-Real JM, Martin C, Fernández-Balsells M, Oliver N. *A Modular Safety System for an Insulin Dose Recommender: A Feasibility Study*. J Diabetes Sci Technol. 2020 Jan; 14(1):87-96 [Online DOI: 10.1177/1932296819851135.]
7) **Avari P,** Ramli R, Reddy M, Oliver N, Fothergill R. *Rationale and protocol for the Assessment of Impact of Real-time Continuous Glucose Monitoring on People Presenting with Severe Hypoglycaemia (AIR-CGM) Study.* BMC Endocr Disord. 2019 Oct 26;19(1):110. [Online DOI: 10.1186/s12902-019-0439-3.]
8) Liu C, Vehi J, **Avari P,** Reddy M, Oliver N, Georgiou P, Herrero P. *Long-Term Glucose Forecasting using a Physiological Model and Deconvolution of the Continuous Glucose Monitoring Signal.* Sensors (Basel). 2019 Oct 8;19(19):4338. [Online DOI: 10.3390/s19194338.]

8.2 Abstracts: Oral presentations at conferences

1) **Avari P***, Leal Y*, Wos M, Sivasithamparam K, Liu C, Jugnee N, Thomas M, Herrero P, Reddy M, Martin C, Fernández-Real JM, Oliver N, Fernández-Balsells M. *Feasibility of Safety System within a Novel Personalised Decision Support Tool for Insulin Dosing.* Abstract ID 0214 Presented at ATTD 2019, Berlin, Germany.
2) **Avari P**, Moscardo V, Jugnee N, Reddy M, Oliver N. The I-HART CGM Study: *Hypoglycaemia episodes reduced with continuous glucose monitoring compared to Flash in adults with type 1 diabetes.* Abstract 85. Presented at EASD 2018, Berlin, Germany.
3) **Avari P**, Moscardo V, Jugnee N, Reddy M, Oliver N. *The I-HART CGM Study: Eight week head-on-head comparison of glycaemic variability between flash and continuous glucose monitoring systems in adults with Type 1 diabetes.* Abstract ID ATTD8-0376. Presented at ATTD 2018, Vienna, Austria.

8.3 Abstracts: Poster presentations at conferences:

1) **Avari P***, Leal Y*, Wos M, Jugnee N, Thomas M, Massana J, Lopez B, Nita L, Martin C, Herrero P, Oliver N, Fernández-Real JM, Reddy M, Fernández-Balsells M. *Efficacy and Safety of the Patient Empowerment through Predictive Personalised Decision Support (PEPPER) System: An Open-Label Randomised Controlled Trial*. Abstract ID 680. Presented at ATTD 2020, Madrid, Spain.
2) Waite M, Aldea A, **Avari P**, Leal Y, Martin C, Fernández-Balsells M, Fernández-Real JM, Herrero P, Jugnee N, Lopez B, Reddy M, Wos M,

Oliver N. *Trust and Contextual Engagement with the PEPPER system: The Qualitative Findings of a Clinical Feasibility Study.* Abstract ID 852. Presented at ATTD 2020, Madrid, Spain.

3) Herrero P, Massana J, Leal Y, Nita L, **Avari P**, Duce D, Aldea A, Georgiou P, Fernández-Real JM, Fernández-Balsells M, Oliver N, Lopez B, Martin C. *The PEPPER System Application Program Interface*. Abstract ID 949. Presented at ATTD 2020, Madrid, Spain.
4) **Avari P**, Siddique M, Samarsinghe S, Plews E, Oliver N and Reddy M. *Increased uptake for continuous glucose monitoring with ongoing clinical benefits within an NHS-Commissioned Service.* Accepted at Diabetes UK 2020, Glasgow, UK. (Conference cancelled due to Covid-19 pandemic)
5) **Avari P**, Moscardo V, Jugnee N, Reddy M, Oliver N. *Ambulatory Glucose Profiling and Glycaemic Outcomes when switching Flash to Continuous Glucose Monitoring.* Abstract ID 0416. Presented at ATTD 2019, Berlin, Germany.
6) Martin C, Aldea A, Alshaigy B, **Avari P**, Duce D, Fernández-Balsells M, Fernández-Real JM, Harrison R, Herrero P, Jugnee N, Lui C, López B, Massana J, Leal Y, Russell A, Reddy M, Waite M, Wos M, Oliver N. *Application of Usability Engineering to the Development of a Personalised Decision Support System for Type 1 Diabetes Self-Management.* Abstract ID 0303. Presented at ATTD, 2019. Berlin, Germany.
7) Liu C, Georgious P, Herrero P, **Avari P**, Oliver N. Coordinating Low-*Glucose Insulin Suspension and Carbohydrate Recommendations for hypoglycaemic minimization.* Abstract ID 0341. Presented at ATTD 2019, Berlin, Germany
8) **Avari P**, Jairam C, Idowu O, Begum F, Oliver N and Reddy M. *Continuous glucose monitoring outcomes in Type 1 diabetes within an NHS-*

commissioned service. Abstract ID P427. Presented at Diabetes UK 2019, Liverpool. UK.

9) Moscardo V, Gimenez M, **Avari P**, Reddy M, Oliver N. *Influence of ambient temperature on glycaemic behaviour in type 1 diabetes patients.* Abstract ID ATTD8-0379. Presented at ATTD 2018, Vienna, Austria.

9 Appendix 2

Data Analysis Plan

9.1 Study Objectives

9.1.1 Primary Objective

To assess safety and feasibility of the complete **P**atient **E**mpowerment through **P**redictive **PER**sonalised decision support (PEPPER) system (i.e. safety system and adaptive bolus calculator) compared to a standard bolus calculator.

9.1.2 Secondary objectives

- To assess the safety system integrated within PEPPER.
- To assess the adaptive bolus advisor within PEPPER.
- To assess psychological outcomes of the PEPPER system using clinical questionnaire data.

9.2 Endpoints

9.2.1 Primary endpoint

- The primary endpoint for the PEPPER clinical trial is the difference in percentage time in range (3.9 – 10mmol/l) between the intervention arm that receives the PEPPER system and the control arm. Endpoints assessment will not be blind to the study intervention arm allocated.

9.2.2 Secondary endpoints

- Secondary outcomes include between-group differences for the variables listed below:

1. **Variables related to glycaemia:**
   - Percentage time in hypoglycaemia (<3.9mmol/l)
   - Percentage time in hypoglycaemia (<3.0mmol/l)
   - Percentage time above range (>10mmol/l)
   - Number of episodes of serious hypoglycaemia (defined as sensor glucose < 3.0mmol/l for > 20 min
   - Episodes of hypoglycaemia within 4- and 6-hours post-prandially
   - Post-prandial area under the curve (AUC) at 4 hours and 6 hours
   - Post-prandial area under the curve (AUC) (<3.9) at 4 hours and 6 hours
   - HbA1c

2. **Variables related to adverse events:**
   - Event rates of severe hypoglycaemia
   - Event rates of diabetic ketoacidosis
   - Event rates of all adverse events

3. **Variables related to glycaemic variability:**
   - Standard deviation (SD)
   - Coefficient of variation (CV)
   - Mean amplitude of glycaemic excursions (MAGE)
   - Continuous overall net glycaemic action (CONGA): 1hr and 2hr
   - Mean of daily differences (MODD)
   - Lability index (LI)
   - Glycaemic variability percentage (GVP)
   - Mean absolute glucose change per unit time (MAG)
   - Glycaemic risk assessment diabetes equation (GRADE)
   - M-value
   - Average daily risk range (ADRR)
   - J-Index
   - Personal glycaemic status (PGS)
   - Index of glycaemic control (IGC)
   - Risk index (RI)
   - Low blood glucose index (LBGI)
   - High blood glucose index (HBGI)

4. **Variables related to anthropometric measurements:**
   - Weight (kg)
   - Basal insulin dose (units)

5. **Psychological outcomes:**
   - Problem Areas in Diabetes (PAID) Questionnaire
   - Diabetes Quality-of-Life (DQOL) Questionnaire
   - Diabetes Treatment Satisfaction Questionnaire (DTSQ)
   - Gold/Clarke score at baseline

6. **Variables related to safety system:**

- Rate of change in number of hypoglycaemia alarms
- Rate of change in number of hypoglycaemia alerts
- Rate of change in number of hyperglycaemia alerts
- Rate of change in number of low glucose suspend incidents (at 50% and complete suspension)
- Rate of change in number of carbohydrate recommendations
- Rate of change in number of carer alarms
- Rate of change in number of insulin dose saturations (low and high)
- Accuracy of the glucose prediction algorithm

7. **Variables related to the adaptive bolus advise (using CBR technique):**
   - Number of CBR revision cases
   - Number of bolus recommendations accepted by user
   - Incidence and usage of various case parameters:
     - Physical activity (past and future)
     - Meal absorption rate
     - Alcohol
     - Stress
     - Tiredness
     - Hormone cycle
     - Fever
     - Digestive illness

9.3 Statistical considerations

Analysis population

- Intention to treat population (ITT)

Primary analyses will be conducted following the intention to treat (ITT) principle. All participants who are randomised into the study will be included in the ITT analysis and the analysis is conducted according to the randomised treatment arm.

- Per protocol population

In addition, the primary endpoint will be analysed with the per protocol population, which consists of those participants in the ITT population who complete the study with no significant deviations from the planned protocol procedures. The exclusion will be as follows:

- Significant protocol deviation such as recruitment outside of inclusion / exclusion criteria
- Pregnancy during study
- Participants who withdraw consent

Data Description

Collected data will be summarised as follows:

Quantitative data: median and interquartile range (IQR); maximum and minimum values
Qualitative data: count (n) and proportion (%);
In addition, for each variable, the proportion of missing data will be reported.

Data review

The distribution of the main variable (percentage time in range) will be assessed using a normal distribution and quantile-quantile plot. Skewness will be assessed for, and additional assessment of normality will be conducted using the Shapiro-Wilk test. Boxplots may be used to detect outliers.

Variables with outliers, missingness and/or problematic distribution will be reviewed with the some/all of the Study Team (where applicable).

If required, data will be adjusted for their baseline value, participant age and sex.

For variables showing strong departure from normality, the non-parametric Mann Whitney Wilcoxon rank sum test (two groups).

Missing data

Missing data will be handled by a last observation carried forward approach unless there is evidence against the assumption of data missing at random. For data computed in EasyGV, periods without glucose values that are longer than the defined 'Max Gap' are considered as gaps. The program will enable glucose interpolation when the time difference between consecutive samples is less than Max Gap. This point is important when the CGM recordings are large since calibration periods or sensor changes could add error to the calculations. The 'Max Gap' will be defined as 50 minutes (default setting of EasyGV 10).

Analysis of the primary endpoint

Derivation:

Measurement. As per protocol, participants have CGM during the clinical study, through which ambulatory glucose profiles will be analysed. Data from each intervention period will be analysed from last 28 days of each phase (PEPPER/control).

Data transformation. Raw glucose data will be exported from the Clinical Portal in to Excel.

Available data from previous studies suggest that percentage time in ranges may not be normally distributed (319). In the study by Avari et al (319), time in ranges showed significant departure from normality with significant skewness (Shapiro–Wilk test of normality; $p < 0.05$).

For this analysis, the preferred approach to handle departures from normality and outliers will be to use non-parametric statistical methods.

Planned analysis:

The primary analysis will be conducted under the ITT principle. Differences in percentage time in range (3.9 – 10.0 mmol/l) between the last 28 days of each intervention phase (PEPPER/control) and the 4 weeks of the run-in phase (baseline) will be calculated and between group differences will be presented as medians with IQR.

The primary null hypothesis is of no difference in median percentage time in range between the intervention and the control arms. It will be tested against the alternative hypothesis of a difference between the two groups. The null hypothesis will be rejected if the statistical analysis indicates $p<0.05$.

Time in ranges	**Baseline (median +/- IQR)**	**Δ Control**	**Δ PEPPER**	**p-value**
		Differences between the last 4 weeks of the intervention phase (Control/ PEPPER) and baseline		

Power of the analysis:

With 50 participants a 0.57 SD difference can be demonstrated as significant with α of 0.05 and 80% power (two-tailed). Based on a pilot study population mean (SD) % time in target (3.9-10mmol/l) of 61.6 (18.8) a 10.7 (=0.57x18.8) difference in % time in target can be demonstrated as significant between the intervention and control in this study. To allow for a 10% drop-out 55 participants will be recruited.

In the event of failure to recruit or collect sufficient completion data to meet the a priori sample size, a post-hoc assessment of achieved power may be undertaken.

Secondary endpoints

The same analyses (described above) will be computed for all of the continuous variables. The additional specific analyses are described in the section below.

- **Post-prandial area under the curve (AUC) at 4 hours and 6 hours**
  - *Derivation:* CGM derived
  - ***Analysis:*** To be calculated using a statistical software package to compute trapezoidal approximation of glucose levels measured every 5 minutes by CGM.

- **Glycaemic variability measures**
  - *Derivation:* Evaluated GV measures to include SD, CV, MAGE, CONGA, MODD, LI, MAG, GVP, PGS, M-Value, IGC, RI, GRADE, M-value, ADRR, J-Index, HBGI and LBGI. GRADE score is also reported as %GRADEhypoglycemia, %GRADEeuglycemia, and %GRADEhyperglycemia representing percentages of GRADE scores attributable to glucose values <3.9 mmol/l, between 3.9–10.0 mmol/l and >10.0 mmol/l respectively.
  - *Analysis:* Measures of GV to be computed using EasyGV (v10.0) software. Between-group analyses and statistical tests to be conducted in similar manner to primary outcome.

- **Safety System measures**
  - *Derivation:* Number of alerts/alarms (including carer alarms)/ carbohydrate recommendations/ low glucose suspend (50% and total suspension), and number of insulin dose saturations (low and high). Accuracy of glucose prediction algorithm.
  - ***Analysis:*** Number of safety system outcomes to be computed through Matlab. Number of safety system outcomes (median ± IQR) for each study week in the intervention phase (i.e. total 12 weeks). For accuracy of the glucose prediction algorithm, the mean absolute relative difference (MARD), root mean square error (RMSE) at 30mins will be calculated.
  - *Potential Additional Exploratory Analysis:* Correlation of safety system outcomes with change in glycaemia from baseline.

- **CBR measures**
  - ***Derivation:*** Number of case revisions, number of bolus recommendations accepted by user, number of individual parameter usage
  - *Analysis:* Number of case revisions to be computed. Number of CBR cases (median ± IQR) in the case base for each study week in the intervention phase (i.e. total 12 weeks). Rate of change to be subsequently calculated.
  - *Potential Additional Exploratory Analysis:* Correlation of number of CBR cases with change in glycaemia from baseline. Correlation of number of bolus recommendations accepted by the user with change in glycaemia from baseline. Number of individual parameter usage outcomes/correlation to be decided dependent on number of individual parameters used. Examples may include:
    - Effect of alcohol intake with meals and hypoglycaemia (e.g. post prandial AUCs or glycaemic variability measures)

Additional information:

Significance level - All analyses will be conducted using a 5% significance level.

Statistical software - Data management and statistical analyses will be performed using statistical software e.g Stata. Glycaemic variability will be analysed using EasyGV10.

Publications - Clinical publications arising would have an author from ICL and IDIBGI as joint first authors.

10 Appendix 3

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Page No.	Type/Name of work	Source of work	Copyright holder and contact	I have permission yes /no	Permission note
34	Figure 1.2: Methods of glucose sensing technology	Avari P, Reddy M, Oliver N. *Is it possible to constantly and accurately monitor blood sugar levels, in people with Type 1 diabetes, with a discrete device (non-invasive or invasive)?* Diabet Med. 2020;37(4):532–44.	© 2019 Diabetes UK	Yes	Permission obtained from John Wiley and Sons
37	Table 1.1: Currently available glucose monitoring systems and their accuracy	Avari P, Reddy M, Oliver N. *Is it possible to constantly and accurately monitor blood sugar levels, in people with Type 1 diabetes, with a discrete device (non-invasive or invasive)?* Diabet Med. 2020;37(4):532–44.	© 2019 Diabetes UK	Yes	Permission obtained from John Wiley and Sons
129	Table 3.3: Glycaemic outcomes in MDI users with safety system on.	*Liu C, *Avari P, Leal Y, Wos M, Sivasithamparam K, Georgiou P, et al. *A Modular Safety System for an Insulin Dose Recommender: A Feasibility Study*. J Diabetes Sci Technol. 2020;14(1):87–96.	© SAGE Publications 2020	Yes – through SAGE's Green Open Access	SAGE Green Open Access policy
129	Figure 3.2: Change in glycaemic outcomes on a fortnightly basis	*Liu C, *Avari P, Leal Y, Wos M, Sivasithamparam K, Georgiou P, et al. *A Modular Safety System for an Insulin Dose Recommender: A Feasibility Study*. J Diabetes Sci Technol. 2020;14(1):87–96.	© SAGE Publications 2020	Yes – through SAGE's Green Open Access	SAGE Green Open Access policy
130	Table 3.4: Safety system outcomes comparing run-in and endpoint	*Liu C, *Avari P, Leal Y, Wos M, Sivasithamparam K, Georgiou P, et al. *A Modular Safety System for an Insulin Dose Recommender: A Feasibility Study*. J Diabetes Sci Technol. 2020;14(1):87–96.	© SAGE Publications 2020	Yes – through SAGE's Green Open Access	SAGE Green Open Access policy

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